69. Functionalized Nitroalkanes in Organic Synthesis. The First Concise Preparation of 4-Hydroxyheptadecan-7-one and 14-Hydroxyoctadecan-8-one, Two New Hydroxy Ketones Isolated from *Chiococca alba*

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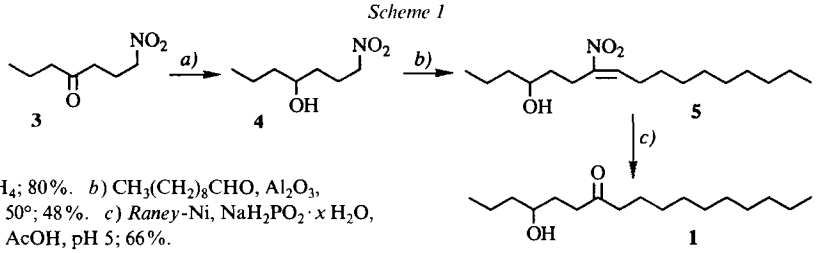
The 4-hydroxyheptadecan-7-one (**1**) and 14-hydroxyoctadecan-8-one (**2**), two new hydroxyketones isolated from leaves of *Chiococca alba*, were synthesized, for the first time, by hydroxy-functionalized nitroalkanes **4** and **9**, respectively, *via* two chemoselective key steps: *i*) nitroaldol condensation with basic alumina, and *ii*) direct *Nef* conversion of nitroalkenes to carbonyl derivatives with sodium hypophosphite, in order to preserve the OH group.

The roots of *Chiococca alba* (*Anguifuga, Brachiata, Racemosa,* and *Trisperma*), of Rubiaceae family, are reported to be used in folk medicine as a tonic for ganglion inflammation, a diuretic, an antivirus, an antioedema, and an aphrodisiac [1]. Neither chemical nor pharmacological studies of the constituents of this genus were reported up to 1991 when *El-Hafiz et al.* [2] published an examination of a leaf-extract and found two new hydroxy ketones: 4-hydroxyheptadecan-7-one (**1**) and 14-hydroxyoctadecan-8-one (**2**) as the main components.

Aliphatic nitro compounds can be considered as versatile building blocks and intermediates in organic synthesis [3]. We reviewed [3d] the use of functionalized aliphatic nitro compounds in assembling C-atoms, without the problems associated with the utilization of organometallic species. The great versatility and the mild conditions required in their manipulation made functionalized nitroalkanes to be crucial precursors for several preparations of important natural products [4].

Due to the high value of the title compounds, we decided to develop the first syntheses of both the hydroxy ketones **1** and **2**, starting from hydroxy-functionalized nitroalkanes **4** and **9**. The key steps of our syntheses are two chemoselective reactions in which the OH group, present in the nitro derivatives, must be preserved: *i*) nitroaldol condensation with basic alumina [3h], and *ii*) direct *Nef* conversion of nitroalkenes to carbonyl derivatives with sodium hypophosphite [3i].

Scheme 1

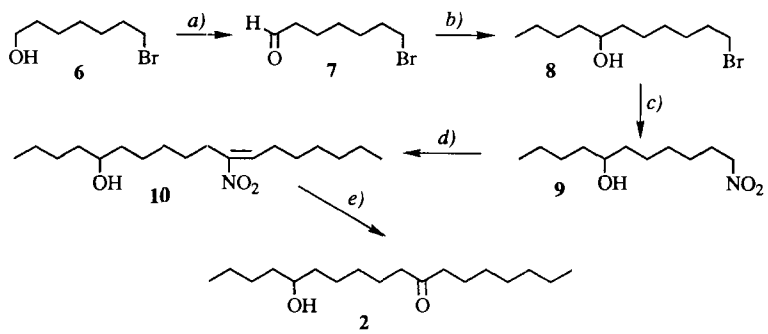


a) $NaBH_4$; 80%. *b*) $CH_3(CH_2)_8CHO$, Al_2O_3, CH_2Cl_2, 50°; 48%. *c*) *Raney*-Ni, $NaH_2PO_2 \cdot x\,H_2O$, NaOAc, AcOH, pH 5; 66%.

