111. (*Z*)-5-Tetradecen-14-olide, a New Macrocyclic Lactone, and Two Unsaturated Straight Chain Acetates from Ambrette Seed Absolute

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Summary

(*Z*)-5-Tetradecen-14-olide (**1**), (*Z*)-5-dodecenyl acetate (**2**), and (*Z*)-5-tetradecenyl acetate (**3**) have been isolated from the absolute oil of *Hibiscus abelmoschus* L. The lactone **1** is a new macrocyclic musk compound, and the occurrence of the two acetates **2** and **3** in a plant is reported for the first time. Syntheses of the three compounds are described.

The essential oil obtained by steam distillation of the seeds of *Hibiscus abelmoschus* L., the so called ambrette seed oil[1]), is a very expensive raw material which finds application both in perfumes of the more sophisticated type and in flavours [1]. It is highly appreciated for the 'exalting' effect which it lends to perfumes, and for its rich floral-musky fragrance.

Nearly fifty years ago, *Kerschbaum* [2] isolated ambrettolide (**4**) ((*Z*)-7-hexadecen-16-olide) from ambrette seed oil, and showed it to be responsible for the typical musky note. It was the first known lactone with more than seven ring-members. While its olfactive properties stimulated synthetic work in this field (today a few macrocyclic lactones like ambrettolide, dihydroambrettolide, cyclopentadecan-15-olide *etc.* are industrially produced perfumery chemicals), systematic analytical work dealing with ambrette seed oil is scarce. Thus, ambrettolide (**4**) remained the only macrocycle so far isolated from this source.

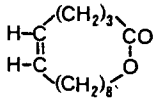
The present paper describes the isolation[2]), identification, and synthesis of a new macrocyclic lactone (*Z*)-5-tetradecen-14-olide (**1**), and of two unsaturated straight chain acetates, (*Z*)-5-dodecenyl acetate (**2**) and (*Z*)-5-tetradecenyl acetate (**3**).

The lactone **1** – we estimate its concentration in ambrette seed absolute to be *ca.* 0.5% – displays a powerful, floral-musky note, similar to the odour of ambrettolide (**4**), but somewhat stronger and much less tenacious. The structurally related[3]) acetates **2** and **3** (0.01 and 0.4%, respectively) exhibit a similar odour to their saturated

[1]) The present work was carried out with commercial ambrette seed absolute which is produced from the essential oil by neutralization and subsequent elimination of the fatty acids [1].

[2]) For details, see experimental part.

[3]) Note that the configuration and the position of the double bond, as well as the length of the carbon chain are identical for compounds **1** and **3**. This probably indicates a close biogenetic relationship between the macrocyclic lactones and the open chain esters.



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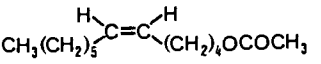

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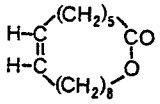

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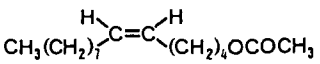
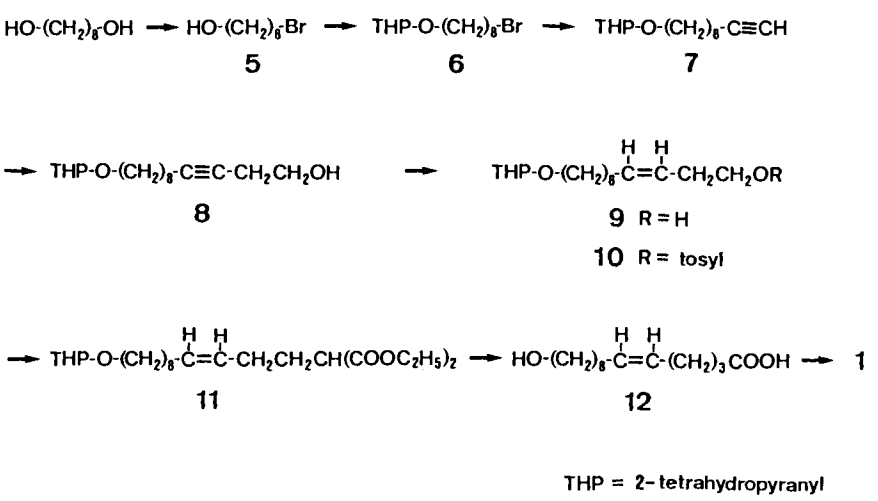


3

analogues (although somewhat stronger) and are thus less interesting for perfumery, although they have attracted attention in connection with insect pheromone activity[4]). This is, to the best of our knowledge, the first report of the occurrence of **2** and **3** in a plant.

