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AN ALTERNATIVE SYNTHESIS OF UNSATURATED ALDEHYDOPHEROMONES

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Abstract—The pheromone 7(Z)-tetradecenal and its isomer 7 (E)-tetradecenal were synthesized in four steps from commercially available starting materials.

Among the hundreds of pheromones isolated and structurally defined during the last decade, there is a large group of aldehydes which contain one double bond (E or Z).[1,2] 7(Z)-Tetradecenal, which belongs to this group, has been used successfully for field control of the citrus flower moth, *Prays citri*, in Israel[3] and the amount required for this is of the order of 100 gram per year. The conventional method for synthesis of these pheromones, based on well-established procedures[4,5]

$$HO(CH_2)_mOH \rightarrow Br(CH_2)_mOH \rightarrow Br(CH_2)_mOR \rightarrow CH_3(CH_2)_nC{\equiv}C(CH_2)_mOR \rightarrow CH_3(CH_2)_nC{\equiv}C(CH_2)_mOH \rightarrow$$

$$\rightarrow CH_3(CH_2)_n\overset{Z/E}{C}{=}C(CH_2)_mOH \rightarrow CH_3(CH_2)_n\overset{Z/E}{C}{=}C(CH_2)_{m-1}\overset{O}{\overset{\|}{C}}H$$

This seven-step process has two main drawbacks: occasionally unsatisfactory yields of halohydrins starting from corresponding diols[6], and the need for addition and removal of protecting groups. In the present paper we describe a four-step procedure based on inexpensive, commercially available, starting materials. In brief, this is based on the synthesis of a symmetric bifunctional intermediate which gives the desired aldehyde in the final step. Specifically, this has been applied to the synthesis of 7(Z)-tetradecenal and of its isomer 7(E)-tetradecenal; however it is probably of more general applicability.

At an early stage of this work we prepared the heneicosa-7(Z)-14(Z)-diene **2**, by a reaction between heptanal and the Wittig reagent prepared from 1,7-dibromoheptane using n-butyllithium in THF as base. The heneicosadiene was isolated in satisfactory yield; however under these conditions geometric stereospecifity was not satisfactory, the product being contaminated by isomers having E geometry as indicated by PMR and CMR (see Tables 1 and 2).

$$CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}H + [BrPPh_3(CH_2)_3]_2CH_2 \rightarrow [CH_3(CH_2)_5CH{=}CH(CH_2)]_2CH_2$$

Indeed, GC-analysis using a 25-m^2 capillary column showed E-isomers were present to the extent of more than 20%. In view of these results, coupled with problems arising from using triphenyl phosphine and butyl lithium on a commercial scale, this approach was abandoned.

A more satisfactory route which was employed is:

$$2CH_3(CH_2)_5C{\equiv}CH + (BrCH_2CH_2)_2CH_2 \longrightarrow \underset{\mathbf{1}}{[CH_3(CH_2)_5C{\equiv}C(CH_2)_2]_2CH_2}$$

$$\longrightarrow \underset{\mathbf{2}}{[CH_3(CH_2)_5\overset{Z}{C}H{=}CH(CH_2)_2]_2CH_2} \longrightarrow \mathbf{2} + \underset{\mathbf{4}}{[CH_3(CH_2)_5\underset{H}{\overset{O}{C}}{-}\underset{H}{\overset{O}{C}}(CH_2)_2]_2CH_2} +$$

$$\underset{\mathbf{3}}{CH_3(CH_2)_5\underset{H}{\overset{O}{C}}{-}\underset{H}{\overset{O}{C}}(CH_2)_5\overset{Z}{C}H{=}CH(CH_2)_5CH_3} \longrightarrow \underset{\mathbf{5}}{CH_3(CH_2)_5\overset{Z}{C}H{=}\overset{O}{\overset{\|}{C}}H(CH_2)_5CH}$$

Table 1. ^{1}H NMR[a]

Compound	$\underset{H}{}$C=CH-	-H$_2$C-CH=	$\underset{H}{\overset{O}{C}}{-}\overset{O}{C}$
2 (Z)	5.33	2.07	
6 (E)	5.4	2.03	
3 (Z)	5.33	2.07	2.75
7 (E)	5.4	2.0	2.53
4 (Z)			2.75
8 (E)			2.53
5 (Z)	5.33	2.03	
9 (E)	5.4	2.0	

[a]Given as δ values.

Table 2. ^{13}C NMR[a] shift values.