The synthesis of **1** was achieved (*Scheme 1*) by $NaBH_4$ reduction of nitroketone [5] **3** to **4**, then nitroaldol condensation of **4** with decanal under basic conditions (basic Al_2O_3), and *Nef* conversion of the obtained conjugated (*E*)-nitroalkene **5** using sodium hypophosphite.

The preparation of **2** (*Scheme 2*) started with pyridinium chlorochromate (PCC) oxidation of commercially available 7-bromoheptan-1-ol (**6**) to aldehyde **7**. *Grignard* addition of butylmagnesium iodide to **7** in THF (−10° to room temperature) gave **8** which by subsequent substitution with $NaNO_2$ in DMF was converted to the nitroalkanol **9**. Following the above procedure for the conversion **4** → **1**, nitroaldol condensation of **9** with heptanal produced **10** which on sodium hypophosphite treatment furnished the 14-hydroxyoctadecan-8-one (**2**).

Scheme 2



a) PCC, CH_2Cl_2; 78%. *b*) BuMgI, THF, −10° to room temperature; 75%. *c*) $NaNO_2$, DMF; 70%. *d*) $CH_3(CH_2)_5CHO$, Al_2O_3, CH_2Cl_2, 50°; 41%. *e*) *Raney*-Ni, $NaH_2PO_2 \cdot x\,H_2O$, NaOAc, AcOH, pH 5; 60%.

In the attribution of ^{1}H-NMR spectra, we found some differences with those reported for the isolated hydroxyketones **1** and **2** [2]; corrected attributions are given in the *Exper. Part*.

In conclusion, the first efficient and simple syntheses of the hydroxyketones **1** and **2** were achieved. Moreover, the present methodologies represent a progressive evolution of a practical utilization of functionalized nitroalkanes as strategic tools for the synthesis of important natural products.

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Experimental Part

General. The 1-nitroheptan-4-one (**3**) was obtained by the standard method [5], while decanal, heptanal, and 7-bromoheptan-1-ol (**6**) were available from *Aldrich*. Solns. were dried over anh. $MgSO_4$. All reactions were monitored by TLC and/or GC. GC: *Carlo Erba Fractovap 4160* using a capillary column of *Duran* glass (0.32 mm × 25 m), stationary phase *OV1* (film thickness 0.4–0.45 nm). TLC: UV and I_2 were used for detection. IR Spectra: as film; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: in $CDCl_3$ at 200 and 50 MHz, resp., with

a *Varian Gemini 200*; δ in ppm, J in Hz, standard $SiMe_4$ (= 0 ppm). Mass spectra: in m/z; *Hewlett-Packard GC/MS 5988A*.

1-Nitroheptan-4-ol (**4**). To a soln. of **3** (3.5 g, 22 mmol) in 80 ml of EtOH at 0°, $NaBH_4$ (1.1 g, 28.7 mmol) was added during 15 min under stirring. After 1 h, the soln. was acidified with 2N HCl (pH 3), extracted with Et_2O (3 × 70 ml), dried (Na_2SO_4), and evaporated giving a crude oil which was purified by flash chromatography [6] (FC; cyclohexane/AcOEt 6:4): 2.83 g (80%) of pure **4**. Oil. IR (film): 3360, 1525. ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, J = 6.9, Me); 1.22–1.6 (*m*, 6 H); 1.78 (*s*, OH); 2.0–2.38 (*m*, $CH_2CH_2NO_2$); 3.55–3.68 (*m*, H–C(4)); 4.41 (*t*, J = 7, CH_2NO_2). Anal. calc. for $C_7H_{15}NO_3$ (161.2): C 52.16, H 9.38, N 8.69; found: C 51.89, H 9.51, N 8.53.

7-Bromoheptanal (**7**). To a stirred suspension of pyridinium chlorochromate (PCC, 9.7 g, 45 mmol) and 3 Å molecular sieves (15 g) in CH_2Cl_2 (100 ml), **6** (5.85 g, 30 mmol) in CH_2Cl_2 (20 ml) was added. After stirring for 2 h at r.t. and addition of Et_2O (200 ml), the soln. was passed through a short pad of *Florisil* (30–60 mesh) and evaporated. Distillation of the oily residue gave 4.52 g (78%) of pure **7**. B.p. 80°/0.3 Torr. IR (film): 1725. ^{1}H-NMR ($CDCl_3$): 1.2–1.9 (*m*, 8 H); 2.42 (*t*, J = 7, CH_2CO); 3.4 (*t*, J = 6.8, CH_2Br); 9.8 (*s*, CHO). Anal. calc. for $C_7H_{13}BrO$ (193.08): C 43.54, H 6.79; found: C 43.38, H 6.66.