The structure of the lactone **1**, except for the position of the double bond, followed from its spectral data (see experimental part). The mass spectrum indicates a molecular weight of 224, and shows nearly the same fragmentation pattern as ambrettolide (**4**). The NMR. spectra of both compounds **1** and **4** are almost identical, differing only in the number of protons in the methylene envelope (1.2–1.8 ppm): 18 protons for **4** and 14 protons for **1**. Consequently, the new lactone may be regarded as a lower homologue of ambrettolide. The *cis* geometry of the double bond was indicated by the absence of the '*trans*'-band (970 cm^{-1}) in the IR. spectrum[5]), and its position at

Scheme 1



[4]) Both acetates **2** and **3** have been synthesized in order to test their effectiveness as insect sex attractants [3] or as pheromone perception inhibitors [4]. Recently, **3** has been identified in the sex pheromone of the oak leaf roller moth [5]. For a recent synthesis of **3**, see [6].

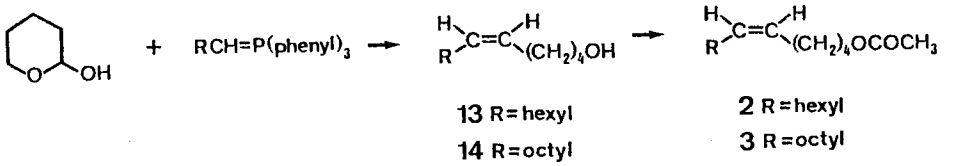
[5]) This band, completely missing in natural ambrettolide (**4**) (*cis* configuration), is quite strong in synthetic 'ambrettolide' (*Givaudan*), consisting of a mixture of positional and geometric isomers.

C(5) was established by oxidative degradation with periodate/permanganate, which led to glutaric acid as the main product (identified as its dimethyl ester). The structure of **1** was confirmed by an unambiguous synthesis outlined in *Scheme 1*.

Treatment of 1,8-octanediol with 48% aqueous hydrobromic acid gave 8-bromo-1-octanol (**5**) (62%)[6]), which was converted to the tetrahydropyranyl ether **6** in nearly quantitative yield. The bromide **6** was treated with lithium acetylide in dimethyl sulfoxide to afford the monosubstituted alkyne **7** in over 95% yield. Alkylation of the magnesium derivative of **7** with oxirane followed by partial reduction of the triple bond over a deactivated Pd catalyst gave pure *cis* olefin **9** in 49% yield. Conversion of the alcohol **9** to the tosylate **10** and subsequent treatment with sodiomalonate yielded the substituted malonate **11** (89% of crude product over two steps). The malonic ester was successively submitted to alkaline hydrolysis, acid hydrolysis, thermal decarboxylation and again alkaline hydrolysis (to convert the polyester to the monomer) without isolation of the intermediates. Crude (*Z*)-14-hydroxy-5-tetradecenoic acid (**12**) was isolated in *ca.* 75% yield and characterized spectroscopically as its methyl ester. The crude hydroxy acid was lactonized under high dilution conditions [8], and afforded the desired lactone **1** in 52% yield (pure distilled product). The compound showed the same spectral, chromatographic, and olfactive properties as (*Z*)-5-tetradecen-14-olide isolated from ambrette seed absolute.

The structure of the acetates **2** and **3** followed from their spectral data (see experimental part) and from the fact that oxidative cleavage with periodate/permanganate yielded mainly heptanoic acid in the case of **2**, and nonanoic acid in the case of **3**. Both acetates could be synthesized with high stereoselectivity (>98%) utilizing the *Wittig* reaction between tetrahydropyran-2-ol [9] and an alkylidenetriphenylphosphorane as the key step (*Scheme 2*)[7]). Subsequent treatment of the alcohols **13** and **14**

Scheme 2



13 R = hexyl
14 R = octyl

2 R = hexyl
3 R = octyl

with acetic anhydride in pyridine gave the desired acetates **2** and **3**, respectively, having the same spectral properties and retention times as the natural compounds.

