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STUDIES IN PHEROMONE BIOSYNTHESIS : PREPARATION OF ^{3}H LABELLED PRECURSORS OF DROSOPHILA PHEROMONES

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Abstract: Two synthetic schemes were designed giving access to tritium labelled potential precursors of *Drosophila* pheromones. An intermediate in the first scheme allowed the preparation of [^{3}H]-labelled vaccenyl acetate.

The discovery[1], structural determination[2] and total synthesis[3] of insect pheromones have been landmarks in the development of biology and organic chemistry.

In a recent paper[4] we reported the synthesis of several insect pheromones using Wenkert's method, namely the reaction of Grignard reagents with cyclic enol ethers catalysed by low-valent Ni complexes as a key step.

For obvious reasons, the biosynthesis of insect pheromones is a much less studied field. The extremely small amounts of pheromones produced by insects explain why their biosynthesis has received less attention in spite of its scientific and economic importance.

Having achieved the total synthesis of a contact pheromone of *Drosophila melanogaster*, we naturally turned our attention to some salient features of its biosynthesis.

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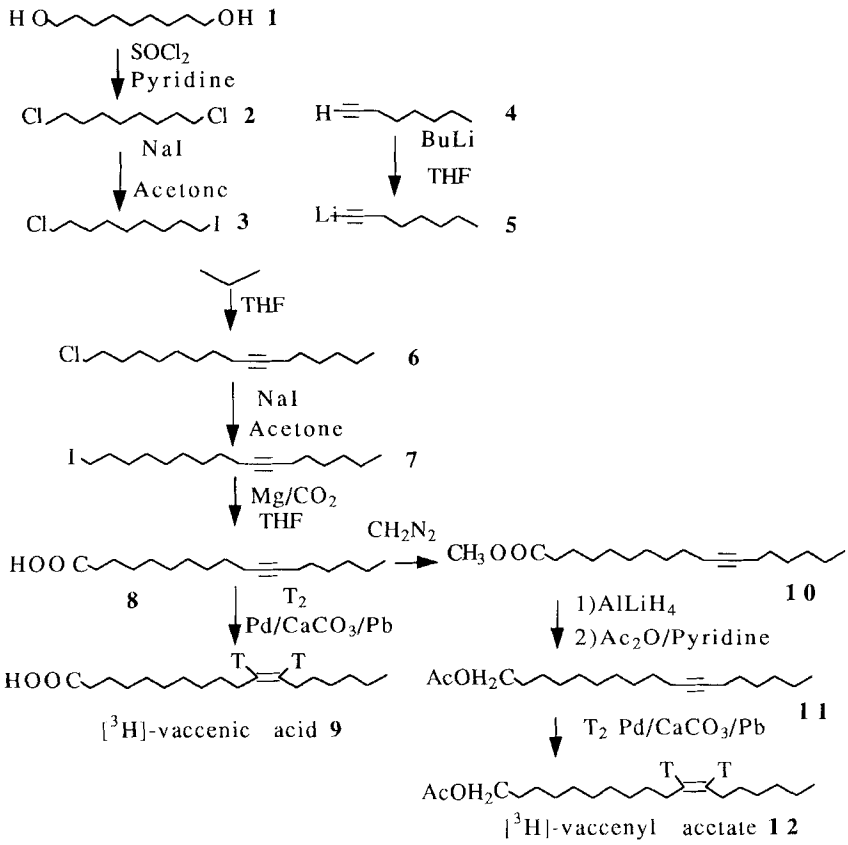
Among others, Jallon *et al.* have provided evidence for female chemical messages in courtship as well as for the presence of aphrodisiacs in *Drosophila* males[5]. Long chain hydrocarbons like (7Z,11Z)-heptacosa-7,11-diene are undoubtedly derived from the homologous carboxylic acids through oxidative decarboxylation. Preliminary experiments with commercially available radioactive precursors aimed at gaining deeper knowledge of the desaturation-elongation sequence have been performed by Jallon's group[5]. They demonstrated that the first double bond is introduced at the palmitic and not the stearic acid level (or their respective biological equivalents). In order to achieve further insight into the desaturation-elongation sequence, we set out to prepare tritium labelled potential precursors. A Δ-11 C_{18} and a Δ-13 C_{20} acid were good candidates for being biological precursors of the cuticular long chain hydrocarbons of *Drosophila*. The presence of vaccenyl acetate in *Drosophila* males pleads in favor of the first possibility, while the participation of a Δ-13 C_{20} acid is backed by the observation that, in several organisms, desaturases are highly specific as to the distance between the carboxyl group and the dehydrogenation site[6].

