Monatshefte für Chemie 126, 565–568 (1995)

Monatshefte für Chemie
Chemical Monthly
© Springer-Verlag 1995
Printed in Austria

An Efficient Synthesis of the Plant Growth Hormone 1-Triacontanol

N. H. Tran-Thi and **H. Falk***

Institut für Chemie, Johannes Kepler Universität Linz, A-4040 Linz, Austria

Summary. A high yield synthesis of 1-triacontanol was based on the cheap and easily available starting materials 1-octadecanol and 1,12-dodecanediol. The first one was converted to octadecanal using a phase transfer system, whereas the second one after phase transfer bromination and reaction with triphenylphosphine provided 1-hydroxy-12-triphenylphosphonium bromide. *Wittig* reaction of these two synthons and subsequent hydrogenation furnished the desired product.

Keywords. 1-Triacontanol: *Wittig* reaction; Phase transfer reaction; Plant growth hormone.

Eine effiziente Synthese des Pflanzenwachstumshormons 1-Triacontanol

Zusammenfassung. Eine Synthese von 1-Triacontanol, basierend auf den einfach zugänglichen Edukten 1-Oktadecanol und 1,12-Dodecandiol, die gute Ausbeuten ergibt, wird beschrieben. Ersteres Edukt wurde mit Hilfe eines Phasentransfersystems zu Oktadecanal umgesetzt. Letzteres gab nach Phasentransfer-Bromierung und Umsatz mit Triphenylphosphin 1-Hydroxy-12-triphenylphosphoniumbromid. *Wittig*-Reaktion dieser beiden Synthone und anschließende Hydrierung lieferte das erwünschte Produkt.

Introduction

1-Triacontanol, which is a natural product contained in alfalfa (*Medicago sativa L.*), has been shown to be a plant growth hormone [1]. It increases the yields of tomatoes, cucumber, lettuce, and several other crop species including rice and corn. In addition to the classical syntheses [2–7] this effect has been prompting the development of new synthetic routes to 1-triacontanol [8–13]. Most of these methods have in common the reduction of triacontanoic acid or its ester as a last step [2–8, 13]. Others involve enamine intermediates [9], oleic acid derivatization [10], alkylations of tosyl-methyl-isocyanides [11], and coupling of a *Grignard* reagent and ω-bromo-tetrahydropyranyl ethers [12]. Nevertheless, there is still a demand to develop syntheses which are efficient, convenient and use easily available starting materials.

Results and Discussion

From the many combinations of two fragments to construct the C_{30}-skeleton and functionality of 1-triacontanol possible, the $C_{18} + C_{12}$ path was chosen. To achieve such a combination one synthon had to be monofunctional, whereas the other one

had to be difunctional. Moreover, one functionality of the latter fragment had to be as close as possible to the hydroxyl group. With respect to availability, monofunctional derivatives with eighteen carbon atoms may be easily obtained from stearic acid, or even better stearyl alcohol, whereas difunctional derivatives are rare in this series. However, the necessary difunctional derivatives are obtainable in quantity in the C_{12} series. For the key step, which involved the joining of the two fragments, the *Wittig* reaction proved to be the most appealing one. Thus, a carbonyl group was chosen for the monofunctional system and ω-bromododecanol had to serve as the difunctional synthon. According to the retrosynthetic scheme

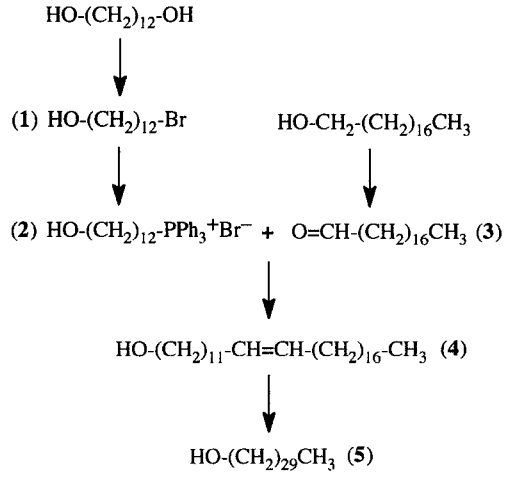
$$CH_3(CH_2)_{18}CH_2OH \Rightarrow CH_3(CH_2)_{16}CHO + Br^-Ph_3P^+CH_2(CH_2)_{10}CH_2OH$$

the latter had to be transformed into the *Wittig* reagent.

The first educt for the coupling reaction, 12-hydroxydodecyltriphenylphosphonium bromide (**2**), was easily prepared by first monobrominating 1,12-dodecandiol with 48% aqueous hydrobromic acid in the presence of the phase transfer catalyst Aliquat-336. This starting material was easily available in quantity and at a reasonable price. 12-Bromododecan-1-ol (**1**) was thus obtained in 75% yield. Secondly, the mixture of **1** with triphenylphosphine was reacted to provide the phosphonium salt **2** in 76% yield. To obtain the second educt, octadecanal (**3**), a phase transfer dichromate oxidation, previously developed to synthesize hexadecanal [14], was applied to stearyl alcohol. This starting material is known as a low price bulk chemical. The yield was as high as 85%.