1 $(CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH \equiv C - CH_2 - CH_2)_2CH_2$

14.5 23.2 32.1 29.8 29.4 19.3 80.8 80.8 19.3 29.4 28.7

2 $(CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH \overset{Z}{=} CH - CH_2 - CH_2)_2 CH_2$

14.75 23.4 32.5 30.4 29.8 28.0 130.7 130.7 28.0 29.8 30.4

6 $(CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH \overset{E}{=} CH - CH_2 - CH_2)_2 CH_2$

14.75 23.4 32.5 30.3 29.6 33.3 131.1 131.1 33.3 29.6 29.4

3 $CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH \overset{Z}{=} CH - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH\underset{O}{\diagup\!\diagdown}CH - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH_3$ (cis)

14.6 23.3 32.5 30.4 29.9 27.8 130.3 130.8 27.8 27.2 28.5 57.75 57.75 28.5 27.2 32.5 23.3 14.6

130.8 130.3

7 $CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH \overset{E}{=} CH - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH\underset{O}{\diagup\!\diagdown}CH - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH_3$ (trans)

14.75 23.3 32.5 30.3 29.5 33.3 130.8 131.3 33.3 26.7 32.8 59.6 59.6 32.8 26.7 32.5 23.3 14.7

131.3 130.8

5 $CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH \overset{Z}{=} CH - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - C\overset{O}{\overset{\|}{H}}$

14.5 23.2 32.2 30.2 29.4 27.6 129.9 130.7 27.6 22.5 44.3 202.6

130.7 129.9

9 $CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - CH \overset{E}{=} CH - CH_2 - CH_2 - CH_2 - CH_2 - CH_2 - C\overset{O}{\overset{\|}{H}}$

14.65 23.2 32.3 30.2 29.4 33.2 131.5 130.4 32.9 22.5 44.4 203.2

130.4 131.5

[a]In ppm down field from TMS in $CDCl_3$.

The first step involves alkylating 1-octyne (3 equiv) with 1,5-dibromopentane in liquid ammonia in the presence of lithium amide as base and HMPA as a cosolvent, a reaction which could be carried out on a 0.3 mol scale with an 88% yield. Dimethyl sulfoxide was found unsatisfactory, as cosolvent since its use led to the formation of sulfur-containing by-products which could not be removed by chromatography or distillation, and which were found to inhibit the subsequent hydrogenation.

The diacetylene product **1** was found to polymerize above 120°, unless, it was distilled in the presence of a stabilizer (2,6 - di - t - butyl - *p* - cresol). However, the crude product was sufficiently pure for the hydrogenation step, which could be carried out in hexane using Lindlar catalyst on a 100 g scale with near quantitative yields. The isolated diene **2** was found to be >99% Z-isomer.

The third step appears problematical, involving as it does a specific oxidation of one of two identical double bonds.[7] Epoxidation using one equivalent of *meta*-chloroperbenzoic acid,[8] gave the expected 1:2:1 mixture of starting material **2** monoepoxide **3** and diepoxide **4** respectively, which could be quantitatively resolved by simple column chromatography on silica.

The direct conversion of the epoxide to an aldehyde group was the final step. This was effected by periodic acid in ether.[9] On a 100 g scale the yield of purified product was 82%; this proved to be biologically active in field tests.[3]

We then examined the possibility of using this approach in the synthesis of corresponding unsaturated aldehydes with E-geometry, since a number of known pheromones are of this type.[10] To this end it was necessary to reduce diacetylene **1** to diene **6**. In our hands reduction with lithium in liquid ammonia at −38° failed, with recovery of starting material, the reason clearly being the low solubility of the C_{21} hydrocarbon in liquid ammonia, even in presence of various ethers as cosolvents.

On the other hand, reduction using LAH in refluxing diglyme for 24 h[11] was successful, giving diene **6** in 84% yield and >96% purity (GC). The latter was now converted into 7(E)-tetradecenal **9** in two steps as described for compound **5**.

Spectral data for the Z- and E-isomers those prepared was substantially differentiated to allow for clear assignment of structure in each case. Thus, in the PMR spectrum of the dienes the vinyl protons appeared at 5.33δ in the Z- and 5.4δ in the E-isomers, and the allyl protons showed similar difference. The most pronounced differentiation however, was shown by the mono and diepoxides (a similar case has been reported previously[12]) (see Table 1).

The CMR spectrum leads itself to similar interpretation, again in good agreement with literature data.[12,13] The availability of similar compounds enable us to assign a chemical shift to nearly every carbon atom in the compounds examined. Here again differences in chemical shifts are much more pronounced in case of the epoxides.

Although this approach was designed for a specific C_{14}-pheromone having a double bond at position 7, it is obviously valid for aldehydes of different chain length and with a double bond at other positions.

The above discussion presents a general method for synthesis of compounds used by certain insects for purpose of chemocommunication. The advantages of the method are the readily available and inexpensive starting materials, the small number of steps, and the high yields, moreover, either the Z- or E isomer is obtainable from the product of the first step, as desired.

