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SYNTHESIS OF THE TWO ENANTIOMERIC FORMS OF 5-HEXADECANOLIDE PROPOSED PHEROMONE COMPONENT FROM *VESPA ORIENTALIS*

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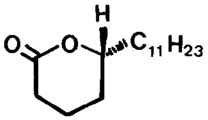
Abstract - The first synthesis of R-(+)-5-hexadecanolide 1 and of it's S isomer 2 has been achieved in 9 steps, from the C_4 chiral synthon 3; the absolute configuration is determined by conversion of the key intermediates 12 and 13 into R-and S-1,2-heptandiol.

5-Hexadecanolide, isolated from the mandibular glands of the oriental hornet *Vespa orientalis*, has been proposed as pheromone playing the rôle of a queen substance.[1] The absolute configuration of the natural product is yet to be defined, since the claim regarding the synthesis of the two enantiomeric forms of 5-hexadecanolide,[2] has not been followed up, in my knowledge, by the results of biological tests. The discrepancy between the physical data of 1 and 2 now obtained, and the ones described in the literature,[2] prompt me to present the synthesis of the enantiomerically pure forms of 5-hexadecanolide, through the unambiguous path outlined below.

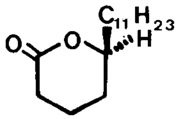
The (2S,3S) aldehyde 3 prepared as previously described[3] from the products obtained from cinnamadehyde, acetaldehyde and fermenting baker's yeast, was reacted with the Grignard reagent obtained from 5-bromo-1-pentene, to give (THF,-70°C,65%) the two diastereoisomeric alcohols[4] 4 $[\alpha]_D^{20}$ +9.4° c=6 and 5 $[\alpha]_D^{20}$ -3.03 c=8 (4:6 ratio), easily separable by flash chromatography. The two purified alcohols were O-benzylated (NaH,DMF,$PhCH_2Br$,90%) to give 6 $[\alpha]_D^{20}$ -8.9° c=1 and 7 $[\alpha]_D^{20}$ -44.4° c=1.8.

When submitted to acidic hydrolysis (50% acetic acid,70°C,1h) the two alcohols 6 and 7, gave the isomeric diols 8 $[\alpha]_D^{20}$ +1.04 c=1 m.p. 86-87°C,and 9 $[\alpha]_D^{20}$+37.74° c=1,in quantitative yield.Periodic acid oxidation (HIO_4,THF,rt) afforded the intermediate aldehydes 10 and 11,which after reduction ($NaBH_4$,MeOH)yielded the alcohols 12 $[\alpha]_D^{20}$ -12.2° c=1.8 and 13 $[\alpha]_D^{20}$ +12.8° c=1.8, in 70% yield from 8 and 9. The absolute configuration and optical purity of compound 12 was determined by quantitative conversion into R-(+)-1,2-heptandiol 14 (H_2,10% Pd/C,MeOH) $[\alpha]_D^{20}$+15.8° c=12 EtOH (lit.[5] +16.8 c=11.8° EtOH). When 13 was catalytically reduced in the same conditions, S-(-)-1,2-heptandiol 15 $[\alpha]_D^{20}$-16.3° c=12 EtOH (lit.[5] -16.6° c=11.9 EtOH) was obtained. Moreover 12 and 13 were transformed into the (+)-α-methoxy-α-trifluoromethyl-phenylacetic acid (MTPA) esters, 16 and 17 respectively. 300 MHz ^1H-NMR studies of these compounds and of artificial mixtures obtained from them, showed the two alcohols 12 and 13 to be more then 95% of each isomer. These experiments show that 12 and 13 have the 2R and 2S absolute configuration respectively, and that they are enantiomerically pure. This procedure also constitutes a convenient approach to both enantiomers of 1,2-heptandiol, a usefull synthon in the synthesis of optically active complex molecules,[5] which are now available from the same chiral starting material 3, in 60% yield from 4 and 5.

