

The Use of Mercury Compounds in the Synthesis of Some Lepidoptera Insect Sex Pheromones with Monoenic Structure

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New and practical synthesis of (E)-11-tetradecen-1-yl acetate and (Z)-11-hexadecen-1-yl acetate were developed. The synthesis were based on a $C_{12}+C_2=C_{14}$ and $C_{12}+C_4=C_{16}$ coupling scheme. The routes involve, as the key step, the use of the same mercury derivative of the terminal-alkyne w-functionalised as intermediate. The first coupling reaction was effected by adding 1-tert-butoxy-10-bromodecane to monosodiate acetylene, obtained in situ from DMSO and sodium hydride. It was prepared 1-tert-butoxy-dodec-11-yne, which is transformed in di[tert-butoxy-dodec-11-yne]mercury, the common intermediate in the synthesis of the two pheromones. In order to obtain (E)-11-tetradecen-1-yl acetate, the mercury derivative was directly lithiated and then alkylated with 1-bromoethane obtaining 1-tert-butoxy-tetradec-11-yne. After reduction with lithium aluminium hydride of 1-tert-butoxy-tetradec-11-yne and acetylation gave (E)-11-tetradecen-1-yl acetate with 99 % isomeric purity. In order to obtain (Z)-11-hexadecen-1-yl acetate, the mercury derivative was directly lithiated and then alkylated with 1-bromobutane obtaining 1-tert-butoxy-hexadec-11-yne. After acetylation of 1-tert-butoxy-hexadec-11-yne and stereoselective reduction in the presence of NiP-2 catalyst gave (Z)-11-hexadecen-1-yl acetate with 90 % isomeric purity.

Keywords: (E)-11-tetradecen-1-yl acetate, (Z)-11-hexadecen-1-yl acetate, Lepidoptera, sex pheromone

(E)-11-tetradecen-1-yl acetate and (Z)-11-hexadecen-1-yl acetate are components for *Lepidoptera* insect sex pheromones [1]. Some important economic pest insects are: *Ostrinia nubilalis* - european corn borer, *Archips podana* - fruittree tortrix, *Mamestra brassicae* - cabbage moth.

The synthesis of (E)-11-tetradecen-1-yl acetate and (Z)-11-hexadecen-1-yl acetate are well known in the literature [2-9]. The synthesis of (E)-11-tetradecen-1-yl acetate has as the key step, Claisen rearrangement of the allylic alcohol with triorthoacetate in the presence of the acetic acid [3]. In the synthesis of Ishmuratov [4], the key step are reaction of in situ formed methylmagnesium cuprate with the diene acetate. The synthesis of (Z)-11-hexadecen-1-yl acetate was realized using organoborone chemistry [5], cross-coupling reaction catalyzed by Pd(II) and Ni(II) complexes [6], Z-stereoselective Wittig reaction and acetylenic route [7, 8], cross-metathesizing 11-eicosenol and 1-hexene in the presence of the ruthenium catalyst [9].

The paper describes new and practical synthesis of (E)-11-tetradecen-1-yl acetate and (Z)-11-hexadecen-1-yl acetate based on the C-alkylation reaction, using the same mercury derivative of the terminal alkyne w-functionalized.

Experimental part

GC-MS analysis were performed on a GC-MS spectrometer Agilent 7890A GC&5975 GC/MS Serie MSD. $^1\text{H-NMR}$ (300 MHz) and $^{13}\text{C-NMR}$ (75 MHz) spectra were recorded at *RT* in CDCl_3 on a Bruker 300 MHz spectrometer, using TMS line as reference. A Perkin Elmer Spectrometer Model 700 was used for IR spectra.

10-bromodecan-1-ol (**4**)

To a solution 87 g (500 mmoles) of 1,10-decanediol solved in 250 mL benzene was added 86 mL hydrobromic acid 47%. The reaction mixture was refluxed for 2.5 h. The organic layer was separated and washed with brine, saturated NaHCO_3 solution and dried over anhydrous MgSO_4 . After distillation of the solvent, 62.7 g of 10-

bromodecan-1-ol (**4**) were obtained. Yield: 62%, GC purity: 97%.

