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Synthesis of a Biologically Active Chlorinated Analog of (E,E)-8,10- Dodecadienol (Codlemone)

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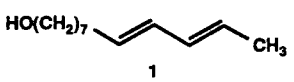
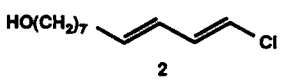
Abstract : *An efficient stereoselective synthesis of a chloro analog of codlemone, based upon the palladium-catalyzed coupling reaction of functionalized alkenylalanes with (E)-1,2-dichloroethylene, is described. This analog is more active than the natural pheromone in field tests.*

The codling moth, *Cydia pomonela* L. (Lepidoptera, Tortricidae) is a major world wide pest of apple orchards. The main component of the sex pheromone produced by the virgin female has been identified as the (E,E)-8,10-dodecadienol (codlemone) **1** [1].

During the past few years, analogs of pheromones [2,3], and more particulary of codlemone [4-5], have been synthesized to study the pheromonal receptors. Jönsson *et al.* have shown that the replacement of a terminal methyl group by a halogen (chlorine, bromine, iodine) led to changes in hydrophobicity of the hydrocarbon chain [6]. Moreover, since a chlorine atom can replace a methyl group without notable steric consequences, it appears that a chloro analog of codlemone might show interesting biological activities. Herein, we report an efficient synthesis of (E,E)-11-chloro-8,10-undecadienol **2**.



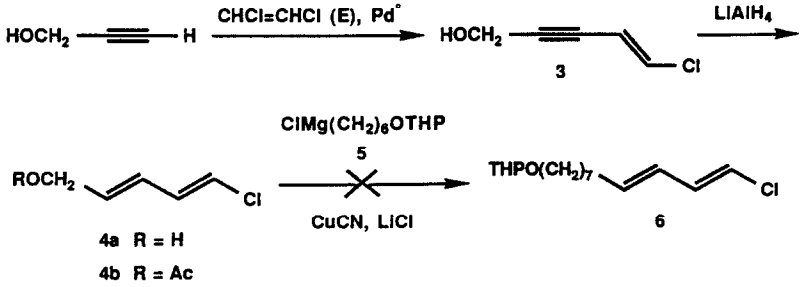
1



2

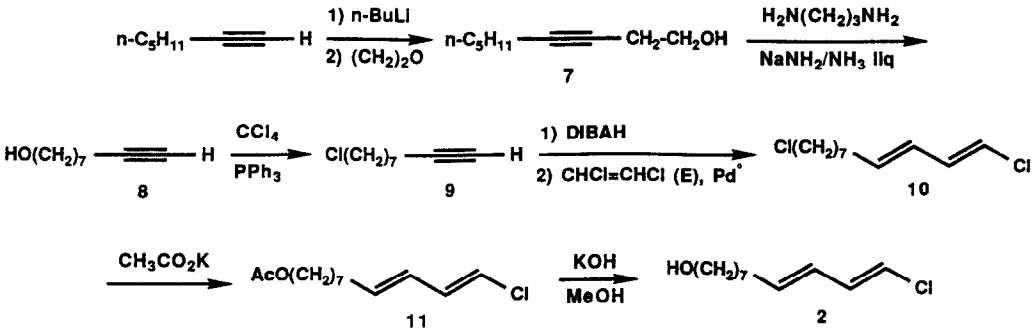
In a previous publication, Descoins *et al.* [7] described a synthesis of codlemone **1** by coupling (E,E)-2,4-hexadien-1-yl acetate with a Grignard reagent **5** in the presence of dilithium tetrachlorocuprate [8]. We studied the same methodology to prepare (E,E)-chlorocodlemone **2**, namely by coupling the Grignard reagent **5** and 5-chloro-2,4-pentadien-1-yl acetate **4b**. This C_5 unit **4b** was easily obtained by a three steps

sequence: (i) palladium-copper catalyzed reaction of (E)-1,2-dichloroethylene with propargyl alcohol [9] which gave (E)-5-chloro-2-pentyn-4-enol **3** in 86% yield, (ii) reduction (78%) with $LiAlH_4$ into (E,E)-5-chloro-2,4-pentadienol **4a**, and (iii) acetylation (80%). Unfortunately, attempts to couple the acetate **4b** with the Grignard reagent **5** failed.



