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A Practical Synthesis of the Sex Pheromone of the Pink Bollworm

P. E. Sonnet

United States Department of Agriculture, Agricultural Environmental Quality Institute, Agricultural Research Service, Beltsville, Maryland 20705

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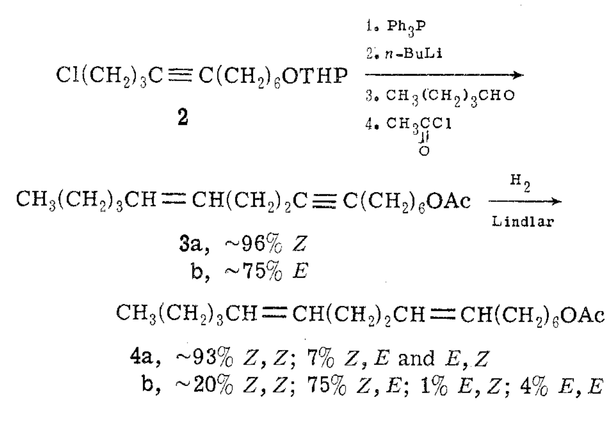
The sex pheromone of the pink bollworm moth, *Pectinophora gossypiella*, is a 1:1 mixture of (*Z,Z*)- and (*Z,E*)-7,11-hexadecadien-1-ol acetates.[1] The presence of the other two isomers of this diene, or a distinctly different ratio of the two natural isomers, causes a loss in potency of the mixture.[2] We sought to develop a route to the two desired isomers, or mixtures thereof, that would be sufficiently free of the other isomers, and that could be used to prepare the quantities of material required for testing and for subsequent control efforts. Preferably such a route would require no more than simple or fractional distillations for purification of intermediates and would avoid column chromatography. Our earlier efforts to synthesize the dienes involved the coupling of allylic Grignard reagents[2,3] and the elaboration of 1,5-hexadiyne[2] and were only partially successful. Another synthesis has been recently reported, but overall yields are low and isomer composition was determined only by infrared data.[4] We report here a useful route that starts with hexamethylene chlorohydrin (see Scheme I).

Scheme I



$$\mathrm{Cl(CH_2)_6OTHP} \xrightarrow{\mathrm{LiC{\equiv}CH}} \underset{\textstyle 1}{\mathrm{HC{\equiv}C(CH_2)_6OTHP}} \xrightarrow[\text{2. }\mathrm{Cl(CH_2)_3Br}]{\text{1. }n\text{-BuLi}}$$

$$\underset{\textstyle 2}{\mathrm{Cl(CH_2)_3C{\equiv}C(CH_2)_6OTHP}} \xrightarrow[\substack{\text{3. }\mathrm{CH_3(CH_2)_3CHO}\\ \text{4. }\mathrm{CH_3\underset{\overset{\|}{O}}{C}Cl}}]{\substack{\text{1. }\mathrm{Ph_3P}\\ \text{2. }n\text{-BuLi}}}$$

$$\mathrm{CH_3(CH_2)_3CH{=}CH(CH_2)_2C{\equiv}C(CH_2)_6OAc} \xrightarrow[\text{Lindlar}]{\mathrm{H_2}}$$