The design of synthetic schemes for the preparation of labelled compounds must take into account -in addition to standard organic chemistry- a few additional criteria: high specific activity of the final product, introduction of the label in the last step and the possibility to control the specificity of incorporation into the various metabolites. The above mentioned arguments led us to conceive two basically different approaches for the two C_{18} compounds and the C_{20} precursor. From the inception of our studies the possibility of introducing a ^{14}C label at position 1 for future double labelling experiments was considered. The reaction sequence shown in Scheme I allowed the preparation of both [^{3}H]-vaccenic acid **9** -a potential precursor of doubly unsaturated hydrocarbons- and [^{3}H]-vaccenyl acetate **12** -necessary for receptor studies- starting from cheap, commercially available nonane-1,9-diol **1**.

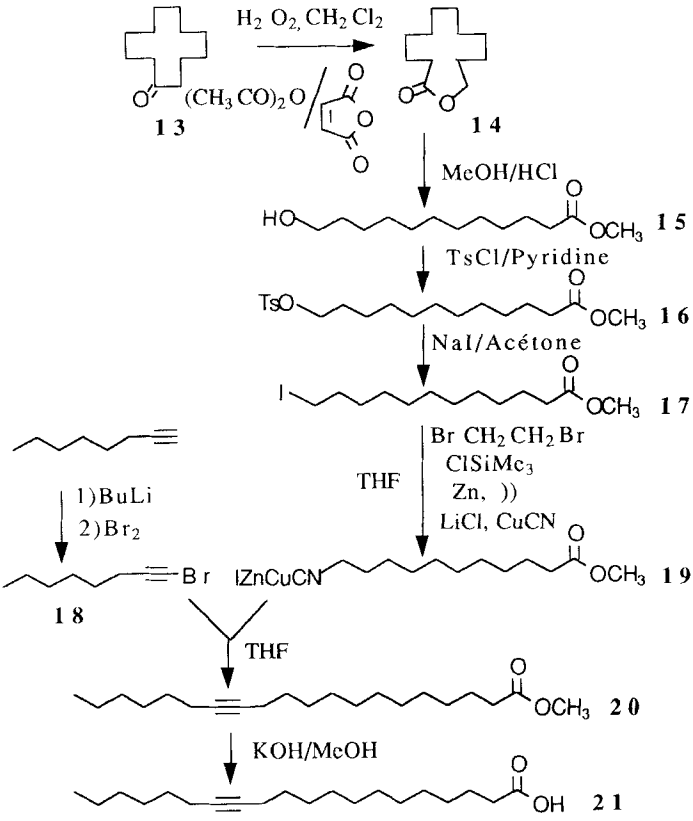
SCHEME I



Classical reactions led to octadec-11-ynoic **8** acid which could be either tritiated directly or transformed into octadec-11-ynyl acetate **11** which provided labelled [^{3}H]-vaccenyl acetate **12** of high specific activity after tritiation.