Mass spectrum (m/z, %): 190(<1), 178(<1), 164(<1), 151(<1), 111(<1), 109(<1), 148(34.80), 97(26.47), 83(43.13), 69(87.25), 55(100), 41(74.01), 31(29.41).

1-tert-Butoxy-10-bromo-decane (**5**)

To a solution 68 g (232 mmoles) of 10-bromodecan-1-ol (**4**) and 317 mL *tert*-butyl-methyl-ether was added dropwise 19.12 mL concentrated sulfuric acid under cooling. The reaction mixture was maintained at 40°C. The reaction was checked by TLC on silica gel G (benzene:ether 2:1, detection with H_2SO_4 d=1.25). The reaction mixture was diluted with water. After removal of the *tert*-butyl-methyl-ether under reduced pressure, the mixture was extracted with ethyl ether (3x50 mL). The combined ethereal extracts were washed with saturated NaHCO_3 solution up to basic (pH=8-8.5) and dried over MgSO_4 . After the removal of the solvent, 62 g of 1-*tert*-butoxy-10-bromo-decane (**5**) were obtained. Boiling point = 125-130°C/2mm Hg. Yield: 77%, GC purity: 97%.

Mass spectrum (m/z, %): 277(<1), 236(<1), 219(<1), 177(<1), 163(<1), 137(<1), 121(<1), 97(<1), 83.29(<1), 59(100), 41(21.56).

1-tert-Butoxy-dodec-11-yne (**6**)

Aparatus: 1L reactor provided with a thermometer dipping into the liquid, a dropping funnel, a stirrer and a 20-30 cm long tube for preventing any splashing out of the reaction mixture. All operations took place in inert atmosphere and vigorous stirring.

16.30 g sodium hydride (60%) were added to 100 mL of dry DMSO and the temperature was risen up to 65-68°C. The conversion was finished when no more hydrogen was evolved.

Acetylene (freed from acetone) was introduced for 15 min. at a rate of about 2L/min. with external cooling in order to moderate the reaction.

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During this process the temperature is maintained between 20 and 30°C.

49 mL of DMSO were added and afterwards, between 20-30°C, 20 g (68 mmoles) of 1-*tert*-butoxy-10-bromodecane (**4**) were added with external cooling.

The reaction was led to completion by stirring for 3 h at room temperature and was interrupted with 50 g crushed ice. The reaction mixture was extracted with four portions of 100 mL petroleum ether. The combined ethereal extracts were washed with brine up to the neutral pH of the washings and dried over Na₂SO₄.

After removal of the solvent 19.4 g of 1-*tert*-butoxy-dodec-11-yne (**6**) were obtained in yield of 89%, GC purity: 90%.

Mass spectrum (m/z, %): 223 (17.56), 182 (≤1), 165 (≤1), 149 (≤1), 135 (v 1), 123 (≤1), 109 (≤1), 81 (23.41), 67 (16.58), 59 (100), 41 (40.97), 29 (14.63).

Di[1-*tert*-butoxy-dodec-11-yne]mercury (**8**)

To 17 g of potassium iodide dissolved in 17 mL water were added 7 g mercury (II) chloride and the mixture was stirred till the mercury salt was dissolved. To the mixture were added 13 mL of 10% sodium hydroxide solution. After external cooling of reaction mixture with ice, were added dropwise 5 g (21 mmoles) of 1-*tert*-butoxy-dodec-11-yne (**7**) dissolved in 74 mL cooling ethyl alcohol. The obtained precipitate was filtrated and washed on the filter with cooling aqueous ethylic alcohol 50%. After drying were obtained, 7.5 g of di(*tert*-butoxy-dodec-11-yne) mercury (**8**). Yield: 53%, m.p.=104°C.

