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JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 22
1982

Published on 01 January 1982. Downloaded by Christian Albrechts Universitat zu Kiel on 26/10/2014 01:01:59.

Synthesis of the Two Enantiomeric Forms of *erythro*-6-Acetoxy-5-hexadecanolide, the Major Component of a Mosquito Oviposition Attractant Pheromone

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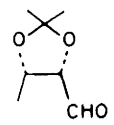
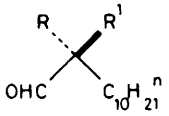
The synthesis of the major component of a mosquito oviposition attractant pheromone, (5*S*,6*R*)-6-acetoxy-5-hexadecanolide (**24**) and the (5*R*,6*S*) enantiomer (**21**) from the (2*S*,3*S*) C_4 aldehyde (**1**), is reported.

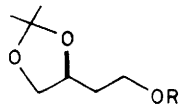
A recent report[1] indicates that *erythro*-6-acetoxy-5-hexadecanolide is the major component of the pheromone from the mosquito *Culex pipiens fatigans* (= *quinquefasciatus*). The racemic synthetic material has a biological activity similar to that of the natural product. γ- and δ-Lactones occur frequently as pheromones and their absolute configuration[2] has often been determined using the two enantiomeric forms obtained by synthesis in a bioassay. This approach takes advantage of the enantioselectivity exerted by insect pheromone chemireceptors. In order to determine the absolute configuration of the natural product, we synthesized (5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**21**) and the (5*S*,6*R*) enantiomer (**24**) using a versatile procedure applicable to the synthesis of other naturally occurring γ- and δ-lactones.



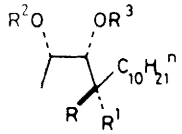
(**1**)



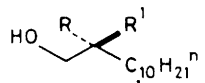
(**8**) R = OCH_2Ph ; R^1 = H
(**9**) R = H ; R^1 = OCH_2Ph



(**12**) R = 4-$MeC_6H_4SO_2$

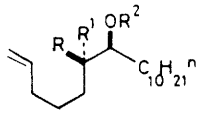


(**2**) R = OH ; R^1 = H ; R^2R^3 = CMe_2
(**3**) R = H ; R^1 = OH ; R^2R^3 = CMe_2
(**4**) R = OCH_2Ph ; R^1 = H ; R^2R^3 = CMe_2
(**5**) R = H ; R^1 = OCH_2Ph ; R^2R^3 = CMe_2
(**6**) R = OCH_2Ph ; R^1 = R^2 = R^3 = H
(**7**) R = R^2 = R^3 = H ; R^1 = OCH_2Ph

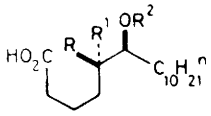


(**10**) R = OCH_2Ph ; R^1 = H
(**11**) R = H ; R^1 = OCH_2Ph
(**13**) R = OH ; R^1 = H
(**14**) R = H ; R^1 = OH

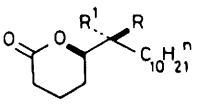
The starting material was the C_4 (2*S*,3*S*) aldehyde (**1**), obtained as described previously,[3] from cinnamaldehyde and acetaldehyde, by the action of baker's yeast. Addition of n-decylmagnesium bromide to (**1**) [tetrahydrofuran (THF), −78 °C], gives (**2**), $[\alpha]_D^{20}$ +8.2°, and the diastereoisomer (**3**), $[\alpha]_D^{20}$ −2°, in *ca.* 6:4 ratio, separated by SiO_2 column chromatography, in *ca.* 55% yield. The two products were *O*-benzylated (NaH, dimethylformamide, $PhCH_2Br$) to give (**4**), $[\alpha]_D^{20}$ −7.6°, and (**5**), $[\alpha]_D^{20}$ −46°, in 95% yield. These were then hydrolysed (50% acetic acid–MeCN) to the benzyloxy diols (**6**), $[\alpha]_D^{20}$ −4.5°, and (**7**), $[\alpha]_D^{20}$ +32°. Compounds (**6**) and (**7**) were oxidized (HIO_4, dry THF, room temp.) (80% yield), to the intermediate C_{12} aldehydes (**8**) and (**9**). The absolute configuration and the optical purity of the two aldehydes, were determined as follows: reduction ($NaBH_4$–MeOH) of (**8**) and (**9**), gave the enantiomeric alcohols (**10**), $[\alpha]_D^{20}$ −17.5°, and (**11**), $[\alpha]_D^{20}$ +17.1°, which upon catalytic hydrogenolysis were transformed into the diols (**13**) and (**14**) (both m.p. 70—70.5 °C). The diols were converted in turn into the



