1-Nitroicosane as the Key Building Block for the First Synthesis of Triacontan-11-ol, A New Fatty Alcohol Isolated from *Argemone mexicana*

Roberto Ballini,* Dennis Fiorini, Alessandro Palmieri

Dipartimento di Scienze Chimiche, Università, via S. Agostino 1, 62032 Camerino, Italy
Fax +39(0737)402297; E-mail: roberto.ballini@unicam.it

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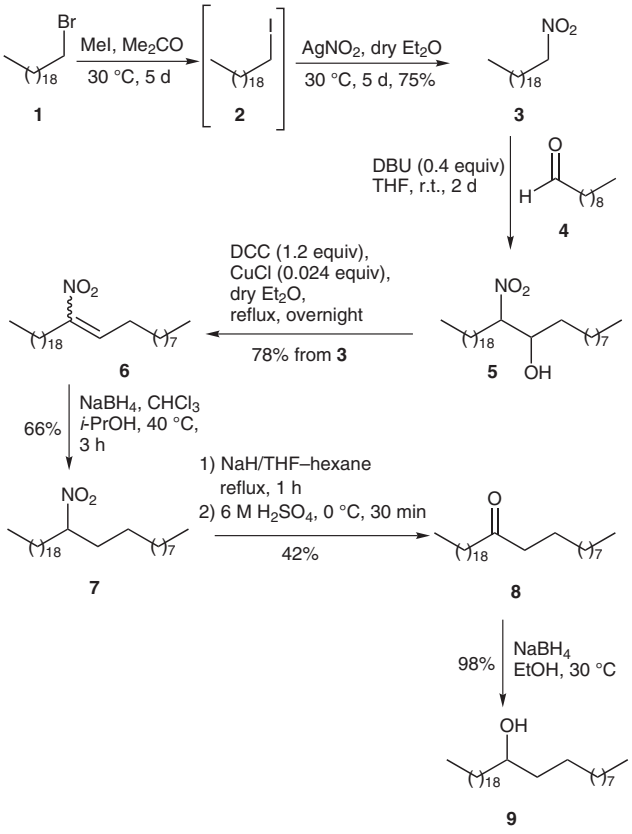
Abstract: The first synthesis of triacontan-11-ol, a new fatty alcohol isolated from *Argemone mexicana*, has been realized starting from the nitroaldol reaction of 1-nitroicosane with decanal. Dehydration of the obtained nitroalkanol gives a long-chain nitroalkene which is then reduced to the corresponding nitroalkane. Nef transformation of the latter produces a ketone that is easily reduced to the fatty alcohol **9** in 21% overall yield.

Key words: triacontan-11-ol, nitroalkanes, Nef reaction, natural products, nitroalkenes

Argemone mexicana L. (Papaveraceae), an erect prickly annual herb is a very common weed in agricultural and waste lands found throughout India. Isoquinoline alkaloids, flavonoids, phenolics, sugars, fatty acids, alcohols, tannins, resins, amino acids and mineral elements have been already isolated from this plant.[1–7] By chemical reinvestigation of the aerial parts of this species, a new monohydric alcohol has been recently isolated[8] and it has been characterized as the triacontan-11-ol (**9**). Now we wish to report here the first synthesis of this fatty alcohol, taking advantage of the well-known versatility of aliphatic nitro derivatives in the preparation of several natural products.[9–11]

As outlined in Scheme 1, the first step is represented by the preparation of the long-chain nitroalkane **3**. Thus, 1-nitroicosane (**3**) can be efficiently obtained from the commercial 1-bromoicosane (**1**), following the Kornblum procedure.[12] In fact, treatment of **1** with iodomethane in acetone converts **1** into the iodo derivative **2**, which without any purification, was reacted with silver nitrite, in anhydrous Et_2O, giving the nitroalkane **3** (75% overall yield from **1**) by substitution of iodine with the nitro group. The nitroalkane **3** was then coupled with decanal (**4**) by a nitroaldol (Henry) reaction, performed under basic conditions with a catalytic amount of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in THF,[13] allowing the formation of the long-chain β-nitro alcohol **5** as a diastereomeric mixture. The next step was the dehydration of **5** to **6**, and although several procedures are available for this transformation,[14] we found the Knochel and Seebach method,[15] the most effective for obtaining our nitroalkanol. Thus, the crude **5** was dissolved in anhydrous diethyl ether and dicyclohexylcarbodiimide (DCC)/CuCl (cat.) were added at room temperature and, after refluxing overnight, the dehydrated nitroalkene **6** was obtained as a diastereomeric mixture (78% yield from **3**, *E*/*Z* = 4:6). Reduction of **6**, with sodium borohydride in $CHCl_3$–*i*-PrOH,[16] furnished the nitroalkane **7** (66% yield). The Nef conversion of **7** to the ketone **8** has been tested by the main reported procedures,[17] but several of these produced very low yields, probably due to the high molecular weight of the nitroalkane, and the best result was obtained treating **7** with NaH under reflux (THF–hexane, 1:1), followed by acidification of the formed nitronate with 6 M H_2SO_4 at 0 °C, giving **8** in 42% yield.