1-*tert*-Butoxy-tetradec-11-yne (**9**)

All operations were performed in an inert gas atmosphere and under stirring.

5.32 g (7.8 mmoles) of di[1-*tert*-butoxy-dodec-11-yne]mercury (**8**) in 20 mL diglyme was treated with 0.1 g lithium (15.6 mmoles) at 120-125°C for 3 h. 1.63 g (15 mmoles) of 1-bromoethane dissolved in 2 mL diglyme was added dropwise at 90-95°C then the temperature was raised to 120-125°C under stirring for 4 h. The mixture was poured out over the 100 g of crushed ice. The reaction mixture was extracted with petroleum ether. The ethereal solution was washed successively with 10% HCl, water and brine till neutral pH of the washings. After drying over MgSO₄, the solvent was removed and 1.77 g of 1-*tert*-butoxy-tetradec-11-yne (**9**) was obtained. Yield: 60%, GC purity: 78%.

Mass spectrum (m/z, %): 251(23.90), 237(<1), 211(<11), 210(<11), 181(<11), 163(<1), 151(<11), 123(13.65), 109(41.95), 95(40.97), 81(47.80), 57(100), 41(80), 29(21.95).

1-*tert*-Butoxy-E-11-tetradecen (**10**)

All operations were performed in an inert gas atmosphere and under stirring.

2.18 g (56 mmoles) of LiAlH₄ was placed in a solution of 5 mL of anhydrous THF and 36 mL of diglyme. The solvent was partially removed (6 mL) and the temperature was raised at 140°C. After cooling at 10°C, the suspension was treated with 4.2 g (17 mmoles) of 1-*tert*-butoxy-tetradec-11-yne (**9**) in 5 mL diglyme. The mixture was heated at 145-150°C which was maintained for 20 h. The reaction was checked by TLC on silicagel G (benzene:ether 15:1, detection with H₂SO₄ d=1.28). After cooling, the solution was treated with 15 mL of diluted H₂SO₄ (d=1.28). The reaction mixture was extracted with 16x5 mL petroleum ether, washed with brine and dried over MgSO₄. After removal of the solvent were obtained 3.5 g of 1-*tert*-butoxy-E-11-tetradecen (**10**). GC purity: 80%. Yield 75%.

Mass spectrum (m/z, %): 243 (21.3), 57 (100), 41(77), 29(22.34).

(*E*)-11-tetradecen-1-yl acetate (**1**)

4.5 g (20 mmoles) of 1-*tert*-butoxy-E-11-tetradecen (**10**) was dissolved in 20 mL of 1:10 mixture of acetyl chloride : acetic acid and was refluxed for 4-5 h. The reaction development was checked up by TLC on silica gel G (benzene:ether 8:1, detection with H₂SO₄ d=1.25). The reaction mixture was poured on crushed ice, extracted with petroleum ether, washed with brine and with aqueous NaHCO₃ till neutral pH of the washings. After drying over MgSO₄ and removal of the solvent was obtained 0.5 g of (*E*)-11-tetradecen-1-yl acetate (**1**). Yield: 68%, GC purity: 99%.

Mass spectrum (m/z, %): 211(<1), 194(11.27), 179(<1), 166(<1), 153(<1), 152(<1), 138(<1), 124(7.75), 109(15.49), 97(9.15), 96(41.89), 82(77.46), 68(76.06), 55(66.20), 43(100), 39(13.38), 29(15.49).

¹H-NMR (CDCl₃, 300 MHz): 0.81 (3H, t, J = 6 Hz, CH₃), 1.14 (14H, s, 7CH₂), 1.42-1.49 (2H, m, CH₂), 1.79-1.86 (7H, m, 2CH₂, CH₃), 3.89 (2H, t, J = 6 Hz, OCH₂), 5.17-5.33 (2H, m, J = 15.51 Hz, HC=CH).