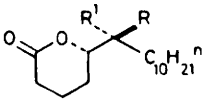
(**15**) R = OH ; R^1 = H ; R^2 = CH_2Ph
(**16**) R = H ; R^1 = OH ; R^2 = CH_2Ph
(**17**) R = OCH_2Ph ; R^1 = H ; R^2 = CH_2Ph
(**18**) R = H ; R^1 = OCH_2Ph ; R^2 = CH_2Ph



(**19**) R = OCH_2Ph ; R^1 = H ; R^2 = CH_2Ph
(**20**) R = H ; R^1 = OCH_2Ph ; R^2 = CH_2Ph



(**21**) R = OAc ; R^1 = H
(**22**) R = H ; R^1 = OAc



(**23**) R = OAc ; R^1 = H
(**24**) R = H ; R^1 = OAc

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corresponding esters with (+)-α-methoxy(α-trifluoromethyl)-phenylacetic acid [(+)-MTPA]. 300 MHz ^{1}H N.m.r. studies on these materials indicated that the products (**13**) and (**14**) were enantiomers and of >95% optical purity. Moreover, compounds (**13**) and (**14**) were assigned the (2*R*) and (2*S*) configuration, respectively, since the (+)-MTPA ester of (**14**) was identical with the compound prepared from (*S*)-malic acid *via* (**12**), and subsequent alkylation and hydrolysis, *via* conventional steps.

Thus, the (2*S*) C_{14} aldehyde (**9**) on treatment with the Grignard reagent prepared from 1-bromopent-4-ene, yielded the C_{17} adduct (**15**), $[\alpha]_D^{20}$ −2.8°, in *ca.* 4:6 ratio with diastereoisomer (**16**), $[\alpha]_D^{20}$ +8.5°, separated by SiO_2 column chromatography, in *ca.* 50% overall yield. Compound (**17**), obtained from (**15**) in quantitative yield, gave the acid (**19**), $[\alpha]_D^{20}$ −2.1°, on ozonolysis and oxidation of the intermediate aldehyde. The acid (**19**) was debenzylated, (H_2, 10% Pd–C) and then converted (acetic anhydride–pyridine) into the (5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**21**), $[\alpha]_D^{20}$ −37.6°, in 65% overall yield from (**15**). The *erythro* configuration of the product (**21**), is assigned on the basis of ^{1}H n.m.r. studies and comparison with an authentic racemic material.[1]

The isomeric C_{17} adduct (**16**) yielded, *via* (**18**) and (**20**), $[\alpha]_D^{20}$ −15.1°, the *threo* (5*S*,6*S*) isomer (**23**), $[\alpha]_D^{20}$ −14.2°. When the (2*R*) aldehyde (**8**) was submitted to the sequence reported for (**9**), (5*R*,6*R*) (**22**), $[\alpha]_D^{20}$ +14.4°, and (5*S*,6*R*) (**24**), $[\alpha]_D^{20}$ +38°, were obtained.

We thank Dr. P. Piccardi, Istituto G. Donegani, Novara, Italy, for his interest in this work. This work has been financially supported by Piano Finalizzato CNR Chimica Fine e Secondaria.

Received, 9th August 1982; Com. 946

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