The 2R-alcohol 12 was then transformed into the tosylate 18 (TsCl,Py,rt,95%) $[\alpha]_D^{20}$+21.3 c=1.1 which when reacted with n-decylmagnesiumbromide (THF,Li_2CuCl_4) gave the 6S-C_{17}compound 20 $[\alpha]_D^{20}$+1.62° c=2. Ozonation of the latter and oxidative work-up, gave the acid 22 $[\alpha]_D^{20}$ +4.6° c=2 in 70% yield.



1



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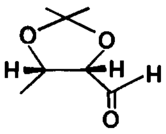

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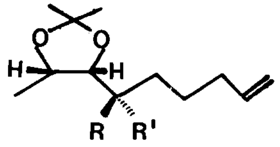
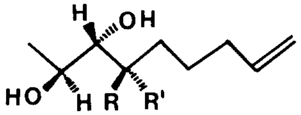
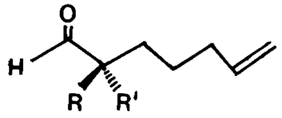


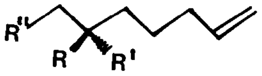
4 R=OH, R'=H 6 R=OCH_2Ph, R'=H
5 R=H, R'=OH 7 R=H, R'=OCH_2Ph



8 R=OCH_2Ph, R'=H
9 R=H, R'=OCH_2Ph

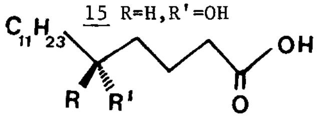


10 R=OCH_2Ph, R'=H
11 R=H, R'=OCH_2Ph



12 R=OCH_2Ph,R'=H,R"=OH
13 R=H,R'=OCH_2Ph,R"=OH
16 R=OCH_2Ph,R'=H,R"=OMTPA
17 R=H,R'=OCH_2Ph,R"=OMTPA
18 R=OCH_2Ph,R'=H,R"=OTs
19 R=H,R'=OCH_2Ph,R"=OTs
20 R=OCH_2Ph,R'=H,R"=$C_{10}H_{21}$
21 R=H,R'=OCH_2Ph,R"=$C_{10}H_{21}$

14 R=OH,R'=H
15 R=H,R'=OH



22 R=OCH_2Ph, R'=H
23 R=H,R'=OCH_2Ph

Catalytic hydrogenation of 22 (EtOAc,10% Pd/C) afforded a mixture of lactone and hydroxy acid, which after SiO_2 chromatography, yielded the lactone 2 as the only product in 90% yield. Crystallization from hexane, gave (S)-(-)-5-hexadecanolide 2 m.p. 40-41°C $[\alpha]_D^{20}$ -39.2° c=1 THF.

When the 2S-alcohol 13 was submitted to the same series of reactions, the tosylate 19 $[\alpha]_D^{20}$-21.8° c=1, compound 21 $[\alpha]_D^{20}$-1.8° c=2,the 5-R acid 23 $[\alpha]_D^{20}$-4.9° c=2 and finally 1, R-(+)-5-hexadecanolide m.p. 40-41°C,$[\alpha]_D^{20}$+39.97° c=1 THF, were obtained in an identical fashion.(The literature data for the two lactones are:[2] R-(+)-5-hexadecanolide 1 $[\alpha]_D^{20}$+2.69° c=0.37 THF. S-(-)-5-hexadecanolide 2 $[\alpha]_D^{23}$-2.65° c=1.13 THF. For the racemic material, m.p.29.5-30°C, is reported.[6])

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REFERENCES AND NOTES

1. R.Ikan,R.Gottlieb,E.D.Bergmann and J.Ishay,*J.Insect Physiol.*,1969, 15, 1709
2. J.L.Coke and A.B. Richon, *J.Org. Chem.*, 1976, 41, 3516
3. G.Fronza,C.Fuganti and P.Grasselli,*J.Chem.Soc.Chem.Commun.* , 1980, 442
4. All isolated compounds have correct spectral and analytical data.$[\alpha]$ values in CH_2Cl_2 unless otherwise stated.
5. J.Barry and H.B.Kagan,*Synthesis*, 1981, 453
6. G.M.Robinson, *J.Chem.Soc.* 1930, 745

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