¹³C-NMR (CDCl₃, 75 MHz): 13.6 (CH₃), 20.3 (CH₂), 25.2 (CH₂), 25.6 (CH₂), 28.3 (CH₂), 28.8 (CH₂), 28.9 (CH₂), 29.2 (CH₂), 29.2 (CH₂), 29.2 (CH₂), 29.3 (CH₂), 32.2 (CH₂), 64.0 (OCH₂), 128.8 (=CH), 131.4 (CH=), 170.2 (C=O).

1-*tert*-Butoxy-hexadec-11-yne (**11**)

All operations were performed in an inert gas atmosphere and under stirring.

6 g (8.8 mmoles) of di[1-*tert*-butoxy-dodec-11-yne]mercury (**8**) in 23 mL diglyme was treated with 0.12 g lithium (17.14 mmoles) at 100-105°C for 3 h. 2 g (14.59 mmoles) of 1-bromobutane dissolved in 2 mL diglyme was added dropwise at 90°C then the temperature was raised to 120-123°C under stirring for 4 h. The mixture was poured out over 100 g of break ice. The reaction mixture was extracted with petroleum ether. The ethereal solution was washed successively with 10% HCl, water and brine till neutral pH of the washings. After drying over MgSO₄, the solvent was removed and 5 g of 1-*tert*-butoxy-hexadec-11-yne (**11**) was obtained. Yield: 76%, GC purity: 50%.

Mass spectrum (m/z, %): 279(13.72), 238(<1), 181(<1), 165(<1), 137(<1), 123(12.74), 109(22.55), 99(49.02), 81(54.90), 67(46.08), 57(100), 41(65.69), 29(18.63).

11-Hexadecyne-1-yl acetate (**12**)

1.74 g (6 mmoles) of 1-*tert*-butoxy-hexadec-11-yne (**11**) was dissolved in 6 mL of 1:10 mixture of acetyl chloride:acetic acid and was refluxed for 4-5 hours. The reaction development was checked up by TLC on silica gel G (benzene:ether, 15:1, detection with H₂SO₄ d=1.25). The solution was poured on crushed ice, extracted with petroleum ether, washed with brine and with aqueous NaHCO₃ till neutral pH of the washings.

After drying over MgSO₄ and removal of the solvent was obtained 1.4 g of 11-hexadecyne-1-yl acetate (**12**). Yield: 65%, GC purity: 82%.

Mass spectrum (m/z, %): 191(<1), 178(<1), 163(<1), 149(<1), 136(<1), 135(<1), 121(10.78), 110(14.7), 107(11.76), 96(47.06), 81(66.7), 67(53.92), 55(41.18), 43(100), 29(10.78).

(*Z*)-11-Hexadecen-1-yl acetate (**2**)

11-Hexadecyne-1-yl acetate (**11**) was hydrogenated at (*Z*)-11-hexadecen-1-yl acetate (**2**) in the presence of the NiP-2/EDA catalyst, prepared in situ according to the

standard procedure [10]. (Z)-11-Hexadecen-1-yl acetate (**2**) was obtained in yield of 74%, GC purity: 90%.

Mass spectrum (m/z , %): 222(9.8), 194(<1), 180(<1), 166(<1), 152(<1), 138(<1), 124(<1), 109(14.7), 96(37.25), 82(42.16), 67(40.2), 55(71.57), 43(100), 29(13.72).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.77 (3H, t, $J = 6\text{ Hz}$, CH_3), 1.15 (18H, s, 9CH_2), 1.41-1.49 (2H, m, CH_2), 1.88-1.97 (7H, m, 2CH_2 , CH_2), 3.90 (2H, t, $J = 6\text{ Hz}$, OCH_2), 5.25-5.42 (2H, m, $J = 11.03\text{ Hz}$, $\text{HC}=\text{CH}$).