Experimental Part

NMR. spectra were recorded on a *Hitachi Perkin-Elmer* R-20 B instrument (60 MHz) or on a *Bruker* HFX-90/3-15 inch instrument (90 MHz), using $CDCl_3$ as solvent and tetramethylsilane as internal standard ($\delta = 0$ ppm); abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, '*t*' = triplet-like multiplet, *qa* = quartet, *m* = multiplet, br. = broad, *J* = spin-spin coupling constant (Hz). IR. spectra were measured on a *Perkin-Elmer* 720 spectrometer; characteristic maxima are given in cm^{-1}; abbreviations: *s* = strong, *m* = medium, *w* = weak, sh = shoulder. Mass spectra were recorded on a *Atlas* CH 4 mass spectrometer, using an inlet temperature of *ca.* 150° and electrons of *ca.* 70 eV energy; the intensity of the molecular ion and of the eight most intense fragment ions are given in %

[6]) For details of the procedure, see [7].

[7]) This reaction has been studied by *Ohloff et al.* [10].

of the most abundant one. Gas chromatography (GC.) was carried out on a *Varian Aerograph* series 1800 instrument, using Carbowax 20 M, 15% on Chromosorb W85 80-100 mesh, acid-washed (4 mm × 1.5 m), and Silicon GE XE-60, 5% on Chromosorb G 60-80 mesh, DMCS-treated and acid-washed (4 mm × 3 m).

1. Isolation of naturally occurring material. – Distillation of commercial ambrette seed absolute on a spinning band column (*Normag*, length 100 cm) yielded two fractions containing the title compounds: A (*ca.* 7%, b.p. 68–72°/0.03 Torr) and B (*ca.* 4%, b.p. 78–84°/0.03 Torr). Chromatography of fraction A on silica gel (*Merck*, 0.05–0.2 mm) with petroleum ether b.p. 50–70° → petroleum ether/ether 95:5 gave a fraction (*ca.* 70%) (mainly decyl acetate and dodecyl acetate[8])) which was immediately followed by a small fraction (*ca.* 3%) containing *ca.* 80% of (*Z*)-5-dodecenyl acetate (**2**). Prep. GC. (Silicon) allowed the isolation of a pure sample of **2** which proved to be a single isomer by GC. on a capillary column.

Spectral data of (Z)-*5-dodecenyl acetate* (**2**): IR. (liq.): 3025*w*, 1735*s*, 1235*s*. – NMR. (90 MHz): 0.89 (degenerate *t*, 3H, CH_3–CH_2–); 1.11–1.78 (br., 12H, 6CH_2); 1.78–2.22 (br., 4H, –CH_2–CH=CH–CH_2–); 2.04 (*s*, 3H, CH_3COO); 4.06 (*t*, *J*=6.5, 2H, –CH_2O–); 5.36 (symmetric *m*, 2H, –*CH*=*CH*–). – MS.: 226 (*M*, 0), 166 (*M* – AcOH, 10), 43 (100), 67 (68), 54 (58), 41 (53), 82 (51), 81 (49), 68 (49), 55 (48).

Chromatography of fraction B on silica gel with petroleum ether → ether allowed a fraction to be eluted (with ether) which was free of hydrocarbons and strongly polar substances. This fraction was shown by GC. (Silicone) to consist mainly of dodecyl acetate, (*Z*)-5-tetradecen-14-olide (**1**), (*Z*)-5-tetradecenyl acetate (**3**), (2*E*,6*Z*)-farnesyl acetate, and (2*E*,6*E*)-farnesyl acetate (eluted in this order). Prep. GC. (Silicone) allowed the isolation of a pure sample of each compound (the homogeneity of which was checked by GC. on a capillary column). The spectral data of decyl acetate, dodecyl acetate and the farnesyl acetates were identical with those of authentic samples.

