Rapid Communication

CSIRO PUBLISHING

Aust. J. Chem. **2007**, *60*, 848–849

www.publish.csiro.au/journals/ajc

Use of the Anti-Oxidant Butylated Hydroxytoluene in situ for the Synthesis of Readily Oxidized Compounds: Application to the Synthesis of the Moth Pheromone (*Z*,*Z*,*Z*)-3,6,9-Nonadecatriene

Noel W. Davies,[A] *Graham Meredith,*[B] *Peter P. Molesworth,*[B] *and Jason A. Smith*[B,C]

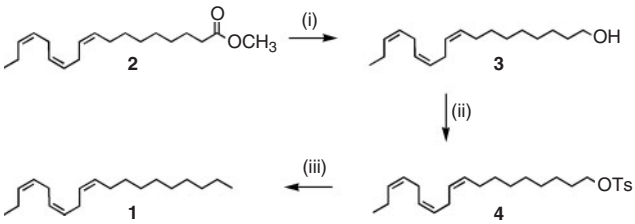
[A]Central Science Laboratory, Private Bag 74, University of Tasmania, Hobart TAS 7001, Australia.
[B]School of Chemistry, Private Bag 75, University of Tasmania, Hobart TAS 7001, Australia.
[C]Corresponding author. Email: jason.smith@utas.edu.au

The triene (*Z*,*Z*,*Z*)-3,6,9-nonadecatriene was synthesized in three steps from methyl linolenate. The key to the synthesis was the use of the anti-oxidant butylated hydroxytoluene in situ to provide protection of the unstable triene from autoxidation during reaction workup. This simple modification resulted in an increase in the yield from 20 to 85% over three steps.

Manuscript received: 27 June 2007.
Final version: 15 August 2007.

The C19 triene (*Z*,*Z*,*Z*)-3,6,9-nonadecatriene **1** has been identified as a pheromone for the autumn gum moth *Mnesampela privata*, which is a threat to blue gum plantations.[1] To collect moths to study their migration pattern, baiting traps with a suitable attractant, such as the appropriate chemical sex attractant, have proved to be a valuable tool.[1] They have also been used to control moth populations by disruption of the mating cycle.[2] However, the high cost of synthesis and low yield of triene **1** obtained in the most recent synthesis,[1] 18%, make large-scale trapping expensive and impractical.[3] The cost of using pure linolenic acid could be alleviated by using less expensive ~70% methyl linolenate obtained from the transesterification of linseed oil. The problem with the latter is that it is contaminated by the diene methyl linoleate, which may interfere with the pheromone response of the triene. To overcome these problems, we set about investigating the use of an organocuprate that has been reported previously, but for the synthesis of pheromone cocktails[3] from mixtures of linolenic, linoleic, and other long-chain fatty esters. To test if the method was suitable when using a pure or enriched triene, we started with a sample of 95% pure methyl linolenate (as determined by gas chromatography/mass spectrometry (GC/MS) analysis), which was obtained by the transesterification of linseed oil and then purified by a previously reported method,[4] before using the more expensive ≥99% pure material.

The synthetic plan was then to take the 95% enriched linolenic ester **2**, which was reduced with lithium aluminium hydride to give the alcohol **3** and which was then transformed to the tosylate **4** (Scheme 1). The final step involved the displacement of the tosylate with dimethyl cuprate,[5] which gave the C19 triene. However, whereas each step occurred cleanly to give the desired compound, the overall yield was low, ~10–20%, and the purity of the triene had decreased significantly to ~80% by GC/MS analysis. This was disappointing as there was no improvement of the overall yield compared with the method of Steinbauer.[1]



Scheme 1. (i) $LiAlH_4$, THF, 0°C to room temp.; (ii) *p*-toluenesulfonyl chloride, pyridine, CH_2Cl_2, 0°C; (iii) $(CH_3)_2CuLi$, THF, 0°C.