11-Bromoundecan-5-ol (**8**). To a vigorously stirred, N_2-flushed 1.8M BuMgCl soln. in THF (16.11 ml) at −10°, a soln. of **7** (4.25 g, 22 mmol) in THF (45 ml) was added dropwise. After 10 min, the mixture was allowed to reach r.t. very slowly (2 h). The mixture was then quenched with sat. aq. NH_4Cl soln. (30 ml) and extracted with Et_2O (3 × 50 ml), the extract dried ($MgSO_4$) and evaporated, and the residue submitted to FC (silica gel, cyclohexane/AcOEt 8:2): 4.15 g (75%) of pure **8**. Oil. IR (film): 3330. ^{1}H-NMR ($CDCl_3$): 0.9 (*t*, J = 6.8, Me); 1.2–1.55 (*m*, 14 H); 1.75–1.95 (*m*, CH_2CH_2Br); 3.38 (*t*, J = 6.8, 2 H); 3.5–3.65 (*m*, H–C(5)). Anal. calc. for $C_{11}H_{23}BrO$ (251.2): C 52.59, H 9.23; found: C 52.8, H 9.08.

11-Nitroundecan-5-ol (**9**). To a stirred soln. of $NaNO_2$ (1.04 g, 15 mmol) in DMF (50 ml), **8** (2.51 g, 10 mmol) was added, and the soln. stirred for 8 h at r.t. Then the mixture was quenched with cold H_2O (100 ml) and extracted with Et_2O (3 × 50 ml), the combined extract dried ($MgSO_4$) and evaporated, and the residue purified by FC (cyclohexane/AcOEt 8:2): 1.52 g (70%) of pure **9**. Oil. IR (film): 1550. ^{1}H-NMR ($CDCl_3$): 0.9 (*t*, J = 7, Me); 1.2–1.6 (*m*, 14 H); 1.9–2.1 (*m*, $CH_2CH_2NO_2$); 3.5–3.65 (*m*, H–C(5)); 4.4 (*t*, J = 7.2, CH_2NO_2). Anal. calc. for $C_{11}H_{23}NO_3$ (217.31): C 60.8, H 9.23, N 6.45; found: C 60.99, H 9.08, N 6.60.

Nitroaldol Condensation: Nitroalkenes **5** *and* **10**. *General Procedure*. A soln. of **4** or **9** (5 mmol) and aldehyde (5 mmol) was mechanically stirred for 10 min at 0° (ice bath). After the addition of basic alumina (for chromatography, act. I; 2 g) and stirring for 1 h at 0°, the mixture was allowed to stand at r.t. for 15 h. CH_2Cl_2 (50 ml) was added and the mixture stirred and heated at 50° for 20 h. The mixture was filtered, the alumina washed with CH_2Cl_2 (3 × 25 ml), the org. layer evaporated, and the residue purified by FC (AcOEt/cyclohexane 1:3) to give the pure **5** and **10**.

(E)-7-Nitroheptadec-7-en-4-ol (**5**): Yield 0.72 g (48%). Oil. IR (film): 3400, 1510. ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, J = 7, Me); 0.9 (*t*, J = 6.9, Me); 1.2–1.7 (*m*, 20 H); 2.2 (*m*, CH_2CH=C); 2.8 (*m*, CH_2CNO_2); 3.6 (*m*, H–C(4)); 7.1 (*t*, J = 7.9, CH=C). Anal. calc. for $C_{17}H_{33}NO_3$ (299.46): C 68.19, H 11.11, N 4.68; found: C 68.00, H 11.24, N 4.49.