3a, ~96% *Z*
b, ~75% *E*

$$\mathrm{CH_3(CH_2)_3CH{=}CH(CH_2)_2CH{=}CH(CH_2)_6OAc}$$

4a, ~93% *Z,Z*; 7% *Z,E* and *E,Z*
b, ~20% *Z,Z*; 75% *Z,E*; 1% *E,Z*; 4% *E,E*

The tetrahydropyranyl ether (THP) of the chlorohydrin was treated with lithium acetylide ethylenediamine complex to give the THP of 7-octyn-1-ol (**1**)[5] in 84% yield. The lithium salt of this acetylene was added to a solution of 1-bromo-3-chloropropane in HMPA–THF to obtain the γ-chloropropylated acetylene, **2** (53% yield); unreacted **1** could be recovered (36%). The triphenylphosphonium salt of **2** was converted to an ylide with *n*-butyllithium in HMPA–THF and allowed to react with valeraldehyde. The use of HMPA as a cosolvent in Wittig condensations has been shown to produce olefins that are ≃96% cis.[6] The resulting THP of (predominantly) (*Z*)-11-hexadecen-7-yn-1-ol was transformed directly to the acetate, **3a** (58% yield from the phosphonium salt). Although **3a** was not resolved by capillary gas chromatography, the diene acetate, **4a**, obtained by hydrogenation of **3a** over Lindlar catalyst was separated into two peaks (7:93). The major peak was identical with a previously prepared sample of the *Z,Z* isomer.[2] The *Z,E* and *E,Z* pair were not distinguishable. Since catalytic hydrogenation of the acetylene was expected to produce about 3–4% (*E*)-7 double bond and the directed Wittig reaction was expected to produce about 4% (*E*)-11 double bond, the minor peak was assumed to be a composite of the *Z,E* and *E,Z* isomers in roughly equal proportions.

Attempts to produce (*E*)-11-hexadecen-7-yn-1-ol THP from **2** by Schlosser's modification to the Wittig reaction[7] failed. Also, the use of a less polar solvent (toluene) increased the proportion of trans, but the cis linkage still predominated. Isomerization of **3a** with aqueous nitrous acid at 70–75°[8] isomerized the 11 double bond to a mixture in which trans predominated, **3b**. This treatment does not shift the double bond;[9] also the gas chromatograms of the diene acetate, **4b**, resulting from hydrogenation of **3b** gave no indication of position isomerization. The *Z,Z* glc peak constituted 20% of the mixture; hence the *E,Z* content could only be ~1%, and the major peak, 75%, must be almost entirely *Z,E*. The *E,E* isomer, ~4%, was due to that proportion of the hydrogenation of **3b** that produced the 7 trans double bond.

Although the synthesis does not produce either desired isomer absolutely pure (to date no reported synthesis does), it is clear that **4a** and **4b** may be relatively easily prepared and that a combination of the two preparations will give the desired isomer ratio with only a few per cent of the unwanted *E,Z* and *E,E* isomers. Preliminary tests revealed that a blend of these preparations is as attractive to male pink bollworm moths as those preparations currently available.[10]

Experimental Section

Boiling points are uncorrected. Ir spectra were determined in CCl_4 using a Perkin-Elmer Model 457A grating spectrophotometer.[11] Nmr spectra were taken in CCl_4 on a Varian Associates T-60 spectrometer and chemical shifts are reported in parts per million (δ) downfield relative to TMS as internal standard. Glc analyses were performed with an Aerograph 1520 instrument employing an SE-30 column (0.92 m × 0.63 cm 5% on Anakrom ABS), and the analyses of the diene acetates were performed with a Hewlett–Packard 5720A instrument employing an EGGS-X SCOT column (15 m × 0.05 cm). Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn.

7-Octyn-1-ol Tetrahydropyranyl Ether (1). This compound was prepared as described:[5] yield from hexamethylene chlorohydrin THP, 84%: bp 83–90° (0.25 mm); $n^{25}\mathrm{D}$ 1.4580 [lit.[4] $n^{25}\mathrm{D}$ 1.4590].

11-Chloro-7-undecyn-1-ol Tetrahydropyranyl Ether (2). Compound 1 (80 g, 0.38 mol) was converted to a lithium salt by adding *n*-butyllithium (206 ml of 2.04 *M* in hexane) to a solution of 1 in THF (200 ml) that was kept under nitrogen and at 0–5° with an ice bath. The resulting solution was transferred to a dropping funnel and then added dropwise to a solution of 1-bromo-3-

chloropropane (48.5 ml, 0.45 mol) in HEMPA–THF (200 ml of each) under nitrogen and kept at −20° with a Dry Ice–methanol bath. The bath was allowed to attain room temperature, and the mixture was kept overnight. The mixture was diluted with cold H_2O and worked up in the usual manner. Distillation (short path) provided 28.5 g of recovered 1 (36%) and 57.8 g of 2 (53%): bp 155–165° (0.8 mm); $n^{25}D$ 1.4757; nmr δ 3.3–4.0 (m, 6, CH_2O, CH_2Cl), 4.50 (bs, 1, OCHO).