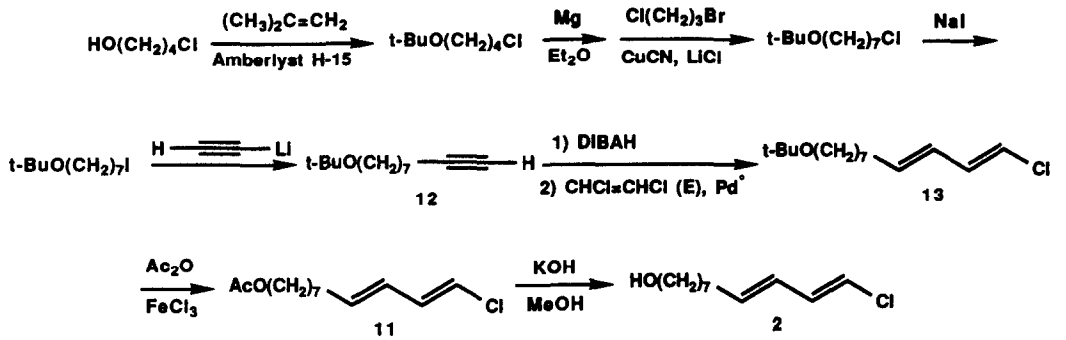
Therefore, we studied another strategy based upon the coupling of (E)-1,2-dichloroethylene with (E)-alkenylalanes which leads to (EE)-1-chloro-1,3-dienes in high stereoisomeric purity [9b,9c].

The hydroalumination is not efficient in the case of alkynols [10]. Therefore, we studied the hydroalumination of a chloro alkyne, (E)-1-chloro-8-nonyne **9** which was obtained from alkynol **7** [11]. Isomerisation of **7** in the presence of sodium amide and diaminopropane [12,13] gave (75% yield) the alkynol **8** which was converted into the corresponding alkyne **9** (85% yield) by treatment with PPh_3 in CCl_4 [14]. Hydroalumination [15] of the alkyne **9** (1 eq.) and coupling of the corresponding alkenylalane with (E)-1,2-dichloroethylene (5 eq.) in the presence of $Pd(PPh_3)_4$ (0.1 eq.) in benzene (16 h, r. t.) afforded in 40% yield, the (E,E) dichlorodiene **10**. This dichloride was then converted into the chloroacetate **11** (64% yield) by treatment with potassium acetate in DMSO, in the presence of a catalytic amount of a phase transfer agent (Aliquat 336) [16]. Saponification of the chloroacetate **11** led to chlorocodlemone **2** (96% yield) in high isomeric purity (≥99.9%).



Scheme 1

An alternative preparation utilized a t-butyl ether as a protective group of the alcohol function. Alexakis *et al.* [17] have pointed out the great advantages of this protective group: preparation and reactivity of ω-t-butoxy Grignard reagents are exactly the same as non-functionalized ones and ω-terbutoxyalkynes undergo smooth hydroalumination with diisobutylaluminium hydride in contrast with the other classical protective groups [10]. Reaction of the (E)-alkenylalane (1 eq.), prepared by hydroalumination [15] of the t-butoxyalkyne **12** [4] (scheme 2), treated with (E)-1,2-dichloroethylene (5 eq.) and $Pd(PPh_3)_4$ (0.1 eq.) in benzene (16 h, r. t.) afforded the (E,E)-chlorodiene **13** in 39% yield after distillation (bp. 100-105°C/0.05 Torr) (≥99.9% isomeric purity). The t-butyl ether **13** was easily cleaved into the corresponding acetate **11** with Ac_2O and $FeCl_3$ in Et_2O (96%) [17]. As previously, saponification of the acetate **11** gave easily the chlorocodlemone **2** (≥99.9% steric purity) [18,19].



Scheme 2

Finally, chlorocodlemone was tested in apple orchards where it exhibited a high pheromonal activity. It was thus shown to be twice as active as the natural pheromone for males *Cydia pomonella*. The results of these tests and other laboratory bioassays will be published later.

References and notes

(1) Roelofs, W.L. ; Comeau, A. ; Hill, A. ; Milicevic, G. *Science* **1971**, *174*, 287.
(2) Camps, F. ; Coll, J. ; Fabrias, G. ; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871.
(3) Carvalho, J.F. ; Prestwich, G.D. *J. Org. Chem.* **1984**, *49*, 1251.
(4) Tellier, F. ; Sauvêtre, R. ; Normant, J.F. *J. Organomet. Chem.* **1989**, *364*, 17.
(5) Svatos, A. ; Kalinova, B. ; Borek, V. ; Vrkoc, J. *Proc. Conf. Insect. Chem. Ecol. Tabor.* **1990**, 41.
(6) Jönsson, S. ; Liljefors, T. ; Hansson, B.S. *J. Chem. Ecol.* **1991**, *17*, 1381.
(7) Samain, D. ; Descoins, C. ; Commerçon, A. *Synthesis* **1978**, *5*, 388.
(8) Tamura, M. ; Kochi, J. *Synthesis* **1971**, *4*, 303.