(E)-11-Nitrooctadec-11-en-5-ol (**10**): Yield 0.64 g (41%). Oil. IR (film): 3400, 1515. ^{1}H-NMR ($CDCl_3$): 0.85–0.95 (*m*, 2 Me); 1.2–1.6 (*m*, 22 H); 2.2 (*m*, CH_2CH=C); 2.6 (*m*, CH_2CNO_2); 3.62 (*m*, H–C(5)); 7.1 (*t*, J = 7.9, CH=C). Anal. calc. for $C_{18}H_{35}NO_3$ (313.48): C 68.97, H 11.25, N 4.47; found: C 69.10, H 11.36, N 4.35.

Direct Nef *Conversion: Hydroxyketones* **1** *and* **2**. *General Procedure*. To a soln. of **5** or **10** (4.1 mmol) and sodium hypophosphite (4.1 g) in EtOH (50 ml) and aq. (25 ml) NaOAc soln./AcOH 2:1, pH 5, a suspension of *Raney*-Ni (50% H_2O, 0.9 ml) was added in several portions at r.t. After maintaining the mixture with stirring at 50° for 3 h, the catalyst was filtered off, H_2O added (40 ml), the soln. extracted with Et_2O (3 × 20 ml), the extract dried ($MgSO_4$) and evaporated, and the crude product purified by FC (AcOEt/cyclohexane 2:8), giving pure **1** or **2**.

4-Hydroxyheptadecan-7-one (**1**): Yield 0.73 g (66%). M.p. 66–68° ([2]: 67–68°). IR (KBr): 3250, 1700. ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, J = 7, Me(17)); 0.93 (*t*, J = 6.9, Me(1)); 1.1–1.9 (*m*, 22 H); 1.6 (*s*, OH); 2.45 (*t*, J = 7.4, CH_2(8)); 2.58 (*t*, J = 7, CH_2(6)); 3.65 (*m*, H–C(4)); (^{1}H-NMR ($CDCl_3$) according to [2]: 0.9 (*t*, Me(1), Me(17)); 1.26 (*s*, CH_2(2), CH_2(3), CH_2(10), CH_2(11), CH_2(12), CH_2(13), CH_2(14), CH_2(15), CH_2(16)); 1.6 (*m*, CH_2(5), CH_2(9)); 2.2 (*t*, CH_2(6), CH_2(8)); 2.43 (*m*, H–C(4)); 3.26 (*s*, OH)). ^{13}C-NMR ($CDCl_3$): 14.54 (C(17)); 14.58 (C(1)); 19.33 (C(2)); 23.15; 24.41 (C(9)); 29.73, 29.78, 29.89, 29.95, 30.05, 31.38, 32.37; 39.58 (C(6)); 40.42 (C(3)); 43.48 (C(8)); 71.70; 212.70 (C(7)). Anal. calc. for $C_{17}H_{34}O_2$ (270.46): C 75.50, H 12.67; found: C 75.61, H 12.78.

14-Hydroxyoctadecan-8-one (**2**): Yield 0.7 g (60%). M.p. 69–70° ([2]: 69–70°). IR (KBr): 3250, 1700. ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, J = 6.8, Me(1)); 0.91 (*t*, J = 7, Me(18)); 1.17–1.5 (*m*, 20 H); 1.5–1.68 (*m*, CH_2(6), CH_2(10)); 2.37 (*t*, J = 7.3, CH_2(7)); 2.39 (*t*, J = 7.3, CH_2(9)); 3.5–3.64 (*m*, H–C(14)); (^{1}H-NMR ($CDCl_3$) according to [2]: 0.82 (*t*, Me(1), Me(18)); 1.22 (*s*, CH_2(2), CH_2(3), CH_2(4), CH_2(5), CH_2(11), CH_2(12), CH_2(13), CH_2(15), CH_2(16),

CH_2(17)); 1.5 (*m*, CH_2(6), CH_2(10)); 2.25 (*t*, CH_2(7), CH_2(9)); 2.42 (*m*, H–C(14)); 3.26 (*s*, OH)). ^{13}C-NMR ($CDCl_3$): 14.02 (C(1)); 22.56 (C(18)); 22.71, 23.74, 23.85, 25.39, 29.03, 29.19, 29.24, 29.25, 31.63, 37.13; 42.63 (C(7)); 42.80 (C(9)); 71.70 (C(14)); 211.31 (C(8)). Anal. calc. for $C_{18}H_{36}O_2$ (284.49): C 75.98, H 12.76; found: C 76.13, H 12.62.

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