Since undecane-1,11-diol is not readily available, we decided to prepare the C_{20} acetylenic acid along a totally different pathway. We chose cyclododecanone **13** as a cheap starting material. Scheme II depicts the synthesis of compound **21**. Baeyer-Villiger oxidation of cyclododecanone **13** furnished the lactone **14** which was then transformed into methyl ω-iododododecanoate **17**. At this stage we took advantage of

SCHEME II



Knochel's recently published method[7] for the coupling of the zinc derivative of iodo ester **17** with bromooctyne **18** catalyzed by a mixture of CuCN and Me_3SiCl. Sonification of the reaction mixture was necessary in order to obtain reasonable yields of the C_{20} acetylenic ester **20** which was then saponified to produce C_{20} acetylenic acid **21** ready for tritiation.

Experimental Section

Proton NMR spectra were obtained in $CDCl_3$ solutions with its signal as an internal standard (7.24 ppm) using a Bruker AM 200 or AM 250 spectrometer. Carbon-13 NMR spectra were

recorded on the same equipment using the center line of $CDCl_3$ as an internal standard (77.0 ppm).
Elemental analysis were performed by CNRS Microanalysis Service at Gif-sur-Yvette.
Infrared spectra were recorded on a Perkin-Elmer 883.
Routine (EI and CI) mass spectra were recorded on a Ribermag R-10-10 at the University of Paris-Sud Facility.
High resolution mass spectra were taken on a Kratos MS-80 at ICSN, CNRS, Gif-sur-Yvette.
TLC was conducted using Merck silica gel 60 F_{254} precoated plastic sheets. Column chromatography was performed using Meck silica gel (70-230 Mesh).
Pyridine was distilled from KOH, acetone over K_2CO_3.
Tetrahydrofurane and ether were distilled over sodium/benzophenone.

1-Iodo-9-chlorononane **3**

In a 1 l three-necked flask, 86 g (0.436 moles) are dissolved in 200 ml of anhydrous acetone.
The solution is refluxed with vigourous stirring and 65.4 g (0.436 moles) of NaI in 500 ml of anhydrous acetone are added dropwise during 3 h. Reflux is maintained for again 3 h, the reaction mixture is cooled, the solvent evaporated. The residue is taken up in CH_2Cl_2, washed with water and the organic phase is dried over K_2CO_3. 110.9 g of crude residue are obtained after evaporation which are then distilled under vacuum (10^{-2} mm Hg) using a Vigreux column (25 cm). The first fraction distills from 90-85°C (1,9-dichlorononane), the second was collected between 95-105°C (51 g) and contains 80% of the desired 1-iodo-9-chlorononane and was used as such in the following step. In order to obtain analytical data, redistillation of the second fraction gave 23.9 g (19%) of pure 1-iodo-9-chlorononane(GC).

$C_9H_{18}ICl$

^1H NMR (250 MHz): 3.15 (t, 7.5 Hz) -$C\underline{H}_2I$; 3.5 (t, 7.5 Hz) -$C\underline{H}_2Cl$

^{13}C NMR (62.89 MHz): 7.27 (C-1); 45.08 (C-9)

MS (EI): $M^{+\cdot}$ at m/z 288 and 290, m/z=161 and 163 ($M\text{-}I^{\cdot}$)

IR (neat oil): v (cm-1): band at 675 (C-Cl).

Analysis: Calculated: C, 37.46; H, 6.29. Found: C, 37.44; H, 6.27.

1-Chloroheptadec-10-yne **6**

a)Preparation of lithio-octyne-1 **5**:

Freshly distilled octyne-1 (23.45 ml, 0.2 moles) is introduced *via* a septum into a 500 ml two-necked flask under argon

atmosphere followed by 125 ml THF. The mixture is cooled to -5°C and 60 ml of a 1.6 M solution of n-butyllithium in hexane are added dropwise with vigourous stirring.

b)Coupling of lithio-octyne-1 with **3**:

17.4 ml (0.1 moles) of HMPT are added to the solution of lithio-octyne at 0°C followed by 16.94 g (0.049 moles) of **3**. The ice bath is removed and the reaction mixture is stirred overnight at room temperature. After quenching with water, the crude product is extracted with ether, the organic phase is washed with bicarbonate and brine and dried over Na_2SO_4. 20.04 g of crude product are obtained after the evaporation of the solvent. The mixture is first recristallised from hexane and then further purified by careful chromatography on silicagel to yield 3.97 g (30%) of pure 1-chloroheptadec-10-yne.