EXPERIMENTAL

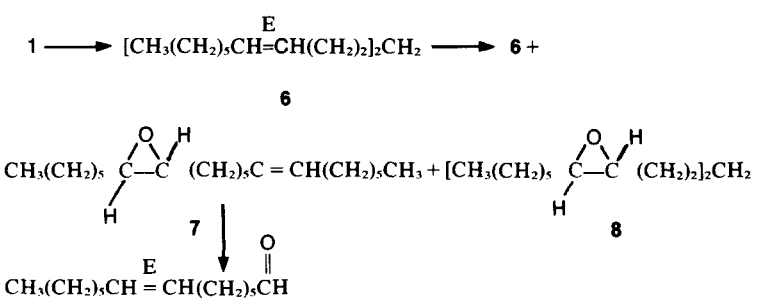
1-Octyne and 1,5-dibromopentane were obtained commercially and used as received. NMR spectra were recorded on 60 MHz Varian T60, and CMR on Bruker WP-60. Mass spectra were recorded on Varian MAT 711. Gas chromatograms were obtained on F & M-810 column A (SE-30, Chromosorb Q, 2 m) and on Packard-427 column B (SE-30, Capillary column, 25 m) carrier gas helium flow 1 ml/min. Silica gel Woelm 100–200, aktiv I (02747).

Heneicosa-7,14-diyne **1**

Lithium amide was prepared from lithium (6 g, 0.86 mol) in 2500 ml of dry ammonia in the usual way. To the stirred solution at −78° octyne (78 g, 0.71 mol) was added dropwise 0.5 h. 1,5-Dibromopentane (70 g, 0.3 mol) in 200 ml of dry hexamethyphosphorictriamide were added dropwise during 1 h. The ammonia was removed at room temperature, 750 ml of brine were added and the orgaic phase was dissolved in 300 ml of hexane and washed five times with 200 ml of water dried over magnesium sulphate, and the solvent was removed. The crude diyne was purified through a short column of 150 g silica gel and eluted with methylene chloride–hexane 1:5 to yield 76 g (88%) of **1**. NMR (CCl_4) δ2.1 (m, 8H), 1.37 (m, 22H), 0.94 (t, 6H); MS for $C_{21}H_{36}$ at 288, 2724 (theory 288, 2816). ^{13}C NMR ($CDCl_3$) 80.81, 32.11, 29.77, 29.39, 28.74, 23.17, 19.29, 14.49. Glc Column A flow 50 ml/min/200°; retention time 6.7 min.

Heneicosa-7(Z), 14(Z)-diene **2**

50 g (0.174 mol) of **1** were dissolved in 200 ml of hexane and reduced over 2 g of 10% Pd on calcium carbonate poisoned with 5 drops of quinoline. Uptake of 8.4 L of hydrogen at atmospheric pressure took 3h, the catalyst was filtered and the solvent removed under reduced pressure to yield 50 g (98%) of **2**. NMR (CCl_4) δ5.33 (t, 4H), 2.07 (br s, 8H), 1.38 (s, 22H), 0.98 (t, 6H); ^{13}C



NMR ($CDCl_3$) δ130.67, 32.5, 30.42, 29.78, 27.96, 23.43, 14.75; MS for $C_{21}H_{40}$ at 292.3164 (theory 292.3129). [*m/e* (rel intensity) 292 (M^+, 14.79). Glc Column B flow 1 ml/min/150°; retention time 72 min.

Heneicosa-7(E), 14(E)-*diene* **6**

5 g of diyne **1** (17.4 mmol) were dissolved in 100 ml of diglyme, added dropwise to 10 g lithium aluminium hydride in 50 ml of diglyme and refluxed for 24 h. To the reaction mixture were added 200 ml of 10% hydrochloric acid and 300 ml of water, and the organic compound was extracted with 250 ml hexane. The solution was dried over magnesium sulphate and the solvent removed under reduced pressure to yield an oily compound which was filtered over 40 g of silica gel and eluted by hexane to yield 4.25 g (84%) of **6**. NMR (CCl_4) δ5.40 (b t, 4H), 2.03 (b s, 8H), 1.38 (s, 22H), 0.98 (t, 6H); ^{13}C NMR ($CDCl_3$) δ131.06, 33.27, 32.49, 30.29, 29.64, 29.38, 23.43, 14.75; MS for $C_{21}H_{40}$ at 292.3129 (theory 292.3129) [*m/e* (rel intensity) 292 (M^+, 23.23)]. Glc Column B/150°; retention time 75.2 min.