Spectral data of (Z)-*5-tetradecen-14-olide* (**1**): IR. (liq.): 3030*w*, 1735*s*, 1245*m*. – NMR. (90 MHz): 1.22–1.44 (br., 10H, 5CH_2); 1.44–1.8 (*m*, 4H, 2CH_2); 1.8–2.27 (*m*, 4H, –CH_2–CH=CH–CH_2–); 2.35 ('*t*', *J*=*ca.* 6, 2H, –CH_2CO–); 4.18 ('*t*', *J*=*ca.* 5, 2H, –CH_2O–); 5.36 (symmetric *m*, 2H, –*CH*=*CH*–). – MS.: 224 (*M*, 9), 67 (100), 81 (99), 41 (93), 55 (87), 82 (74), 96 (57), 80 (50), 68 (48).

Spectral data of (Z)-*5-tetradecenyl acetate* (**3**): IR. (liq.): 3025*w*, 1735*s*, 1235*s*. – NMR. (90 MHz): 0.87 (degenerate *t*, 3H, CH_3–CH_2–); 1.1–1.78 (br., with a strong peak at 1.26, 16H, 8CH_2); 1.8–2.17 (br., 4H, –CH_2–CH=CH–CH_2–); 2.04 (*s*, 3H, CH_3COO); 4.06 (*t*, *J*=6.5, 2H, –CH_2O–); 5.35 (symmetric *m*, 2H, –*CH*=*CH*–). – MS.: 254 (*M*, 0), 194 (*M* – AcOH, 10), 43 (100), 82 (81), 67 (80), 81 (66), 68 (65), 55 (57), 54 (55), 95 (54).

2. Oxidative degradation with periodate/permanganate. – A solution of 10 mg of the compound to be oxidized (**1**, **2** or **3**) in 7 ml of *t*-butyl alcohol was mixed at 20° with 12 ml of oxidizing solution (prepared by dissolving 1.04 g of sodium periodate and 20 mg of potassium permanganate in 250 ml of distilled water). The mixture was diluted with 27 ml of water, adjusted to pH 8.5 by the addition of a solution of potassium carbonate, and stirred at 20° for 24 h. The solution was acidified with 10% sulfuric acid and extracted continuously with ether for 24 h. The solvent was removed at atmospheric pressure, the residue esterified with diazomethane in ether, and the main product purified by preparative GC. (Silicone) and identified by its MS. Dimethyl glutarate, methyl heptanoate, and methyl nonanoate were obtained by this method from **1**, **2**, and **3**, respectively.

3. Synthesis of (*Z*)-5-tetradecen-14-olide (1). – *8-Bromo-1-octanol* (**5**). 1,8-Octanediol (200 g, 1.37 mol) and aqueous 48% hydrobromic acid (200 ml, 1.75 mol) were placed in a 500-ml liquid-liquid extractor, and heated to 90° in an oil bath and extracted continuously with octane for 72 h. The octane extracts were dried (Na_2SO_4) and after removal of the solvent, distillation of the residue through a *Vigreux* column yielded 197.6 g (62%) of 8-bromo-1-octanol, b.p. 77–78°/0.01 Torr. The product, which was contaminated with *ca.* 5% of 1,8-octanediol and *ca.* 5% of 1,8-dibromooctane by GC., exhibited the expected spectral data and was used without further purification.

2-(8-Bromooctyloxy)-tetrahydropyran (**6**). Dihydropyran (84 g, 1.0 mol) was added slowly with stirring and cooling to the crude alcohol **5** (197.6 g, 0.850 mol) containing 2 drops of conc. hydrochloric acid, so that the temp. did not exceed 60°. The mixture was stirred at 20° overnight, and

[8]) Decyl and dodecyl acetate are main constituents (*ca.* 7% each). The occurrence of dodecyl acetate in ambrette seed absolute is reported for the first time.

powdered sodium hydroxide (2 g) was added. Distillation of the product through a *Vigreux* column yielded 234 g (94%) of a colourless oil, b.p. 97–100°/0.008 Torr, of *ca.* 95% purity. The spectral data were in accord with the structure of **6**.

