Tetrahedron Letters, Vol. 34, No. 38, pp. 6107-6108, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Short Synthesis of 15-Pentadecanolide

Stephan Stanchev*[a], Branimir Milenkov[a] and Manfred Hesse[b]

[a] Institute of Organic Chemistry, Bulgarian Academy of Sciences, BG-1113 Sofia, Bulgaria

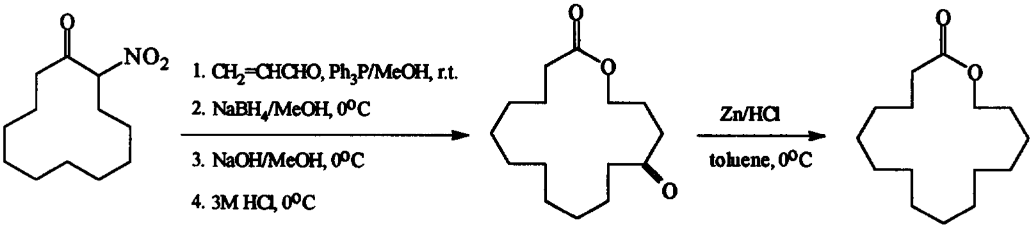
[b] Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Abstract: 15-Pentadecanolide was synthesised by a five step, two pot reaction sequence, starting from 2-nitrocyclododecanone in a 60% overall yield.

Since the first discovery of 15-pentadecanolide (**3**)[1] in the vegetable musk oils of Angelica roots (*Archangelica officinalis* Hoffm.) and ambrette seeds (*Abelmoschus moschatus* Moench) by *Kerschbaum*[2] a large number of syntheses has been published[3-5]. 15-Pentadecanolide has a musk-like odour and is an important ingredient of several perfumes[4].

In the course of our investigations in the field of macrolide syntheses by ring enlargement reactions[6], we have already synthesised compound **3**, using ring enlargement by fragmentation[5] of [1-3'-hydroxypropyl)-2-oxo-cyclododecyl]methyltrimethylammonium-iodide which was prepared from 1-(3'-hydroxypropyl)-2-oxocyclo-dodecane-1-carbonitrile. In this communication we report a new short and efficient synthesis of 15-pentadecanolide.

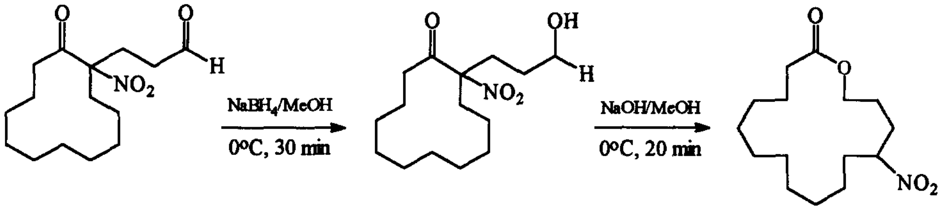
Scheme 1



1 **2** **3**

Starting from 2-nitrocyclododecanone[7] (**1**), the 12-oxo-15-pentadecanolide (**2**) was synthesised by a four step, one pot reaction sequence in 72% yield (scheme 1). The *Michael* addition of **1** to acrylaldehyde was catalysed by triphenylphosphine and was complete within 30 min in MeOH. The available data about the rates of reaction of $NaBH_4$ with cyclic[8a] and aliphatic ketones[8b] and aldehydes[8c] encouraged us to use this reagent for the selective reduction of the *Michael* adduct 3-(1-nitro-2-oxocyclododecyl)propanal (**4**). Thus, the latter was selectively reduced with 0.5 equivalents of $NaBH_4$, which was added in small portions[9] at 0°C within 30 min and yielded 2-nitro-2-(3'-hydroxypropyl)cyclododecane-1-on (**5**) together with small amounts (*ca.* 3%) of the ring enlargement product 12-nitro-15-pentadecanolide (**6**) (scheme 2). This reaction mixture was treated with one equivalent of 1M methanolic soln. of NaOH at 0°C for 20 min to produce the nitrolactone **6** (as nitronate salt). To accomplish the *Nef* reaction[10] ten fold excess of 3M aq. HCl soln. was added and after 10 min stirring at 0°C the 12-oxo-15-pentadecanolide (**2**) was formed. Using modified *Clemmensen* reduction[11] (Zn in toluene, saturated at 0°C with HCl-gas) of the 12-keto group in **2** we obtained 15-pentadecanolide (**3**) (colourless crystals; m.p.: 33-34°C[12]) in 84% yield (scheme 1). Thus we have synthesised this macrolide in 60% overall yield, starting from 2-nitrocyclododecanone (**1**).

Scheme 2



4 **5** **6**

The present synthesis of 15-pentadecanolide (**3**) by ring enlargement reaction is very simple and it is easy to scale up to 1 mole quantities with the same yield and purity.

References and Notes:

1. Exaltolide® is a registered trademark of *Firmenich* S.A., Geneve, Switzerland for 15-pentadecanolide.
2. Kerschbaum, M. *Ber. Dtsch. Chem. Ges.* **1927**, *60B*, 902-909.
3. For a recent synthesis of 15-pentadecanolide see: (a) Kaino, M.; Naruse, Y.; Ishihara, I.; Yamamoto, H. *J. Org. Chem.* **1990**, *55*, 5814-5815; (b) Matsuyama, H.; Nakamura, T.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 5218-5223; (c) Torra, N.; Urri, F.; Vilarrasa, J. *Tetrahedron* **1989**, *45*, 863-868; (d) Bestmann, H. J.; Schobert, R. *Synthesis* **1989**, 419-423; (e) Suginome, H.; Yamada, S. *Chem. Lett.* **1988**, 245-248; (f) Cossy, J.; Pete, J.-P. *Bull. Soc. Chim. Fr.* **1988**, 989-994 and references cited therein about earlier synthesis of 15-pentadecanolide.
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9. When $NaBH_4$ was added at once reduction of the both carbonyl groups occurred.
10. The acidification of the nitronate salt is the key step of the conversion of the nitro to carbonyl compounds. For a detailed discussion concerning the mechanism of the *Nef* reaction see: Pinnick, H. W. *Organic Reactions* **1990**, *38*, 655-792.
11. Zaharkin, L. I.; Pryanishnikov, A. P. *J. Org. Chem. USSR, Engl. Trans.* **1987**, *23*, 262-263.
12. Satisfactory analytical and spectral results were obtained for all compounds, described in this paper. The spectral data of the synthetic 15-pentadecanolide (**3**) were identical with those obtained from 15-pentadecanolide purchased by *Sigma*.

(Received in UK 28 May 1993; accepted 23 July 1993)