Carbohydrate Research, 147 (1986) 145–148
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

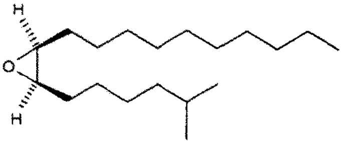
Note

An enantiospecific synthesis of (+)-disparlure from carbohydrate precursors

VEERAPPA B. JIGAJINNI AND RICHARD H. WIGHTMAN
Department of Chemistry, Heriot-Watt University, Edinburgh EH14 4AS (Great Britain)

(Received July 23rd, 1985; accepted for publication, August 15th, 1985)

The sex attractant of the female gypsy moth (*Porthetria dispar*) has been identified as (+)-(7*R*,8*S*)-7,8-epoxy-2-methyloctadecane (**1**), named disparlure[1,2]. Previous syntheses of optically active disparlure have proceeded from L-glutamic acid[2] and (−)-menthyl *p*-toluenesulphinate[3], but separation of diastereoisomers was necessary in both cases. A multistage synthesis from L-tartaric acid has been reported[4], and a synthesis involving resolution is available[5]. More recently, the advent of asymmetric epoxidation has led to efficient chiral syntheses of (+)-disparlure using this approach[6]. We now report an alternative, efficient synthesis of this pheromone from carbohydrate precursors.

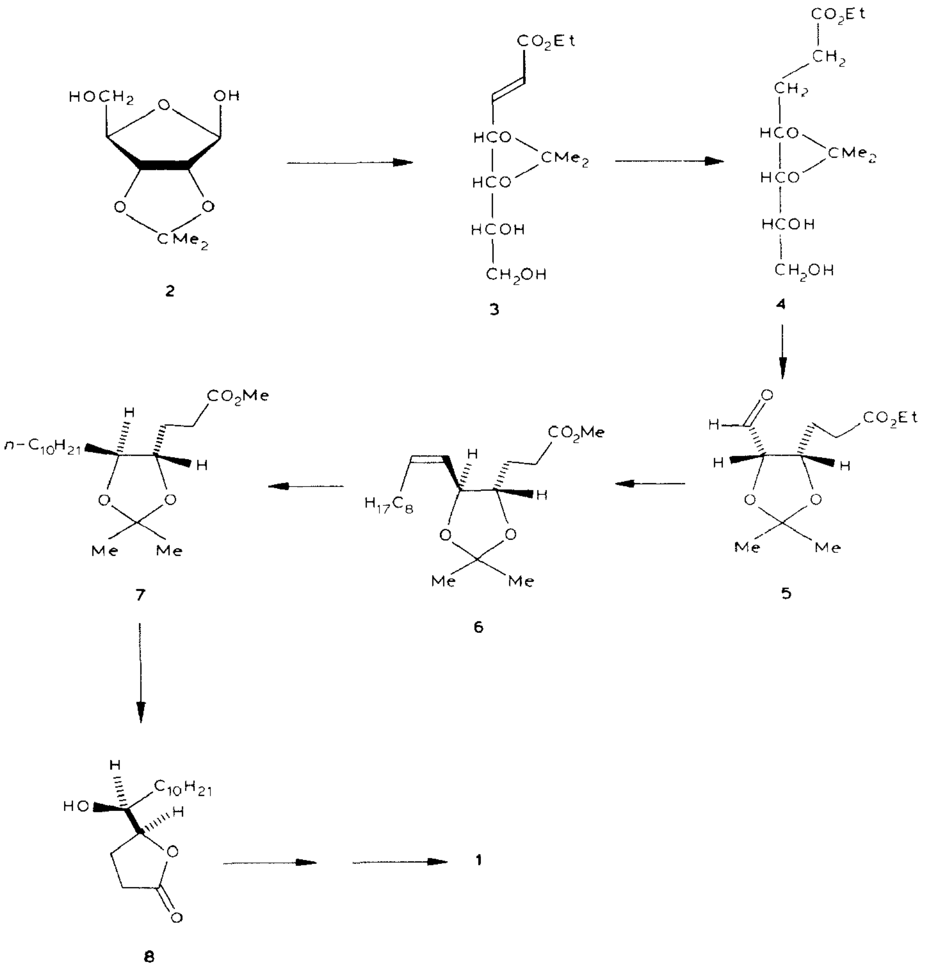


1

Reaction of 2,3-*O*-isopropylidene-D-ribose[7] (**2**) with ethoxycarbonylmethylenetriphenylphosphorane gave the *trans*-alkene **3** which was hydrogenated to yield the saturated ester **4**. This material, or alkene **3**, could be separated from triphenylphosphine oxide by careful chromatography, but it was most convenient to treat **4** directly with sodium periodate to give aldehyde **5** in 81% overall yield from **2**[8]. On treatment with potassium carbonate in methanol, **5** underwent epimerisation to the more stable *trans*-disubstituted dioxolane system[8,9] with concomitant ester exchange; the crude product after epimerisation, which is probably mainly a mixture of diastereomeric hemiacetals[9], was treated with excess of nonylidenetriphenylphosphorane to give the alkene **6** in 79% yield from **5**. That epimerisation to the *trans*-disubstituted dioxolane system had indeed occurred was strongly indicated by the ^{1}H-n.m.r. spectrum of **6**, in which the *gem*-dimethyl