To join the two synthons, the phosphonium salt **2** and the aldehyde **3** were subjected to a *Wittig* reaction. The best results were obtained using $LiN(SiMe_3)_2$ as the base [15]; however, other bases like *n*-butyl-lithium could also be used. Applying this procedure, (*Z*)-12-triaconten-1-ol (**4**) was obtained in 55% yield. The (*Z*) configuration at the double bond of **4** was assigned from the ^1H NMR coupling constant. Hydrogenation of **4** at room temperature and atmospheric pressure with 10% Pd/C as the catalyst provided the desired product, 1-triacontanol (**5**), in nearly quantitative yield.

Thus, a high overall yield few step synthesis of triacontanol (**5**) from cheap and easily available starting materials was developed.



Scheme 1

Experimental

Melting points were measured on a Kofler hot stage microscope (Reichert, Vienna). ^1H and ^{13}C NMR spectra were recorded by means of a Bruker AC-200 (200 MHz) spectrometer. IR spectra were obtained on a Biorad-FT-IR-45 instrument. The mass spectrum was recorded on a Hewlett Packard 5989A MS instrument.

12-Bromododecan-1-ol (**1**; $C_{12}H_{25}OBr$)

To the stirred solution of 1.01 g 1,12-dodecandiol (5.0 mmol) and Aliquat 336 (2 mol% of the diol) in 15 ml benzene at 60 °C, 1.8 ml of HBr (48% aq., 15 mmol) were added dropwise. Then 15 ml of benzene were added. The mixture was stirred at this temperature for 30 min, and then additional 4 h at 90 °C. During the reaction, water was removed by azeotropic distillation. The reaction mixture was cooled to 0°C and the unreacted diol, which precipitated, was removed by filtration. The filtrate was washed with $NaHCO_3$ (10%), saturated NaCl solution and then dried with Na_2SO_4 and evaporated. Crystallization from hexane afforded 1.0 g of **1** (75%), m.p.: 28–29 °C, 28–29 °C [12]. IR (KBr): 3325, 1056, 1253, 722 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 1.28 (broad s, 16 H, $(CH_2)_8$), 1.52 (m, 2H, CH_2CH_2OH), 1.85 (m, 2H, CH_2–CH_2–Br), 3.4 (t, $J = 7$ Hz, 2H, CH_2–Br), 3.63 (t, $J = 7$ Hz, 2H, CH_2–OH) ppm.

12-Hydroxydodecyltriphenylphosphonium bromide (**2**; $C_{30}H_{40}OBrP$)

1.32 g **1** (5 mmol), 1.31 g triphenylphosphine (5 mmol), and 10 ml ethanol were heated under reflux for 48 hours. The mixture was cooled and evaporated to give an oil, which was extracted with three 10 ml portions of boiling ether. The residue was crystallized from ethyl acetate to yield 2.0 g of **2** (76%); m.p.: 98–100 °C. IR (KBr): 3274 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 1.15 (broad m, 14 H, $(CH_2)_7$), 1.55 (broad m, 6H, $(CH_2)_3$), 3.55 (broad t-like, 4H, CH_2–OH + CH_2–P^+Ph_3), 7.7 (m, 15 H, P^+Ph_3) ppm.

1-Octadecanal (**3**; $C_{18}H_{36}O$)

2.7 g 1-Octadecanol (10.0 mmol) and 0.33 g tetrabutylammonium bisulfate (1.0 mmol) were dissolved in 25 ml dichloromethane. Then 0.98 g sodium dichromate (3.3 mmol) in 25 ml of a 10 *M* sulfuric acid solution was added in one portion to the stirred alcoholic solution. After stirring for another 2 min, the two layers were separated and the aqueous layer was extracted with two 20 ml portions of dichloromethane. The combined organic layers were washed with $NaHCO_3$ (5%), water, and then dried with Na_2SO_4 and evaporated. Column chromatography on silica gel using a mixture of petrol ether/ethyl acetate = 7/3 as the eluent gave 2.27 g of pure **3** (85%); m.p.: 54 –55 °C, 55 °C [17]. IR (KBr): 1712, 2746 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 0.87 (t, $J = 6$ Hz, 3H, CH_3), 1.25 (broad s, 28H, $(CH_2)_{14}$), 1.62 (m, 2H, CH_2–CH_2–CHO), 2.42 (dt, $J_1 = 2$ Hz, $J_2 = 7$ Hz, 2H, CH_2–CHO), 9.76 (t, $J = 2$ Hz, 1H, CHO) ppm.