$^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): 13.2 (CH_3), 20.0 (CH_2), 21.5 (CH_2), 25.2 (CH_2), 26.1 (CH_2), 26.4 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 31.2 (CH_2), 63.7 (OCH_2), 128.9 ($2\text{CH}=\text{}$), 169.9 ($\text{C}=\text{O}$).

Results and discussions

For the synthesis of (E)-11-tetradecen-1-yl acetate (**1**) and (Z)-11-hexadecen-1-yl acetate (**2**), we explored the pathway outlined in scheme 1. The synthesis were based on $\text{C}_{12} + \text{C}_2 = \text{C}_{14}$ and $\text{C}_{12} + \text{C}_4 = \text{C}_{16}$ coupling schemes, the routes involving the use of the same mercury derivative of the terminal alkyne ω -functionalised as intermediate (scheme 1).

1,10-Decanediol (**3**), starting material, was transformed in 10-bromodecan-1-ol (**4**).

Use has been made of methyl-*tert*-butyl-ether [11] in acid catalysis in order to protect the -OH function of 10-bromodecan-1-ol (**4**).

The first coupling reaction was effected by adding 1-*tert*-butoxy-10-bromo-decane (**5**) to monosodiate acetylene, obtained in situ from DMSO and sodium hydride. It was prepared 1-*tert*-butoxy-dodec-11-yne (**7**), which was transformed in di[1-*tert*-butoxy-dodec-11-yne]mercury (**8**), the common intermediate in the synthesis of the two pheromones.

1-*tert*-Butoxy-dodec-11-yne (**7**) was checked by means of IR spectrum (film, cm^{-1} : 895 m, 1110 vs, 1220 vs, 2160 w -C \equiv C-, 3280 s \equiv CH), which presents the vibration of terminal triple bond and the mass spectrum characteristic to a *tert*-butyl ether.

The molecular peak of 1-*tert*-butoxy-dodec-11-yne (**7**) was not identified, the mass spectrum presenting only

characteristic fragmentations. It is necessary to mention the base peak in the spectrum ($m/z=59$), the peak m/z 57 which is generated by the very stable tertiary carbocation $+\text{C}(\text{CH}_3)_3$, the peak corresponding to the cleavage of a methyl group from the branch part ($m/z=223$) and of a neutral molecule of isobutylene ($m/z=182$) (scheme 2).

1-*tert*-Butoxy-dodec-11-yne (**7**) with mercuric chloride in an aqueous solution containing potassium iodide and sodium hydroxide (Nessler's reagent) [12] was precipitated as di[1-*tert*-butoxy-dodec-11-yne]mercury (**8**), the common intermediate in the synthesis of the two sex pheromones.

The key step in our acetylenic route consisted in transmetalation of compound **8**, which was directly lithiated by treating with lithium metal in diglyme and then alkylated.

In order to obtain (E)-11-tetradecen-1-yl acetate (**1**), compound **8** was alkylated with 1-bromoethane obtaining 1-*tert*-butoxy-tetradec-11-yne (**9**), which was reduced with lithium aluminium hydride and then acetylated.