(9) a) Ratovelomanana, V. ; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315;
b) Ratovelomanana, V. ; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001.
c) Ratovelomanana, V. ; Linstrumelle, G. *Bull. Soc. Chim. France* **1987**, *1*, 174.
(10) Bernady, K.F. ; Floyd, M.B. ; Poletto, J.F. ; Weiss, M.J. *J. Org. Chem.* **1979**, *44*, 1438.
(11) Doolittle, R.E. *Org. Prep. Proc. Int. Rec. Trav. Chim.* **1980**, *12*, 1.
(12) Brown, C.A. ; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891.
(13) Hommes, H. ; Brandsma, L. *Rec. Trav. Chim. Pays Bas* **1977**, *96*, 160.
(14) Weiss, R.G. ; Synder, E.I. *J. Org. Chem.* **1971**, *3*, 403.
(15) Zweifel, G. ; Whitney, C.C. *J. Am. Chem. Soc.* **1967**, *89*, 2753.
(16) Wagenknecht, J.H. ; Baizer, M.M. ; Chruma, J.L. *Synth. Commun.* **1971**, *2*, 215.
(17) a) Alexakis, A. ; Gardette, M. ; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2951;
b) Alexakis, A. ; Duffault, J.M. *Tetrahedron Lett.* **1988**, *29*, 6243.

(18) The products described therein were characterized by spectroscopic and analytical properties: Infrared spectra were measured on a Perkin-Elmer 397 spectrometer (neat, cm^{-1}) and NMR spectra were recorded on a Varian VXR 300 spectrometer ($CDCl_3$;δ(ppm) from TMS, J(Hz)).

IR : 10: 1640, 1585, 975, 730; **13**: 1575, 1450, 1380, 1355, 1190, 1075, 970, 810; **11**: 3060, 3010, 1735, 1570, 1235, 1030, 975, 810, 720; **2**: 3340, 3050, 3010, 1575, 1450, 1050, 970, 810, 720.

^{1}H NMR : 10: 1.22-1.52 (m,8H), 1.76 (q,2H), 2.08 (q,2H), 3.54 (t,2H); **13**: 1.18 (s,9H), 1.20-1.60 (m,10H), 2.05 (q,2H), 3.32 (t,2H); **11**: 1.31 (m,8H), 1.60 (q,2H), 2.04 (s,3H), 2.06 (m,2H), 4.05 (t,2H); **2**: 1.31 (m,8H), 1.54 (q,2H), 1.99 (s,1H), 2.06 (q,2H), 3.61 (t,2H); **10,13,11,2**: (data of the double bond system are the same) 5.69 (dt,H^8), 5.96 (ddt,H^9), 6.07 (d,H^{11}), 6.40 (dd,H^{10}), JH^8H^9=15.2, $JH^{10}H^{11}$=13.1, JH^9H^{10}=10.7, JH^7H^8=6.9, JH^7H^9=1.3.

^{13}C NMR : 10: 5.2, 26.7, 28.6, 28.9, 32.5, 45.0, 65.8, 118.3, 126.1, 133.8, 135.9; **13**: 26.2, 27.6, 29.0, 29.1, 29.4, 30.7, 32.6, 61.6, 72.4, 118.2, 126.1, 133.9, 136.3; **11**: 21.0, 25.9, 28.6, 28.97, 29.03, 29.1, 32.6, 64.6, 118.4, 126.2, 133.9, 136.1, 171.25; **2**: 25.7, 29.0, 29.1, 29.3, 32.6, 32.7, 62.9, 118.3, 126.1, 133.9, 136.2.

Mass spectra were obtained by using a Nermag R10X10.

2: m/z: 166, 114, 101, 96, 90, 88 (100%), 79, 67, 55.

(19) The stereoisomeric purity of the products was evaluated by gas chromatographic analyses which were performed on a model 2900 Carlo Erba instrument equipped with fused silica capillary column (25 m WCOT 0.32 id FFAP CB, He 0.4 b, temp. inj. 140 to 240°C (5°C/min)).