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

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Received 31 May 2005

SYNTHESIS 2005, No. 17, pp 2835–2837

Abstract: The first synthesis of triacontan-11-ol, a new fatty alcohol isolated from Argemone mexicana, has been realized starting from the nitroaldehyde reaction of 1-nitrocicose with decanal. Dehydration of the obtained nitroalkene gives a long-chain nitroalkene which is then reduced to the corresponding nitroalkane. Nef dehydration 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 monohydrate alcohol has been recently isolated8 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-nitrocicose (3) can be efficiently obtained from the commercial 1-bromocisose (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 Et2O, 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 nitroaldehyde (Henry) reaction, performed under basic conditions with a catalytic amount of 1,8-diazo-bicyclo[5.4.0]undec-7-ene (DBU) in THF,13 allowing the formation of the long-chain β-nitro aldehyde 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 Knoechel and Seebach method,15 the most effective for obtaining our nitroalkanol. Thus, the crude 5 was dissolved in anhydrous diethyl ether and dicyclohexylcarbodiimide (DCC) with catalyst was 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 CHCl3–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 H2SO4 at 0 °C, giving 8 in 42% yield.

Scheme 1

The last step is easily conducted 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
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.

11-Nitrotripentadecane (7)
To a magnetically stirred solution of nitroalkene 6 (115 mg, 0.247 mmol) in CHCl3-i-PrOH (5 mL, 5:1), was added NaBH4 (38 mg, 1 mmol). The mixture was stirred at 40 °C for 3 h, until all the starting material had disappeared. The excess of NaBH4 was decomposed carefully with a few drops of 2 NHCl and the product was extracted with CH2Cl2 (3 × 15 mL). The combined Et2O extracts were washed with brine, dried (Na2SO4) 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.

11-Nitrotriacontane (7)
To a magnetically stirred solution of nitroalkene 6 (115 mg, 0.247 mmol) in CHCl3-i-PrOH (5 mL, 5:1), was added NaBH4 (38 mg, 1 mmol). The mixture was stirred at 40 °C for 3 h, until all the starting material had disappeared. The excess of NaBH4 was decomposed carefully with a few drops of 2 NHCl and the product was extracted with CH2Cl2 (3 × 15 mL). The combined Et2O extracts were washed with brine, dried (Na2SO4) 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.

11-Oxytriacontane (8)
To a magnetically stirred solution of the nitroalkene 5 (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 H2SO4 (6 mL) kept at 0 °C under magnetic stirring. After 30 min, the mixture was extracted with Et2O (3 × 5 mL), and the combined Et2O extracts were dried and concentrated. The crude product mixture was purified by flash column chromatography on silica gel (hexane–Et2OAc, 97:3) allowing the isolation of pure 11-oxytriacontane 8 (14.3 mg, 42%) as a white solid; mp 72–74 °C.

11-Triacontanol (9)
To a solution of 11-oxytriacontane 8 (28 mg, 64 µmol) in EtOH (2 mL) at r.t. was added NaBH4 (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 CH2Cl2 (3 × 5 mL) and the combined extracts were dried (Na2SO4) and concentrated to give pure 9 (27.5 mg, 98%) as white solid; mp 81–83 °C.

Synthesis 2005, No. 17, 2835–2837 © Thieme Stuttgart · New York

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


Acknowledgment

Financial support from University of Camerino and MIUR (National Project ‘Sintesi e Reattività-Attività di Sistemi Insaturi Funzionalizzati’) is gratefully acknowledged.

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