(Z)-12-Triaconten-1-ol (**4**; $C_{30}H_{60}O$)

To a suspension of 0.527 g **2** (1.0 mmol) in 2 ml tetrahydrofuran, 2.2 ml of a 1 *M* $LiN(SiMe_3)_2$ solution in tetrahydrofuran (2.2 equiv.) were added dropwise under nitrogen at room temperature. The organge-red ylide solution was allowed to stir for another 30 min. Then 0.268 g **3** (1.0 mmol) dissolved in 1 ml dry tetrahydrofuran was slowly added. The red color of the ylide gradually disappeared. The mixture was stirred for 1 h and 30 min. Then 1 ml water was added. After stirring for further 30 min, the organic layer was extracted with 100 ml ether. Column chromatography of the crude product on silica gel using a mixture of benzene/ethyl acetate = 10/1 as the eluent gave **4** (55%), m.p.: 56–58 °C. IR (KBr): 3368(OH), 1066(C–OH), 1645(C=C), 965(HC=CH), 723(CH_2) cm^{-1}; ^1H NMR ($CDCl_3$, δ,

200 MHz): 0.87 (t, $J = 6$ Hz, 3H, CH_3), 1.25 (broad s, 46H, $(CH_2)_{23}$), 1.56 (m, 2H, CH_2CH_2OH), 2.0 (m, 4H, CH_2–CH=), 3.63 (t, $J = 7$ Hz, 2H, CH_2–OH), 5.34 (t, $J = 5$ Hz, 2H, HC=CH) ppm.

1-Triacontanol (**5**; $C_{30}H_{62}O$)

A solution of 0.218 g of **4** (0.5 mmol) and 10% Pd/C (25 mg) in ethyl acetate (15 ml) was hydrogenated at room temperature and atmospheric pressure for 8 hours. The catalyst was filtered off and washed with 20 ml benzene. The combined organic solutions were evaporated. Upon crystallization from hexane the crude 1-triacontanol furnished 0.197 g of the pure product **5** (90%); m.p.: 86–87 °C, 87–88 °C [9]. IR (KBr): 3330(OH), 1064(C–OH), 720(CH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 0.87 (t, $J = 6$ Hz, 3H, CH_3), 1.25 (broad s, 54H, $(CH_2)_{27}$), 1.56 (m, 2H, CH_2CH_2OH), 3.64 (t, $J = 7$ Hz, 2H, CH_2OH) ppm; MS (70 eV, 200°C): *m/e* (%) = 438 (0.1, M^+), 420 (2, M^+-18), 392 (0.2), 349 (0.5), 293 (0.8), 195 (2), 167 (3), 153 (6), 97 (67), 83 (71), 69 (63), 57 (100), 43 (94).

Acknowledgment

A stipendium of the *Österreichischer Akademischer Austauschdienst* to *N.H.T.T.* is gratefully acknowledged.

References

[1] Ries S. K., Wert V., Sweely C. C., Leavitt R. A. (1977) Science **195**: 1339; Laughlin R. G., Munyon R. L., Ries S. K., Wert V. F. (1983) Science **219**: 1219
[2] Bleyberg W., Ulrich H. (1931) Chem. Ber. **64B**: 2504
[3] Robinson G. M. (1934) J. Chem. Soc. **1934**: 1543
[4] Jones R. G. (1947) J. Am. Chem. Soc. **69**: 2350
[5] Oura H., Hase H., Honda K., Fukai S. (1956) J. Pharm. Soc. Japan **76**: 1433
[6] Anes D. E., Bowman R. E., Mason R. G. (1950) J. Chem. Soc. **1950**: 174
[7] Watanabe A. (1961) Bull. Chem. Soc. Japan **34**: 398
[8] Maruyama K., Terada K., Yamamoto Y. (1980) J. Org. Chem. **45**: 737
[9] Rama Rao A. V., Deshmukh M. N., Kamalam M. (1981) Tetrahedron **37**: 227
[10] Villemin D. (1983) Tetrahedron Lett. **24**: 2855
[11] Rama Rao A. V., Yadav J. S., Annapurna G. S. (1983) Synthetic Communications **13**: 331
[12] Kulkarni S. M., Mamdapur V. R., Chadha M. S. (1983) Ind. J. Chem. **22B**: 683
[13] Rao B. V. S. K., Subbarao R. (1992) Oppi Briefs **24**: 67
[14] Pletcher D, Tait S. J. D. (1979) J. Chem. Soc., Perkin Trans. II, **1979**: 788
[15] Maryanoff B. E., Reitz A. B., Duhl-Emswiler B. A. (1985) J. Am. Chem. Soc. **107**: 217
[16] Logemann E., Schill G. (1978) Chem. Ber. **111**: 2615
[17] Handbook of Chemistry and Physics, 70th ed

Received November 8, 1994. Accepted November 9, 1994