$C_{17}H_{31}Cl$

^1H NMR (250 MHz): 0.85 (t, 7.5 Hz) -C$\underline{H}_3$; 3.5 (t, 7.5 Hz) -C$\underline{H}_2$Cl.

^{13}C NMR (62.89 MHz): 45.05 (C-1); 80.0 and 80.09 (C-10 and C-11).

MS (EI): $M^{+\cdot}$ at m/z 270 and 272, m/z=161 and 163 ($M-I^{\cdot}$).

IR (neat oil): ν (cm-1): 2235 (triple bond).

Analysis: Calculated: C, 75.35; H, 11.54. Found: C, 75.13; H, 11.58.

1-Iodoheptadec-10-yne **7**

To a solution of 9.83 g (0,047 moles) of **6** in 20 ml of anhydrous acetone is added under reflux a solution of 6.34 g (0,042 moles) of NaI in 35 ml of acetone. The mixture is refluxed overnight, then filtered and the filtrate is evaporated. The residue is dissolved in CH_2Cl_2, washed with water and the organic phase is dried over K_2CO_3. After evaporation of the solvent, 10.2 g of crude product are obtained, which are chromatographied over silicagel providing a fraction, 6.37 g, 37% yield of pure 1-iodoheptadec-10-yne.

$C_{17}H_{31}I$

^1H NMR (250 MHz): 0.85 (t, 7.5 Hz) -C$\underline{H}_3$; 2.10; 3.15 (t, 7.5 Hz) -C$\underline{H}_2$I.

^{13}C NMR (62.89 MHz): 7.29 (C-1); 80.13 and 80.26 (C-10, C-11).

MS (EI): $M^{+\cdot}$ at m/z 362 and 272.

IR (neat oil): ν (cm-1): 2361 (triple bond)

High resolution measurement of the molecular peak calculated for $C_{17}H_{31}I$: 362,1472. Found: 362,1461.

11-Octadecynoic acid **8**

In a 50ml two-necked flask, 2 ml of anhydrous THF and 2.37

ml of EtBr are added to 770 mg of Mg previously dried at 100°C. After addition of 18 ml of THF, the reaction of Mg is completed by heating to reflux.

After cooling to room temperature, the above Grignard derivative of ethyl bromide is added to a mixture of 3 g (8.3 mmoles) of **7** and 201 mg of freshly dried Mg in 20 ml of anhydrous THF. When the spontaneous reaction slows down, the mixture is refluxed for 3 h. CO_2 gas is then bubbled into the solution via a needle and the reaction is continued in a CO_2 atmosphere at room temperature overnight.

The resulting mixture is then acidified with 10% HCl, extracted with ether, the organic phase washed with water, dried over Na_2SO_4 and evaporated to yield 2.53 g of crude product. 1.89 g (81%) of pure **8** (GC after methylation with CH_2N_2) are obtained after chromatography over silicagel (hexane/ethyl acetate, 98/2).

$C_{18}H_{34}O_2$

F=45-46°C

^1H NMR (250 MHz): 0.9 (t, 7.5 Hz) -C<u>H</u>$_3$; 2.15 (t, 7.5 Hz) -C<u>H</u>$_2$≡C<u>H</u>$_2$- ; 2.36 (t, 7.5 Hz) -C<u>H</u>$_2$COOH.

^{13}C NMR (62.89 MHz): 14.05 (C-18); 80.0 and 80.09 (C-11 and C-12); 179.55 (C-1).

MS (CI/NH_3): M+18 at m/z 298.

IR (KBr): ν (cm-1): 1688 (CO).

Analysis: Calculated: C, 77.09; H, 11.50. Found: C, 77.00; H, 11.25.