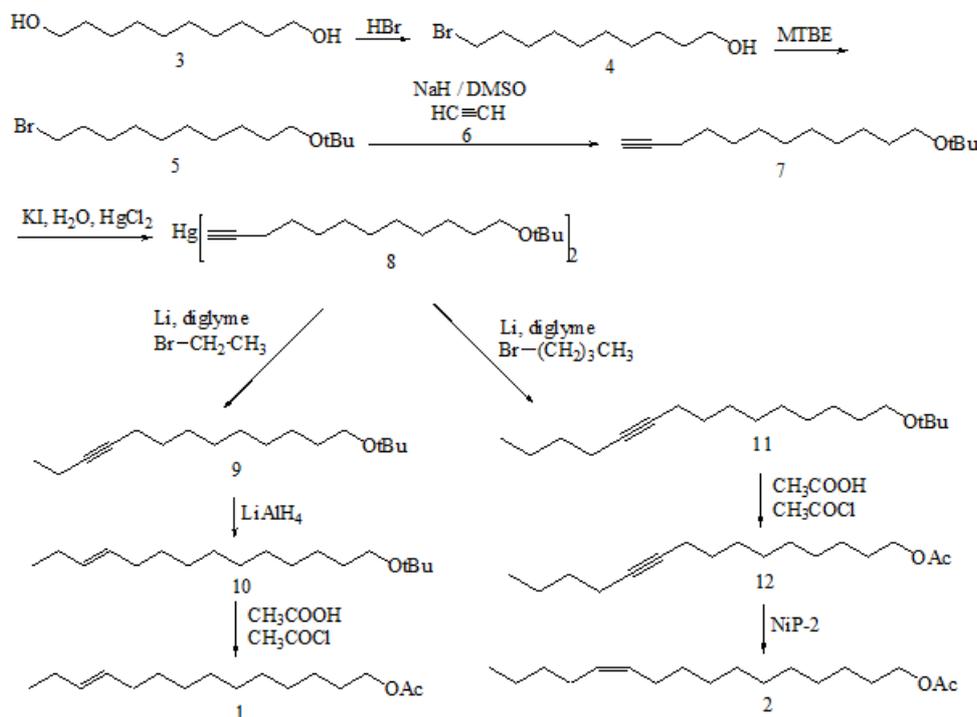
In order to obtain (Z)-11-hexadecen-1-yl acetate, compound **8** was alkylated with 1-bromobutane, obtaining 1-*tert*-butoxy-hexadec-11-yne (**11**). The conversion of the *tert*-butyl ether **11** into the acetate **12** was effected with acetyl chloride. 11-Hexadecyne-1-yl acetate (**12**) was hydrogenated using Ni-P2/EDA catalyst [10], obtaining (Z)-11-hexadecen-1-yl acetate (**2**) with 90% isomeric purity.

The mass spectrum of (E)-11-tetradecen-1-yl acetate (**1**) and (Z)-11-hexadecen-1-yl acetate (**2**) are characteristic to alkenol acetates.

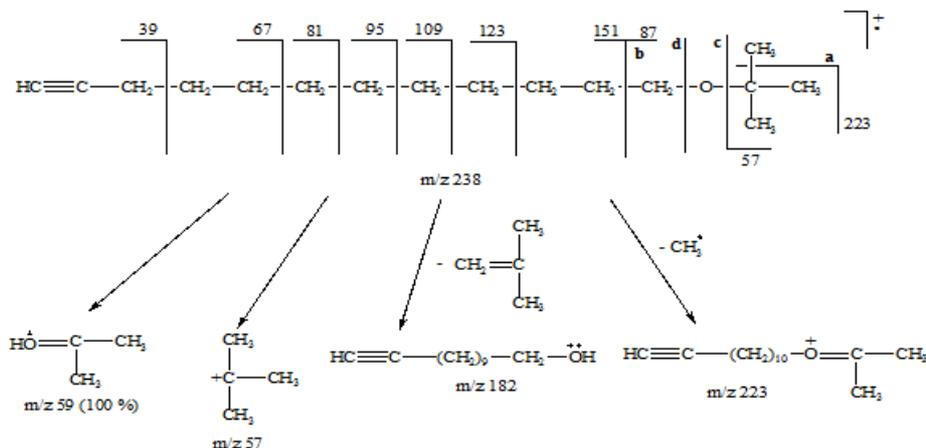
Are present: m/z 194 and m/z 222 resulted from the cleavage of acetic acid from the molecular ion, m/z 61 as ion of double transposition ($\text{CH}_3\text{COOH}_2^+$) and m/z 43 (CH_3CO^+).

The position and configuration of the final compounds was confirmed by $^1\text{H-NMR}$ spectrum and $^{13}\text{C-NMR}$ spectroscopy.