cis-7,8-*Epoxy*-14(Z)-*Heneicosene* **3**

To a stirred solution of 100 g (0.34 mol) diene in 500 ml methylene chloride at 0°C were added dropwise during 2h 66g (0.34 mol) of *m*-chloroperbernzoic acid 90% disolved in 1000 ml of methylene chloride. The *m*-chlorobenzoic acid was filtered off and the solution was washed with 5% sodium carbonate water and dried over magnesium sulphate. The solvent was removed under reduced pressure to yield 100 g of a crude mixture containing 1:2:1 of **2**, **3**, **4** according to gas chromatography. The mixture was separated over 200 g of silica gel to yield 23 g of **2** eluted with hexane and 51.7 g (50%) of **3** eluted with hexane: methylene chloride 2:1. Elution with methylene chloride yielded 15 g of diepoxide **4**. **3**: NMR (CCl_4) δ5.33 (t, 2H), 2.75 (b s, 2H), 2.07 (b d, 4H), 1.4 (b s, 26H), 0.97 (t, 6H). ^{13}C NMR ($CDCl_3$) δ 130.80, 130.28, 57.75, 32.50, 30.43, 29.91, 28.48, 27.84, 27.19, 23.30, 14.62 M.S. for $C_{21}H_{40}O$ at 308.3094 (theory 308.3079). **4** NMR (CCl_4) δ2.75 (b s, 4H), 1.48 (b s, 30H), 0.97 (t, 6H). MS for $C_{21}H_{40}O_2$ at 324.3035 (theory 324.3028); Glc **2**, **3**, **4** on column A 50 ml/min 200°; retention time 5.8, 10.8, 18 min respectively.

trans-7,8-*Epoxy*-14(E)-*heneicosene* **7**

1 g (0.0034 mol) of **6** were oxidized as described for oxidation of **3** to yield 450 mg (0.0015 mol) of **7** in 44% yield and 250 mg of **6** were recovered. **7**: NMR (CCl_4) δ5.40 (t, 2H), 2.53 (b s, 2H), 2.0 (b s, 4H), 1.4 (b s, 26H), 0.97 (t, 3H). ^{13}C NMR ($CDCl_3$) δ131.32, 130.80, 59.57, 33.27, 32.76, 32.50, 30.29, 29.78, 29.52, 26.67, 23.30, 14.75. MS for $C_{21}H_{40}O$ at 308.3056 (theory 308.3079). Elution with methylene chloride yielded 200 mg (20%) of diepoxide **8**. NMR (CCl_4) δ2.53 (b s, 4H), 1.5 (b s, 30H), 0.98 (t, 6H).

7(Z)-*Tetradecenal* **5**

15 g (0.049 mol) of monoepoxide **3** were dissolved in 30 ml of dry ether and added at once to mechanically stirred solution of 16.7 g (0.073 mol) anhydrous periodic acid H_5IO_6 in 700 ml ether at 0°C under nitrogen. After 30 min additional 10 g (0.04 mol) of periodic acid were added in ether and the reaction mixture was stirred for 1 h. To the cooled solution were added 400 ml of buffer solution pH 7.3, the organic layer was removed and the aqueous layer extracted three times with 100 ml of ether. The combined organic extracts were washed with 100 ml of buffer solution and dried over anhydrous magnesium sulphate. The solvent was removed on a rotatory evaporator to yield 10.5 g of crude oil. The oil was stabilized with D.B.P.C. and distilled at reduced pressure under nitrogen to yield the main fraction at 100°, 0.1 mm Hg, 8.5 g (0.4 mol) of **5** yield 82%. NMR (CCl_4) δ9.83 (t, 1H), 5.33 (t, 2H), 2.4 (t, 2H), 2.03 (b d, 4H), 1.37 (s, 14H), 0.95 (t, 3H). ^{13}C NMR ($CDCl_3$) δ202.6, 130.7, 129.9, 44.3, 32.2, 30.2, 29.4, 27.6, 23.2, 22.5, 14.5. Glc Column B 100°C; retention time 10 min. Prog 100–170° (5°/min); retention time 93 min. MS for $C_{14}H_{26}O$ at 210.1978 (theory 210.1983).

7(E)-*Tetradecenal* **9**

7 (0.5 g) was oxidized as described for **5** to yeild **9** in 80% yield. NMR (CCl_4) δ9.8 (t, 1H), 5.4 (t, 2H) 2.4 (t, 2H), 2.0 (m, 4H), 1.4 (s, 14H) 0.98 (t, 3H). ^{13}C NMR ($CDCl_3$) δ203.2, 131.5, 130.4, 44.4, 33.2, 32.9, 32.3, 30.2, 29.8, 29.4, 29.2, 23.2, 22.5, 14.65. MS for $C_{24}H_{26}O$ at 210.1989 (theory 210.1983). Glc Column B 100°; retention time 10 min. Prog 100–170° (5°/min); retention time 94 min.

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