<u>Octadec-11-ynol</u>

1 g of 11-octadecynoic acid was methylated with an excess of freshly prepared diazomethane and the resulting ester was used as such after evaporation of the solvent. The residue is dissolved in 40 ml of anhydrous THF and then added dropwise to a suspension of 0.129 g of LiAlH4 in 40 ml of anhydrous THF. After 4.5 h at room temperature, the reaction mixture is acidified with 10% HCl, extracted twice with ether, the combined organic phases are washed with $NaHCO_3$ and brine and dried over Na_2SO_4. 598 mg of crude product are obtained after evaporation yielding 330 mg (35%) of pure alcool after purification over silicagel (hexane/ethyl acetate: 0→10%).

$C_{18}H_{34}O$

^1H NMR (250 MHz): 0.85 (t, 7.5 Hz) -C<u>H</u>$_3$; 3.6 (t, 7.5 Hz) -C<u>H</u>$_2$OH.

^{13}C NMR (62.89 MHz): 14.04 (C-18); 80.19 and 80.23 (C-11 and C-12).

MS (EI): $M^{+\cdot}$ at m/z 266.
IR (KBr): ν (cm-1): 3153 (OH)
Analysis: Calculated: C, 81.13; H, 12.86. Found: C, 80.88; H, 12.69.

Octadec-11-ynyl acetate **11**

300 mg of octadec-11-ynol are acetylated with acetic anhydride and pyridine under standard conditions and purified by flash chromatography (hexane/ethyl acetate= 95/5). The major fraction provides 231 mg(70%) of pure acetate.

$C_{20}H_{36}O_2$
^{1}H NMR : 0.85 (t, 7.5 Hz) -C$\underline{H}_3$; 2.05 (s) OCOC$\underline{H}_3$; 4.05 (t, 7.5 Hz) -C$\underline{H}_2$OAc.
^{13}C NMR : 14.04 (C-18); 80.0 (C-11 and C-12); 173.0 (CO).
MS (EI): $M^{+\cdot}$ at m/z 308, m/z=248 (M-CH_3COOH).
IR (KBr): ν (cm-1): 1744 (CO).
Analysis: Calculated: C, 77.86; H, 11.76. Found: C, 78.15; H, 11.71.

Determination of the Hydrogenation Conditions for Tritiation:

A series of preliminary hydrogenations was undertaken in order to determine the best conditions for both the yield and the selectivity of the reaction. An intensive survey of the literature[9] favoured a rapid filtration over silicagel of the acetylenic precursor. The following optimised procedures were adopted and used for tritiation:

10 mg dissolved in 3 ml of ethyl acetate of acetylenic precursor were filtered through a micro-column containing 500 mg of silicagel. The filtrate was evaporated to dryness. A double-necked flask was used for the hydrogenation procedure. For the preparation of *Z*-vaccenic acid, 7.5 mg of Lindlar catalyst in 1 ml of a mixture of toluene/pyridine (6/1) were treated with vigourous stirring in a H_2 atmosphere. 5mg of the acetylenic precursor in 1 ml of the same solvent mixture were then added through a rubber septum. The reaction was controlled by GC (after methylation with diazomethane). Under these conditions, optimum yield and selectivity (i.e. absence of starting material and saturated acid) were achieved after 3 h.

Slightly different conditions had to be adopted for the hydrogenation (and tritiation) of **11**. 15 mg of Lindlar catalyst are necessary but the reaction is complete after 1 h.

Under the above reaction conditions, **8** and **11** were tritiated

by Amersham to give [^{3}H]-vaccenic acid **9** and [^{3}H]-vaccenyl acetate **12** of high specific activity and excellent radiochemical purity. Using pure tritium instead of hydrogen, the following data could be measured for the two labelled compounds:

[11,12-$^3H_2$]-(11Z)-octadec-11,12-enoic acid :

Specific activity: 1,83 TBq/mmol, 49,5 Ci/mmol
6,43GBq/mg, 174 mCi/mg

Molecular weight (as determined by MS) : 285

Radiochemical purity: 95-99% (5 different solvent systems and two different absorbents were used).