It was obvious that the low yield and subsequent decrease of the triene to diene ratio was due to autoxidation of the compounds by adventitious oxygen. As the samples were stored refrigerated under an atmosphere of nitrogen, it was assumed that the decomposition was occurring during reaction workup and purification as silica chromatography was required to remove polar decomposition products. The use of anti-oxidants, such as butylated hydroxytoluene (BHT) or 2,6-di-*t*-butyl-4-methylphenol, to inhibit autoxidation of readily oxidized compounds, such as methyl linolenate, is well established[6] but its use in situ during a reaction has been typically associated with inhibiting polymerization of alkenes under thermal conditions such as in the Diels–Alder reaction.[7] We hypothesized that, provided the anti-oxidant is not consumed or transformed under the reaction conditions employed in a synthesis, it could be added to the methyl linolenate and carried through the synthesis, providing the required protection from undesired autoxidation. Owing to the synthetic sequence employed for the transformation of methyl linolenate, the anti-oxidant BHT was chosen as it would be regenerated on workup after reaction with lithium aluminium hydride and would not affect the tosylation or cuprate reactions.

10.1071/CH07223 0004-9425/07/110848

Therefore, the modified synthesis started with a small amount (1%) of BHT (2,6-di-*t*-butyl-4-hydroxytoluene) added to the 95% methyl linolenate, which was then subjected to the reaction sequence discussed above. Reaction of the ester with lithium aluminium hydride gave the alcohol, still containing the BHT, in ~80% while tosylation proceed similarly. As predicted, the removal of BHT before reaction was not required and therefore simplified the method while maintaining the required protective properties. The final cuprate step also proceeded in the presence of BHT to yield the desired triene in quantitative yield without need for chromatography at any step. This was surprising as the tosylate was contaminated by traces of tosyl chloride, yet no traces of it or any by-products were observed on workup. The addition of BHT increased the product yield significantly from 10–20 to 65% over the three steps while maintaining the purity of the triene at ~95% (GC). This was a pleasing result and now meant that beginning with the more expensive starting material would not result in unnecessary loss due to decomposition during workup. As such, the reaction of the ≥99% methyl linolenate[8] containing 1% of BHT gave 0.947 g of the triene **1** with no detectable C19 contaminants in 85% overall yield for the three steps.

In conclusion, not only have we developed a reliable and efficient synthesis of these unstable long-chain unsaturated hydrocarbons, but we have also shown that anti-oxidants can be used in situ to provide unstable compounds protection from autoxidation during workup.

Experimental

General Experimental

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Varian Mercury 2000 spectrometer. Spectra were run in $CDCl_3$ unless otherwise stated. Chemical shifts are measured in ppm and referenced internally to residual $CHCl_3$.

Linolenyl Alcohol *3*

A solution of the ≥99% methyl ester **2** (2.50 g, 8.56 mmol) containing 1% BHT in anhydrous THF (60 mL) was added dropwise to a suspension of lithium aluminium hydride (430 mg, 11.3 mmol) in anhydrous THF (30 mL) at −5°C under a nitrogen atmosphere. After addition was complete, the mixture was stirred at room temperature before two further portions of lithium aluminium hydride (425 mg, 11.2 mmol; and 435 mg, 11.5 mmol) were added after 2 h and 4 h. After 6 h, the reaction was quenched by the addition of methanol and the lithium salts were dissolved by the addition of saturated $KHSO_4$ (100 mL) before extraction with diethyl ether (3 × 80 mL). The combined organic extracts were washed with brine, then dried with sodium sulfate, filtered, and the solvent removed under reduced pressure yielding the alcohol **3** (2.171 g, 96%) as a pale oil. δ_H 5.38 (6H, m), 3.64 (2H, t, *J* 6.9), 2.80 (4H, m), 2.08 (4H, m), 1.25–1.60 (12H, m), 0.97 (3H, t, *J* 7.5). δ_C 132.2, 130.6, 128.5, 127.9, 127.3, 125.8, 63.3, 33.0, 30.5, 29.9, 29.7, 29.6, 29.5, 27.5, 25.9, 25.8, 25.7, 14.5.