In $^1\text{H-NMR}$ spectrum of (E)-11-tetradecen-1-yl acetate (**1**) can be observed a triplet (3H, $J=6\text{ Hz}$) at 0.81 ppm corresponds to the methyl protons; a singlet (14H) at 1.14 ppm corresponds to the methylene protons; a multiplet (2H) at d 1.42-1.49 ppm corresponds to the protons; a multiplet (7H) at d 1.79-1.86 ppm corresponds to the



Scheme 1
Synthesis of (E)-11-tetradecen-1-yl acetate (**1**) and (Z)-11-hexadecen-1-yl acetate (**2**)



Scheme 2

protons; a triplet (2H, $J=6\text{Hz}$) at 3.89 ppm corresponds to a methylene bonded to oxygen and a multiplet (2H) indicates a disubstituted double bond (d 5.17-5.33 ppm).

In ^{13}C -NMR spectrum of (E)-11-tetradecen-1-yl acetate (1) the carbon atoms from double bond are easily recognised because of the larger chemical shifts at 128.8 ppm and 131.4 ppm. The signal at 170.2 ppm corresponds to the carbon in carbon-oxygen double bond.

The ^{13}C -NMR spectrum of (Z)-11-hexadecen-1-yl acetate (2) shows the signal of the carbon atoms from double bond at 128.9 ppm. The signal at 169.9 ppm corresponds to the carbon in carbon-oxygen double bond.

Conclusions

It was presented new synthesis of (E)-11-tetradecen-1-yl acetate and (Z)-11-hexadecen-1-yl acetate, components of Lepidoptera insects sex pheromones, using as intermediate the same mercury derivative of the terminal-alkyne ω -functionalized. The mercury compounds were directly lithiated and then alkylated with 1-bromoethane, respectively 1-bromobutane, followed by reduction with lithium aluminium hydride and acetylation for (E)-11-tetradecen-yl acetate, respectively acetylation and hydrogenation in the presence of Ni-P2 catalyst for (Z)-11-hexadecen-1-yl acetate.

References

- 1.*** <http://www.pherobase.com>
- 2.GÂNSCĂ, L., ANDREICA, A., CIOTLĂUȘ, I., MAXIM, S., OPREAN, I., EXO- AND ENDOHORMONES XXIV, Rev. Chim. (Bucharest) **62**, no. 9, 2011, p. 878
- 3.SHAKHMAEV, R.N., ISHBAEVA, A.U., SHAYAKHMETOVA, I.S., Russ. J. Gen. Chem., Vol. **79(6)**, 2009, p. 1171
- 4.ISHMURATOV, G.YU., YAKOVLEVA, M.P., KHARISOV, R.YA., MUSLUKHOV, R.R., TOLSTIKOV, G.A., Russ. Chem. Bull. **46(5)**, 1997, p. 1035
- 5.BROWN, H.C, WANG, K.K., J. Org. Chem. **51(24)**, 1986, p. 4514
- 6.FIANDANESE, V., MARCHESE, G., NASO, F., RONZINI, L., J. Chem. Soc. Perkin Trans I, 1985, p. 1115
- 7.SCHAUB, B., BLASER, G., SCHLOSSER, M., Tetrahedron Lett., **26**, 1985, p. 307
- 8.NESBITT, B.F., BEEVOR, P.S., HALL, D.R., LESTER, R., DYCK, V.A., Insect Biochem., **6**, 1976, p. 105
- 9.GRUBBS, R.H., HERBERT, M.B., WICKENS, Z.K., MARX, V.M., P, US Pat., 0231499, Sep.5, 2013
- 10.BROWN, C.A., AHNIA, V. K., Chem. Commun. 1973, p. 553
- 11.GOCAN, A. V. M., POP, L. M., CIUPE, H., OPREAN, I., HODOSAN, P., Rom. Pat., 93050, Nov.28, 1985
- 12.MULLER, E., JOHNSON, J. K., MC EWEN, W. L., J. Am. Chem. Soc. **48**, 1928, p.469

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