[11,12-$^3H_2$]-(11Z)-octadec-11,12-enyl acetate:

Specific activity: 1,74 TBq/mmol, 47 Ci/mmol
5.55GBq/mg, 150mCi/mg

Radiochemical purity: 98-99% as determined TLC and HPLC in4 different solvent systems.

Dodecanolide **14**

In a three necked flask, 160 ml of CH_2Cl_2 and 125 ml of acetic anhydride are cooled to 0°C. 100 ml of hydrogen peroxide are added through a dropping funnel. After 1 h, 100 g of maleic anhydride are added in portions and the resulting mixture is stirred for 1 h with frequent temperature control (0°C). The addition of 25 g of **13** leads to spontaneous reflux, which ceases after about 15 mn. The solution is then heated to reflux for 15 h. After cooling, the precipitate maleic acid is filtered, the filtrate is then washed with H_2O, 10% Na_2SO_4, 10% KOH and brine and finally dried over Na_2SO_4. 22 g (81%) of dodecanolide are obtained after evaporation of the solvent.

$C_{12}H_{22}O_2$

^{1}H NMR : 2.35 -C$\underline{H_2}$CO; 4.15 -C$\underline{H_2}$O.

^{13}C NMR : 64.4 (C-12); 174.0 (C-1).

MS (CI/NH_3): $M^{+\cdot}$ at m/z 198.

IR (neat oil): ν (cm-1): 1736 (CO).

Analysis: Calculated: C, 72.68; H, 11.18. Found: C, 72.87; H, 11.12.

Methyl 12-hydroxydodecanoate **15**

Dry gaseous HCl is bubbled through a solution of 20 g of dodecanolide in 35 ml of anhydrous MeOH at 0°C. When the solution is saturated with HCl, the reaction is continued for 5 h at room temperature. The MeOH is then evaporated, the residue is dissolved in Et_2O and the organic phase is washed several times with water and dried over Na_2SO_4. 17.15 g (73%) are obtained after evaporation of the solvent.

$C_{13}H_{26}O_3$
F= 31-33°C
^{1}H NMR : 0.9 (t, 7.5 Hz) -C<u>H</u>$_3$; 2.25 (t, 7 Hz) -C<u>H</u>$_2$CO-; 3.60 (t, 7 Hz) -C<u>H</u>$_2$-OH; 3.65 (s) -O-C<u>H</u>$_3$.
^{13}C NMR (62.89 MHz): 51.41 (C-12); 62.95 (C-13); 174.45 (C-1).
MS : EI : the molecular peak is not observed, major fragment at m/z= 200 (M-H_2O).
CI/NH_3: M+18 at m/z 248 and M+1 at m/z 231.
IR (KBr): ν (cm-1): 1736 (CO).
Analysis: Calculated: C, 67.77; H, 11.38. Found: C, 68.14; H, 11.33.

<u>Methyl 12-tosyloxydodecanoate</u> **16**

10 g (0.043 moles) of methyl hydroxydodecanoate are tosylated under standard conditions (pyridine, excess tosyl chloride, room temperature) to provide 13.5 g (81%) of the title compound.
$C_{20}H_{32}O_5S$
F= 36-37°C
^{1}H NMR : 2.25 (t, 7 Hz) -C<u>H</u>$_2$CO-; 3.65 (s) -O-C<u>H</u>$_3$; 7.3-7.7 aromatic protons.
^{13}C NMR (62.89 MHz): 51.39 (C-12); 70.64 (C-13); 174.26 (C-1).
MS : CI/NH_3: M+18 at m/z 402 and M+1 at m/z 385.
IR (KBr): ν (cm-1): 1736 (CO).
Analysis: Calculated: C, 62.48; H, 8.39; S, 8.32. Found: C, 62.62; H, 8.40, S, 8.45.