Anal. Calcd for $C_{16}H_{27}ClO_2$: C, 66.99; H, 9.49; Cl, 12.36. Found: C, 66.97; H, 9.29; Cl, 12.28.

(*Z*)-11-Hexadecen-7-yn-1-ol acetate (3a). Triphenylphosphine (43.3 g, 0.165 mol) and 2 (45 g, 0.157 mol) were heated at 145° under nitrogen for 16 hr. Magnetic stirring was required because the mixture became heterogenous for a time during the course of the reaction. The cooled mixture was agitated with ether several times. The ether washes, which contained unreacted starting materials, were stored for subsequent salt preparations. The oily salt (72.2 g, 84% yield) was dissolved in THF (260 ml) and transferred to a 1-l. three-neck round-bottom flask for the Wittig reaction. The solution was placed under nitrogen and cooled to ~ −5° (ice–methanol bath). Conversion to the ylide was effected by adding *n*-butyllithium (64.5 ml, 2.04 *M*) beyond the permanent coloration point. HMPA (130 ml) was added to this solution (no difference in product was noted if *n*-butyllithium was added to a salt solution in both solvents). Valeraldehyde (14.0 ml, 0.131 mol) was added to the mixture at one time. The bath was removed, and the mixture was stirred for 1 hr. The crude product was obtained by dilution of the mixture with H_2O and extraction with petroleum ether. Replacement of the tetrahydropyranyl group by acetyl was effected by warming the crude product at 35–40° for 16 hr in a mixture of acetyl chloride (13.9 ml) and HOAc (140 ml). The presence of triphenylphosphine oxide (TPO) was not deleterious. The acetate, **3a**, was isolated by dilution of the mixture (H_2O) and extraction (petroleum ether). Filtration of the crude acetate through 85 g of alumina with petroleum ether removed most of the TPO. Distillation (short path) afforded 21 g (58%) of **3a**: bp 145–150° (0.7 mm); $n^{25}D$ 1.4628; ir 1740, 975 cm^{-1} (trans, optical density extrapolatd to a 1.0 *M* solution, 0.12); nmr δ 1.93 (s, CH_3CO), 3.97 (bt, 2, CH_2O), 5.32 (bt, 2, CH=).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.42 H, 10.70.

(*Z,Z*)-7,11-Hexadecadien-1-ol Acetate (4a). Hydrogenation of **3a** (5.6 g, 20 mmol) was carried out in pentane (60 ml) with 5% Pd on $BaSO_4$ (250 mg) and quinoline (0.25 ml).

The product was worked up in the usual manner and distilled (short path) giving **4a** (4.7 g, 84%): bp 137–146° (0.5 mm); $n^{25}D$ 1.4578; ir 1740, 975 cm^{-1} (trans, optical density extrapolated to a 1.0 *M* solution, 0.20); nmr δ 1.95 (s, CH_3CO), 3.97 (bt, 2, CH_2O), 5.28 (bt, 4, CH=); analysis by capillary glc discussed in text.

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.00; H, 11.32.

Isomerization of 3a to 3b and Subsequent Reduction to 4b. Compound **3a** (5.0 g, 17.9 mmol) was warmed under nitrogen to 70–75°. Aqueous $NaNO_2$ (1.25 ml of 2 *M*) and HNO_3 (0.85 ml of 6 *M*) were added. The mixture was stirred vigorously for 0.5 hr. The crude product was diluted with petroleum ether, washed with H_2O, dried ($MgSO_4$), and concentrated. Filtration through alumina (20 g) with petroleum ether was followed by distillation to give **3b** (3.7 g, 74%): bp 150–160° (0.5 mm); $n^{25}D$ 1.4601; ir 1740, 975 cm^{-1} (much more intense).