2-(9-Decynyloxy)-tetrahydropyran (**7**). A 1-l round-bottomed three-necked flask equipped with a mechanical stirrer, a gas inlet tube, and a gas outlet was charged with 500 ml of liquid ammonia. While a strong stream of acetylene was introduced, small pieces of lithium (3.5 g, 0.5 mol) were added. 200 ml of dry dimethyl sulfoxide were carefully added to this colourless solution of lithium acetylide. The bromide **6** (89.7 g, 0.306 mol) was added dropwise (40 min) with stirring. The ammonia was removed by evaporation (4 h), 500 ml of ether/pentane 1:1 were added, the reaction mixture was hydrolysed by careful addition of ice/water (1 l), and the aqueous phase extracted 4 times with 500-ml portions of ether/pentane 1:1. The combined extracts were washed with water and dried over Na_2SO_4. After removal of the solvent, 72.6 g (99%) of the monosubstituted acetylene **7** of *ca.* 95% purity were obtained as a colourless oil. The product could be used without purification. – IR. (liq.): 3340*m*, 2130*w*. – NMR. (90 MHz): 1.26–1.86 (br., 18H, 9CH_2); 1.96 (*t*, *J*=2.5, 1H, C≡C*H*); 2.17 (*m*, 2H, –CH_2–C≡CH); 3.22–4.04 (*m*, 4H, 2–CH_2O–); 4.60 (br., 1H, O–C*H*–O). – MS.: 238 (*M*, <1), 85 (100), 41 (60), 55 (58), 67 (38), 81 (32), 56 (29), 95 (21), 39 (21).

12-(2-Tetrahydropyranyloxy)-3-dodecyn-1-ol (**8**). To a stirred solution of ethyl magnesium bromide (0.054 mol, prepared from 1.31 g of magnesium and 9 g of ethyl bromide in 50 ml of dry tetrahydrofuran) was added dropwise a solution of crude **7** (10.7 g, 0.045 mol) in 100 ml of dry tetrahydrofuran at 5°. When the exothermic reaction had subsided, the mixture was stirred at 50° for 1 h and cooled again to 5°. Oxirane (9 g, 0.227 mol) was introduced through a gas inlet tube at such a rate that the temp. did not exceed 10°. After stirring overnight at room temp., the mixture was poured onto crushed ice (300 g), and extracted with ether. The solvent was removed by distillation and the residue (11.9 g) distilled in a bulb tube. After a forerun of 2.5 g of the starting material **7** (bath temp. *ca.* 120°/0.005 Torr), 6.3 g (49%) of the desired alcohol **8** (bath temp. 130–135°/0.005 Torr) were obtained in *ca.* 95% purity as an oil. – IR. (liq.): 3450*s*, 1035*s*. – NMR. (90 MHz): 1.22–1.78 (br., 18H, 9CH_2); 2.0–2.27 (br., 3H, –CH_2–C≡C–CH_2–CH_2O*H*); 2.42 (*m*, 2H, ≡C–CH_2–CH_2OH); 3.24–4.02 (*m*, 6H, 3–CH_2O–); 4.56 (br., 1H, O–C*H*–O). – MS.: 282 (*M*, 0), 85 (100), 55 (69), 41 (59), 56 (30), 29 (30), 43 (29), 97 (28), 84 (27).

(Z)-*12-(2-Tetrahydropyranyloxy)-3-dodecen-1-ol* (**9**). A solution of the alkynol **8** (6.1 g, 21.6 mmol) in dry ethanol (60 ml) was hydrogenated over 600 mg Pd/$BaSO_4$ (5%, *Fluka*) at ordinary pressure and temperature. After 50 min the theoretical amount of hydrogen (500 ml) was consumed. The catalyst was filtered off, the solvent evaporated, and the residue distilled *in vacuo*. Yield 6.07 g (99%) of a colourless, homogenous oil, b.p. 140°/0.005 Torr. – IR. (liq.): 3450*s*, 3030*w*, 1035*s*. – NMR. (60 MHz): 1.22–1.80 (br., 18H, 9CH_2); 1.80–2.20 (br., 2H, =CH–CH_2–CH_2OH); 3.20–4.1 (*m*, 6H, 3–CH_2O–); 4.59 (br., 1H, O–C*H*–O); 5.45 (symmetric *m*, 2H, –C*H*=C*H*–). – MS.: 284 (*M*, 0), 55 (100), 41 (73), 85 (62), 67 (51), 81 (38), 29 (38), 54 (35), 68 (34).