Scheme 1

The last step is easily conduced by sodium borohydride reduction of the ketone **8**, at 30 °C for 30 minutes, and the target alcohol **9** was synthesized in 98% yield (16% overall yield from **1** and 21% overall yield from **3**). Physical properties of the synthetic sample agree well with those reported by the original authors.[8]

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In conclusion, we have described the first synthesis of the fatty alcohol **9** in good yield and using simple chemicals, moreover, our strategy clearly shows how the nitroalkanes are: (i) able to couple to other long-chain molecules (**3** with **4**), (ii) versatile molecules (conversion of the nitro moiety to the hydroxy group, **7** to **9**), and (iii) prone to give good yields, even with long-chain structures.

IR spectra were recorded with a Perkin-Elmer 1310 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz and 50 MHz, respectively, on a Varian Gemini 200 spectrometer. Chemical shifts were recorded relative to internal TMS. MS were determined with a non-polar capillary column, utilizing electron impact (EI) at 70 eV. Elemental analyses were performed using a C, H, N Analyzer Model 185 from Hewlett-Packard 5890 series. Flash chromatography was performed[18] on Merck SiO_2 gel (0.040–0.063 mm) with hexane–EtOAc as eluent.

1-Nitroicosane (3)

To a solution of 1-bromoicosane **1** (1.041 g, 2.88 mmol) in acetone (50 mL) at r.t. was added MeI (860 mg, 5.74 mmol). The mixture was stirred at 30 °C for 5 d and then the solvent was removed in vacuo. The residue was mixed with sat. aq $NaHSO_3$ solution (50 mL) and extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was dissolved in anhyd Et_2O (30 mL) and $AgNO_2$ (812 mg, 5.28 mmol) was added. After stirring at 30 °C for additional 5 d, the mixture was concentrated and the residue was subjected to flash column chromatography on silica gel (cyclohexane–EtOAc, 90:10) to give the pure nitroicosane **3** (0.707 g, 75%) as a white solid; mp 49–51 °C.

IR (Nujol): 1560 (s, NO_2) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 3 H, *J* = 6.6 Hz, CH_3), 1.15–1.45 (m, 34 H, H-3 to 19), 1.94–2.10 (m, 2 H, H-2), 4.39 (t, 2 H, *J* = 7.1 Hz, CH_2NO_2).

^{13}C NMR ($CDCl_3$): δ = 14.4, 22.9, 26.4, 27.6, 29.1, 29.5, 29.6, 29.7, 29.8, 29.9, 32.1, 76.0 (CH_2NO_2).

Anal. Calcd for $C_{20}H_{41}NO_2$: C, 73.34; H, 12.62; N, 4.28. Found: C, 73.61; H, 12.83; N, 4.05.

11-Nitrotriacont-10-ene (6)

A solution of 1-nitroicosane (**3**; 128 mg, 0.392 mmol), decyl aldehyde (**4**; 61 mg, 0.392 mmol) and DBU (24 mg, 0.157 mmol) in THF (10 mL) was kept at r.t. under magnetic stirring for 2 d. Most of the solvent was then removed under vacuum to give the crude nitroalkanol **5** as a white diastereomeric mixture. To a solution of the crude **5** in anhyd Et_2O (5 mL), were added CuCl (0.81 mg, 0.00817 mmol) and DCC (84 mg, 0.409 mmol). The mixture was magnetically stirred and refluxed overnight. The product formed was purified by flash column chromatography on neutral aluminum oxide (hexane) to give the nitroalkene **6** (142 mg, 78% from **3**) as a *E*/*Z* diastereomeric mixture (*E*/*Z* = 40:60).

IR (Nujol): 1650 (m, C=C), 1520 (s, NO_2) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ [diastereomeric mixture (*E*/*Z* = 40:60)] = 0.88 (t, 6 H, *J* = 6.4 Hz, CH_3 at H-1 and H-30), 0.98–2.00 (m, 46 H, H-2 to -8, H-14 to -29), 2.15–2.41 (m, 2 H, H-13), 2.46–2.63 (m, 2 H, H-9), 3.13–3.26 (m, 2 H, H-12), 5.67 (t, 0.6 H, *J* = 7.5 Hz, H-10 *Z*), 7.09 (t, 0.4 H, *J* = 8.1 Hz, H-10 *E*).

^{13}C NMR ($CDCl_3$): δ [diastereomeric mixture (*E*/*Z* = 40:60)] = 14.2, 17.3, 22.87, 22.90, 24.9, 25.6, 26.5, 27.1, 27.4, 28.1, 28.2, 28.5, 28.7, 28.9, 29.1, 29.4, 29.47, 29.55, 29.66, 29.69, 29.7, 29.9, 30.4, 32.07, 32.14, 32.9, 35.1, 43.7 (C-12 *E*), 56.0 (C-12 *Z*), 132.0 (C-10 *E*), 136.6 (C-10 *Z*), 151.5 (C-11 *E*), 152.1 (C-11 *Z*).