Hydrogenation of **3b** (5.6 g, 19.5 mmol) as described for **3a** gave **4b** (4.5 g, 80%): bp 125–135° (0.3 mm); $n^{25}D$ 1.4564; ir 1740, 975 cm^{-1} (trans, optical density extrapolated to a 1.0 *M* solution, 1.30); nmr, virtually identical with **3b**; analysis by capillary glc discussed in text.

Registry No.—**1**, 16695-31-1; **2**, 53042-77-6; **3a**, 53042-80-1; **3b**, 53042-78-7; **(*Z,Z*)-4**, 52207-99-5; **(*Z,E*)-4**, 51607-94-4; **(*E,Z*)-4**, 53042-79-8; **(*E,E*)-4**, 53042-81-2; 1-bromo-3-chloropropane, 109-70-6; triphenylphosphine, 603-35-0; valeraldehyde, 110-62-3.

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(11) Mention of a proprietary product does not constitute an endorsement by the USDA.

Proton Nuclear Magnetic Resonance Spectra of 1,2-Disubstituted Acenaphthenes

Sever Sternhell* and P. W. Westerman[1]

Department of Organic Chemistry, The University of Sydney, N.S.W. 2006, Australia

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In conjunction with the study[2] of the nmr spectra of 1-substituted acenaphthenes, and as an extension of our earlier examination[3] of the additivity of substituent effects on chemical shifts, we have analyzed the benzylic portions of the nmr spectra of several 1,2-disubstituted acenaphthenes. The results are shown in Table I. It can be seen that in the five-membered ring of acenaphthene chemical shift relationships are found to be similar to those observed previously[5a] in a limited range of compounds with three-membered rings and in several multiring structures. That is, where a substituent (*e.g.*, Cl, CH_3, OH, OAc) deshields a trans proton (dihedral angle ≈120°) with respect to an eclipsed proton in the fragment 1, the signal resulting from the trans isomer of the related 1,2-disubstituted compound is upfield of the signal resulting from the cis isomer. Where a substituent (*e.g.*, COOH, COOMe) shields a trans proton with respect to an eclipsed proton in the fragment 1 the reverse applies. It follows that stereochemical assignments (*i.e.*, cis–trans relationships) in a 1,2-disubstituted compound, incorporating a flat five-membered ring, may be made from chemical shift data alone, although it can be seen (Table I) that in most cases this relationship is of limited diagnostic utility because the actual differences of chemical shifts may be very small.

1

If $\Delta\delta_x$(gem), $\Delta\delta_x$(cis), and $\Delta\delta_x$(trans) are defined as the differences between the chemical shifts of the geminal, cis-vicinal, and trans-vicinal protons, respectively, in a 1-substituted acenaphthene,[2] and the chemical shift of the corresponding proton in acenaphthene (X = H), then if the principle of simple additivity[3] applies, a value $\Delta\delta_x$(calcd) may be calculated for the benzylic protons in a cis-disubstituted acenaphthene by summing $\Delta\delta_x$(gem) and $\Delta\delta_x$(trans), and for a trans-disubstituted acenaphthene by summing $\Delta\delta_x$(gem) and $\Delta\delta_x$(cis).

It can be seen (Table II) that there is a fair additive relationship between data based on 1-substituted acenaphthenes[2] [$\Delta\delta_x$(calcd)] and experimental data obtained in this work for 1,2-disubstituted acenaphthenes ($\Delta\delta_x$(exptl)). In most cases, the predicted deshielding by the two substituents is slightly more than that observed.

An obvious source of discrepancy between the calculated and experimental results is the possibility of steric distortion in 1,2-disubstituted acenaphthenes.