0008-6215/86/$ 03.50

system gave rise to a 6-proton singlet; in *cis*-disubstituted systems such as **3**, **4**, or **5**, the two methyl groups appear at different chemical shifts ($\Delta\delta$ ~0.15). Hydrogenation of the double bond of **6** occurred virtually quantitatively, and the reduced material **7**, on treatment with aqueous trifluoroacetic acid, gave 90% of the crystalline lactone **8** (55% from **2**). This lactone was an intermediate in a previous synthesis of (+)-disparlure (**1**), into which it may be converted in 42% overall yield[2]. The material prepared as described above had physical and spectroscopic properties in excellent agreement with those previously reported[2]; in particular, the ^{1}H-n.m.r. spectrum of **8** showed a multiplet due to H-5 at δ 3.56, with no sign of a signal at δ 3.96 due to the corresponding proton of the 5-epimer[2].



EXPERIMENTAL

General methods. — Optical rotations were measured at room temperature with a Bendix-NPL 143D automatic polarimeter with a pathlength of 1 cm. N.m.r. spectra were recorded for solutions in $CDCl_3$, using a JEOL MH-100, Bruker WP-200, or WH-360 spectrometer. Column chromatography was performed on silica gel (Merck).

Ethyl (4S,5S)-4,5-isopropylidenedioxy-6-oxohexanoate (**5**). — A solution of ethoxycarbonylmethylenetriphenylphosphorane (3.82 g, 0.011 mol) in dichloromethane (20 mL) was added dropwise to a solution of 2,3-*O*-isopropylidene-D-ribose[7] (1.90 g, 0.01 mol) in dichloromethane (40 mL). The mixture was stored overnight and then concentrated, and a solution of the residue in methanol (20 mL) was hydrogenated at 1 atm. using Pd/C (10%, 0.1 g) as catalyst. After hydrogen uptake was complete, the mixture was filtered and concentrated.

Chromatography (ether–toluene, 1:4) of the residue gave the diol **4** (2.35 g, 90%). ^{1}H-N.m.r. data (100 MHz): δ 1.24 (t, 3 H), 1.32, 1.40 (2 s, each 3 H), 2.0 (m, 2 H), 2.5 (m, 2 H), 3.3 (bs, 2 H, exchangeable with D_2O), 3.7 (m, 2 H), 4.1 (m, 5 H).

A solution of crude **4** in methanol (20 mL) was treated with a solution of sodium periodate (2.35 g, 0.011 mol) in water (20 mL). The mixture was stirred overnight at room temperature and then extracted with ethyl acetate. The combined and dried extracts were concentrated to give an oil, column chromatography (toluene–ether, 9:1) of which gave **5** (1.86 g, 81%) as an oil, $[\alpha]_D$ −20° (*c* 0.7, chloroform). ^{1}H-N.m.r. data (100 MHz): δ 1.24 (t, 3 H), 1.40, 1.58 (2 s, each 3 H, CMe_2), 1.9 (m, 2 H, H-2), 4.1 (q, 2 H, ester), 4.3 (m, 2 H, H-4,5), 9.65 (d, 1 H, *J* 3 Hz, CHO). Mass spectrum: *m/z* 215.093 $(M - Me)^{+}$ (calc. for $C_{10}H_{15}O_5$: *m/z* 215.092).

Methyl (4S,5S,6Z)-4,5-isopropylidenedioxypentadec-6-enoate (**6**). — Anhydrous potassium carbonate (0.126 g) was added to a solution of **5** (0.20 g, 0.87 mmol) in dry methanol (10 mL). The mixture was stirred for 2 h, then filtered, and concentrated to an oil. A solution of butyl-lithium in hexane (2 mmol) was added to a stirred suspension of nonyltriphenylphosphonium bromide (0.94 g, 2 mmol) in tetrahydrofuran (10 mL) at 0°, followed after 10 min with a solution of the epimerised aldehyde in tetrahydrofuran (2 mL). The mixture was stirred for a further 2 h, and then partitioned between ethyl acetate and water. The dried organic layer was concentrated, and the oily residue was subjected to column chromatography (ether–hexane, 1:9) to give **6** (0.225 g, 79%) as an oil, $[\alpha]_D$ −77° (*c* 1.1, chloroform). ^{1}H-N.m.r. data (200 MHz): δ 0.9 (t, 3 H), 1.3 (m, 12 H), 1.40 (s, 6 H, CMe_2), 1.85 (m, 2 H, H-3,3), 2.10 (m, 2 H, H-8,8), 2.45 (m, 2 H, H-2,2), 3.65 (m, 1 H, H-4), 3.70 (s, 3 H, OMe), 4.37 (td, 1 H, *J* 9 and 1 Hz, H-5), 5.32 (m, 1 H, $J_{6,7}$ 11, $J_{6,5}$ 9, $J_{6,8}$ 1.5 Hz, H-6), 5.68 (ddt, 1 H, $J_{7,8}$ 7.5, $J_{7,5}$ 1 Hz, H-7). Mass spectrum: *m/z* 311.224 $(M - Me)^{+}$ (calc. for $C_{18}H_{31}O_4$: *m/z* 311.222).