Anal. Calcd for $C_{30}H_{59}NO_2$: C, 77.36; H, 12.77; N, 3.01. Found: C, 77.59; H, 12.99; N, 2.87.

11-Nitrotriacontane (7)

To a magnetically stirred solution of nitroalkene **6** (115 mg, 0.247 mmol) in $CHCl_3$–*i*-PrOH (5 mL, 5:1), was added $NaBH_4$ (38 mg, 1 mmol). The mixture was stirred at 40 °C for 3 h, until all the starting material had disappeared. The excess of $NaBH_4$ was decomposed carefully with a few drops of 2 N HCl and the product was extracted with CH_2Cl_2 (3 × 15 mL). The combined Et_2O extracts were washed with brine, dried (Na_2SO_4) and the solution evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (hexane) to give pure **7** (76 mg, 66%) as a white solid; mp 28–30 °C.

IR (Nujol): 1550 (s, NO_2) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 6 H, *J* = 6.5 Hz, CH_3 at H-1 and 30), 1.00–1.42 (m, 50 H, H-2 to 9, H-13 to 29), 1.55–2.00 (m, 4 H, H-10, H-12), 4.40–4.52 (m, 1 H, $CHNO_2$).

^{13}C NMR ($CDCl_3$): δ = 14.3, 22.9, 26.0, 27.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 30.4, 32.0, 32.1, 34.1, 89.3 (C-11).

Anal. Calcd for $C_{30}H_{61}NO_2$: C, 77.02; H, 13.14; N, 2.99. Found: C, 76.79; H, 12.88; N, 3.22.

11-Oxytriacontane (8)

To a magnetically stirred solution of the nitroalkane **7** (36 mg, 0.078 mmol) in anhyd THF–hexane (3 mL, 1:1), was added NaH (6 mg, 0.24 mmol). The mixture was stirred at reflux for 1 h, cooled to r.t. and poured into a solution of 6 M H_2SO_4 (6 mL) kept at 0 °C under magnetic stirring. After 30 min, the mixture was extracted with Et_2O (3 × 5 mL), and the combined Et_2O extracts were dried and concentrated. The crude product mixture was purified by flash column chromatography on silica gel (hexane–EtOAc, 97:3) allowing the isolation of pure 11-oxytriacotane **8** (14.3 mg, 42%) as a white solid; mp 72–74 °C.

IR (Nujol): 1700 (s, C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 6 H, *J* = 6.6 Hz, CH_3 at H-1 and 30), 1.20–1.34 (m, 46 H, H-2 to 8, H-14 to 29), 1.52–1.62 (m, 4 H, H-9, H-13), 2.37 (t, 4 H, *J* = 7.4 Hz, H-10, H-12).

^{13}C NMR ($CDCl_3$): δ = 14.3, 22.9, 24.1, 29.4, 29.50, 29.53, 29.58, 29.6, 29.71, 29.79, 29.84, 29.88, 29.92, 32.11, 32.15, 43.0, 212.0 (C=O).

EI-MS: *m*/*z* = 436 (M^+, 4), 296 (99), 207 (36), 185 (27), 170 (100), 97 (25), 71 (38), 57 (52), 41 (35).

Anal. Calcd for $C_{30}H_{60}O$: C, 82.49; H, 13.85. Found: C, 82.87; H, 14.07.

11-Triacontanol (9)

To a solution of 11-oxytriacotane (**8**; 28 mg, 64 μmol) in EtOH (2 mL) at r.t. was added $NaBH_4$ (2.4 mg, 64 μmol). The mixture was stirred at 30 °C for 30 min, then 2 N HCl (2 mL) was added carefully and the mixture was left for 30 min under magnetic stirring. Finally the mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to give pure **9** (27.5 mg, 98%) as a white solid; mp 81–83 °C.

IR (Nujol): 3260 (m, OH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 6 H, *J* = 6.8 Hz, CH_3 at H-1 and H-30), 1.13–1.23 (m, 50 H, H-2 to 9, H-13 to 29), 1.36–1.48 (m, 4 H, H-10, H-12), 1.62–1.73 (m, 1 H, OH), 3.55–3.62 (m, 1 H, C*H*OH).

^{13}C NMR ($CDCl_3$): δ = 14.4, 22.9, 25.9, 27.11, 27.13, 29.57, 29.58, 29.60, 29.85, 29.87, 29.90, 29.91, 29.94, 30.38, 32.14, 32.16, 37.7, 43.7, 72.2 (C-11).

EI-MS: m/z = 420 (M^+ – 18, 3), 297 (28), 171 (33), 111 (44), 97 (100), 83 (76), 57 (64), 43 (45).

Anal. Calcd for $C_{30}H_{62}O$: C, 82.11; H, 14.24. Found: C, 82.40; H, 14.42.

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