<u>Methyl 12-iodododecanoate</u> **17**

4.2 g (0.028 moles) of NaI in 38 ml of anhydrous acetone are added dropwise through a dropping funnel to a solution of 10 g (0.025 moles) of methyl tosyloxydodecanoate in 38 ml of anhydrous acetone in a three-necked bottle at reflux. At the end of reaction (TLC), the solvent is evaporated, the residue is dissolved in CH_2Cl_2 and the organic phase is washed with sodium thiosulfate, water and brine, dried over Na_2SO_4 and the solvent evaporated. 8.34 g of crude product are obtained, yielding 3.6 g (42%) of pure product after Kugelrohr distillation (180°C, 10^{-2}mm Hg).
$C_{13}H_{25}O_2I$
^{1}H NMR : 2.25 (t, 7.5 Hz) -C<u>H</u>$_2$CO-; 3.14 (t, 7.5 Hz) -C<u>H</u>$_2$I; 3.65 (s) -O-C<u>H</u>$_3$.
^{13}C NMR (62.89 MHz): 7.25 (C-12); 174.19 (C-1).
MS : (EI) : $M^{+\cdot}$ at m/z 340.

IR (neat oil): ν (cm-1): 1741 (CO).
High resolution analysis of the molecular ion peak:
Calculated for $C_{13}H_{25}O_2I$: 340.0919; Found: 340.0910

1-Bromooctyne **18**

1-Bromooctyne was prepared according to reference[10] and freshly distilled before use.

Methyl eicosa-13-ynoate **20**

a) Formation of the zinc derivative of iodoester:
Applying described techniques[7] to our synthesis, only poor yields were obtained. The following procedure gives finally the best results: in an ultrasound reactor[8], powdered zinc (1.635 g, 25 mmoles) is activated with 40 µl of trimethylsilyl chloride for 30 mn. 3.4 g (10 mmoles) of iodoester **17** are added, the volume is adjusted to 5 ml (2M concentration). After ultrasound irradiation during 130 mn, the reaction is stopped after 73% transformation (GC analysis).
b) Preparation of the cooper-zinc reagent **19**:
895 mg (10 mmoles) of CuCN and 770 mg of (10 mmoles) of LiCl and 10 ml of anhydrous THF are placed into a three-necked flask and deoxygenated in an argon stream. The resulting solution is cooled to 0°C and the above zinc derivative is added through a syringe via a rubber septum. The reaction mixture is further stirred during 1 h at 0°C.
c) Coupling reaction of **18**
The above reaction mixture is then cooled to -20°C and 1.89 g of freshly distilled **18** are added. Cooling is removed and the stirring is continued for 15 h. The reaction is then quenched by addition of a saturated solution of NH_4Cl followed by extraction with hexane. After usual work up, 3.05 g of crude product containing 63% of the desired ester (plus methyl laurate resulting from reduction) were obtained. The chromatographic purification of this mixture turned out to be difficult. We therefore saponified 500 mg of the reaction products (KOH, MeOH), obtaining 370 mg of crude acids. Repeated cristallisation from hexane provided 50 mg (10% yield based on iodododecanoate) being more than 99% pure. (GC after methylation by diazomethane).
$C_{20}H_{36}O_2$:
F=51-52°C (from hexane)
^1H NMR : 0.90 (t, 7.5 Hz) -$C\underline{H}_3$; 2.15 (t, 7.5 Hz) -$C\underline{H}_2$–≡–$C\underline{H}_2$-; 2.36 (t, 7.5 Hz) -$C\underline{H}_2$COOH.

^{13}C NMR : 14.05 (C-20); 80.23 (C-13, C-14); 174.19 (C-1).
High resolution analysis of the molecular ion peak:
Calculated for $C_{20}H_{36}O_2$: 308.2715; Found: 308.2718

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