Diethyl (Z)-[*12-(2-tetrahydropyranyloxy)-3-dodecenyl*]*malonate* (**11**). A solution of *p*-toluenesulfonyl chloride (7.6 g, 38.5 mmol) in 50 ml of dry pyridine was slowly added at 0° to a stirred solution of alcohol **9** (5.7 g, 20 mmol) in 50 ml of dry pyridine. After 2 days at 0° the mixture was poured into ice/water/ether. The organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent, 8.8 g (100%) of crude *p*-toluenesulfonate **10** were obtained as an oil, which showed the expected spectral data. The product was dissolved in 30 ml of dry ethanol and added to a solution of diethyl sodiomalonate (prepared by dissolving 2.95 g (18.2 mmol) diethyl malonate in a solution of 750 mg sodium in 20 ml of dry ethanol). The mixture was boiled for 12 h, poured into ice/water, and extracted with ether. The extract was dried over Na_2SO_4, and the solvent removed. 6.91 g (89%) of crude **11** were obtained as an oil, which was used for the next step without purification. – IR. (liq.): 3030sh, 1750*s*, 1735*s*, 1120*s*, 1030*s*. – NMR. (60 MHz): 1.27 (*t*, *J*=7, 6H, 2–OCH_2–CH_3); 1.2–1.8 (br., 18H, 9CH_2); 1.8–2.5 (br., 6H, 3CH_2); 3.2–3.95 (*m*, 5H, 2–OCH_2– and –C*H*(COOEt)$_2$); 4.20 (*qa*, *J*=7, 4H, 2OCH_2–CH$_3$); 4.57 (br., 1H, O–C*H*–O); 5.40 (symmetric *m*, 2H, –C*H*=C*H*–). – MS.: 426 (*M*, 0), 59 (100), 31 (89), 85 (69), 55 (53), 41 (51), 29 (46), 67 (31), 54 (22).

(Z)-*14-Hydroxy-5-tetradecenoic acid* (**12**). 6.91 g (16.2 mmol) of crude ester **11** were mixed with a solution of 5 g of sodium hydroxide in 80 ml of 50% aqueous ethanol and boiled for 6 h. The mixture was poured into water (200 ml), washed with ether, acidified with 100 ml of conc. hydrochloric acid, and stirred for 2 h at 20°. The solution was then saturated with NaCl and extracted

several times with ether. After evaporation of the solvent, the crude substituted malonic acid (5.18 g) was decarboxylated by heating it at 160° for 30 min. This operation caused partial polymerization of the hydroxy acid. Therefore, the residue was hydrolysed by boiling it for 6 h with aqueous ethanolic sodium hydroxide. Work-up as described above yielded 2.97 g (75%) of crude **12** as an oil. A small sample was esterified with diazomethane in ether and purified by prep. GC. (Silicone).

Spectral data of methyl (Z)-*14-hydroxy-5-tetradecenoate*: IR. (liq.): 3450*s* br., 3030*w*, 1740*s*, 1640*w*. – NMR. (60 MHz): 1.2–1.8 (br., 14H, 7CH_2); 1.8–2.5 (br., 7H, CH_2–CH=CH–CH_2 and –CH_2CO and O*H*); 3.62 (*t*, *J* = 6, 2H, partially hidden, –CH_2O–); 3.64 (*s*, 3H, OCH_3); 5.33 (symmetric *m*, 2H, –C*H*=C*H*–). – MS.: 256 (*M*, 0), 41 (100), 55 (98), 67 (86), 74 (81), 81 (81), 43 (62), 82 (48), 96 (47).

(Z)-*5-Tetradecen-14-olide* (**1**). A solution of the crude hydroxy acid **12** (190 mg, 0.785 mmol) in dry benzene (20 ml) was added over 24 h to a boiling solution of 20 mg of *p*-toluenesulfonic acid in 180 ml of dry benzene. The water was removed by azeotropic distillation. The organic phase was washed with 10% sodium carbonate solution and water, dried over Na_2SO_4, and the solvent removed *in vacuo*. Distillation of the residue (178 mg) in a bulb tube afforded 92 mg (52%) of pure macrocyclic lactone **1** as a colourless oil (bath temp. 100°/0.005 Torr). The compound exhibited a strong musk odour and showed the same spectral and chromatographic data as natural **1**.

4. Synthesis of the acetates 2 and 3. – Both acetates **2** and **3** were prepared with > 98% stereoselectivity in 60 and 45% yield, respectively, following the procedure described by *Ohloff et al.* [10]. The synthetic compound proved identical both spectrally and in retention time with the acetates from ambrette seed absolute.

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