Linolenyl Tosylate *4*

p-Toluenesulfonyl chloride (2.04 g, 10.7 mmol) was added to a solution of the alcohol **2** (2.171 g, 8.21 mmol), and pyridine (1.00 mL) in anhydrous dichloromethane (3 mL) under an atmosphere of nitrogen with protection from light, and the reaction mixture stirred at ambient temperature for 24 h. The reaction mixture was diluted with dichloromethane (50 mL) and quenched with 2 M HCl (30 mL). The organic phase was separated, washed with 2 M Na_2CO_3 (30 mL), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield the tosylate **4** (3.43 g, 95%) as a pale yellow oil. δ_H 7.79 (2H, d, *J* 8.7), 7.34 (2H, d, *J* 8.7), 5.35 (6H, m), 4.01 (2H, t, *J* 6.6), 2.80 (4H, m), 2.45 (3H, s), 2.05 (4H, m), 1.83 (2H, m), 1.25 (10H, m), 0.97 (3H, t, *J* 7.5). δ_C 132.2, 130.5, 130.0, 128.5, 128.4, 128.2, 128.1, 127.9, 127.32, 127.29, 70.9, 30.5, 29.8, 29.5, 29.3, 29.1, 29.0, 27.4, 25.8, 25.7, 25.5, 21.8, 14.5.

(*Z,Z,Z*)-3,6,9-Nonadecatriene *1*

Me_2CuLi (12.7 mmol) was prepared in situ by dropwise addition of methyllithium (18.2 mL, 1.4 M in diethyl ether) to a stirred solution of cuprous iodide (2.41 g, 12.7 mmol) in ether (55 mL) at 0°C under an atmosphere of nitrogen, yielding a clear near-colourless solution that was stirred for 30 min. A solution of the tosylate **4** containing BHT (1.60 g, 3.84 mmol in ether, 77 mL) was added dropwise to the cuprate and the resultant solution stirred for 3.5 h. The yellow solution was quenched with saturated ammonium chloride and the product extracted with ether (3 × 80 mL). The combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure, yielding the desired product **1** as a pale oil (0.947 g) in 94% yield. The product still contained ~1% BHT by NMR spectroscopy. δ_H 5.38 (6H, m), 2.80 (4H, m), 2.15 (4H, m), 1.27 (14H, m), 0.98 (3H, t, *J* 7.5), 0.88 (3H, m). δ_C 132.2, 130.7, 128.5, 128.4, 127.8, 127.3, 32.1, 30.5, 29.8, 29.8, 29.5, 27.4, 25.8, 25.7, 22.9, 21.4, 20.7, 14.5, 14.3.

Acknowledgements

P. P. M. is thankful to the University of Tasmania and the Thomas Crawford Foundation for a postgraduate scholarship.

References

[1] M. J. Steinbauer, F. Östrand, T. E. Bellas, A. Nilsson, F. Andersson, E. Hedenström, M. J. Lacey, F. P. Schiestl, *Chemoecology* **2004**, *14*, 217. doi:10.1007/S00049-004-0281-5

[2] R. T. Carde, A. K. Minks, *Annu. Rev. Entomol.* **1995**, *40*, 559. doi:10.1146/ANNUREV.EN.40.010195.003015

[3] (a) H. Yu, H. K. Mangold, *Chem. Ind.* **1988**, 787.
(b) H. Yu, H. Becker, H. K. Mangold, *Chem. Ind.* **1989**, 836.

[4] J. D. Nadenicek, O. S. Privett, *Chem. Phys. Lipids* **1968**, *2*, 409. doi:10.1016/0009-3084(68)90014-5

[5] (a) C. R. Johnson, G. A. Dutra, *J. Am. Chem. Soc.* **1973**, *95*, 777.
(b) W. Huang, S. P. Pulaski, J. Meinwald, *J. Org. Chem.* **1983**, *48*, 2270. doi:10.1021/JO00161A025

[6] K. E. Peers, D. T. Coxon, H. W. S. Chan, *J. Sci. Food Agric.* **1984**, *35*, 813. doi:10.1002/JSFA.2740350720

[7] (a) L. Evanno, A. Deville, L. Dubost, A. Chiaroni, B. Bodo, B. Nay, *Tetrahedron Lett.* **2007**, *48*, 2893. doi:10.1016/J.TETLET.2007.02.089
(b) E. L. Pearson, L. C. H. Kwan, C. I. Turner, G. A. Jones, A. C. Willis, M. N. Paddon-Row, M. S. Sherburn, *J. Org. Chem.* **2006**, *71*, 6099. doi:10.1021/JO0607818

[8] At the time of the present study, ≥99% methyl linolenate from Sigma-Aldrich Australia was A$151 per gram.