Anal. Calc. for $C_{19}H_{34}O_4$: C, 69.94; H, 10.43. Found: C, 70.20; H, 10.75.

Methyl (4S,5S)-4,5-isopropylidenedioxypentadecanoate (**7**). — A solution of **6** (0.35 g, 1.26 mmol) in methanol (5 mL) was hydrogenated using 10% Pd/C, filtered, and concentrated. Column chromatography (ether–hexane, 1:9) of the residue gave **7** (0.33 g, 95%) as an oil, $[\alpha]_D$ −23° (*c* 0.9, chloroform). ^{1}H-N.m.r. data (200 MHz): δ 0.85 (t, 3 H, Me), 1.3 (m, 16 H), 1.35 (s, 6 H, CMe_2), 1.5 (m, 2 H, H-6,6), 1.8 (m, 2 H, H-3,3), 2.4 (m, 2 H, H-2,2), 3.6 (m, 2 H, H-4,5), 3.67 (s, 3 H, OMe). Mass spectrum: *m/z* 313.239 $(M - Me)^{+}$ (calc. for $C_{18}H_{33}O_4$: *m/z* 313.238).

Anal. Calc. for $C_{19}H_{36}O_4$: C, 69.51; H, 10.98. Found: C, 69.93; H, 11.41.

(4S,5S)-5-Hydroxy-4-pentadecanolide (**8**). — A solution of **7** (0.17 g, 0.52 mmol) in trifluoroacetic acid–water (4:1, 1 mL) was stored for 2 h at room temperature and then concentrated. Column chromatography (ether–hexane, 1:4) of the residue and crystallisation from ethyl acetate–hexane gave **8** (0.12 g, 90%), m.p. 64°, $[\alpha]_D$ +30° (*c* 1.2, chloroform) [lit.[2] m.p. 66°; +29.2° (*c* 1.2, chloroform) for a sample of 89% enantiomeric excess, +25.4° (*c* 0.5, chloroform) for a sample contaminated with 8% of the 5*R* isomer[10]]; $\nu_{max}^{CHCl_3}$ 3300, 1775 cm^{-1}. ^{1}H-N.m.r. data (360 MHz): δ 0.87 (t, 3 H), 1.25 (m, 16 H), 1.5 (m, 2 H), 2.10 (dddd, 1 H, *J* 12.8, 9.95, 8.96, and 7.51 Hz, H-3a), 2.24 (dddd, 1 H, *J* 12.6, 9.45, 7.31, and 5.14 Hz, H-3b), 2.53 (dt, 1 H, *J* 17.8, and ~9 Hz, H-2a), 2.59 (ddd, 1 H, *J* 17.8, 9.93, and 5.17 Hz, H-2b), 3.56 (m, 1 H, H-5), 4.40 (dt, 1 H, *J* 4.58 and ~7.4 Hz, H-4).

REFERENCES

1 J. R. Plimmer, B. A. Leonhardt, R. E. Webb, and C. P. Schwalbe, *A C S Symp Ser.*, 190 (1982) 231–242.

2 S. Iwaki, S. Murumo, T. Saito, M. Yamada, and K. Katagiri, *J. Am. Chem. Soc.*, 96 (1974) 7842–7844

3 D. G. Farnum, T. Veysoglu, A. N. Carde, B. Duhl-Emswiler, T. A. Pancoast, T. J. Reitz and R. T. Cardé, *Tetrahedron Lett.*, (1977) 4009–4012

4 K. Mori, T. Takigawa, and M. Matsui, *Tetrahedron*, 35 (1979) 833–837

5 W. H. Pirkle and P. L. Rinalde, *J. Org. Chem.*, 44 (1979) 1025–1028

6 B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, 103 (1981) 464–565, K. Mori and T. Ebata, *Tetrahedron Lett.*, 22 (1981) 4281–4282.

7 N. A. Hughes and P. R. H. Speakman, *Carbohydr. Res.*, 1 (1965) 171–175

8 R. D. Cooper, V. B. Jigajinni, and R. H. Wightman, *Tetrahedron Lett.*, 25 (1984) 5215–5218.

9 *cf.* A. W. M. Lee, V. S. Martin, S. Masamune, K. B. Sharpless and F. J. Walker, *J. Am. Chem. Soc.*, 104 (1982) 3515–3516

10 M. Larcheveque and J. Lalande, *J. Chem. Soc., Chem. Commun.*, (1985) 83–84