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ON THE ABSOLUTE STEREOCHEMISTRY OF C-2 AND C-3 IN STEGOBINONE

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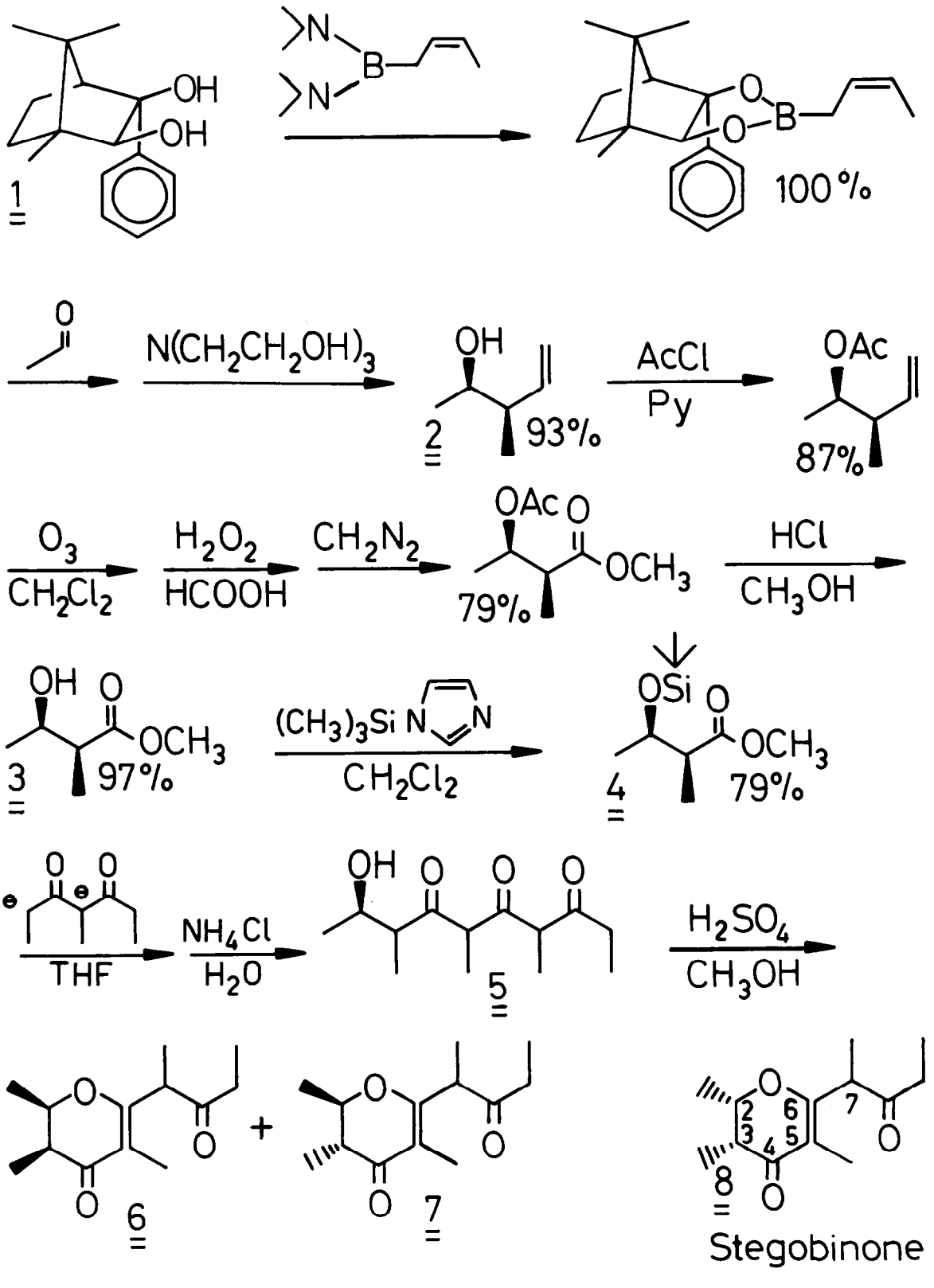
Summary: By comparison of the CD-spectra of synthetic material with that of stegobinone it is established that stegobinone has the 2S,3R-configuration. The stereochemistry at C-7 remains unknown at present.

Stegobinone is the sex pheromone of stegobium paniceum (L.), the drugstore beetle [1]. Its molecular structure has been elucidated [2], whereas the absolute configuration of its three chiral centers is not known yet. Two syntheses [3,4] of racemic material led to a 1:1 mixture of diastereomers at C-7, which has not been separated yet. The biological activity of this mixture was at least 10^3 lower than that of the natural pheromone [4]. Thus either the unnatural antipode of the pheromone or its C-7 epimer are inhibitors of the biological activity. In order to develop a rational synthesis of the optically pure pheromone its absolute configuration had to be established.

Recently we published a diastereoselective synthesis of β-methyl homoallyl alcohols via crotylboronates [5]. The C-C-bond forming reaction of allylboronates can be subjected to chiral modification by 3-endo-phenyl-2-exo-3-=exo-dihydroxy-bornane (1) [6] resulting in enantioselectivities of 65 to 75 %. Therefore it appeared likely that a similar reaction of the Z-crotylboronate of 1 should lead to erythro 3-methyl-pent-1-en-4-ol (2) of predominantly 3R,4R-configuration. This material appeared suitable for further elaboration of 5 and hence of stegobinone.

Reaction of 1 with Z-crotyl-bis-dimethylamino-borane [5] gave a quantitative


OH
OH
1
100 %
O
N(CH2CH2OH)3
OH
2
93%
AcCl
Py
OAc
87%
O3
CH2Cl2
H2O2
HCOOH
CH2N2
OAc O
OCH3
79%
HCl
CH3OH
OH O
OCH3
3
97%
(CH3)3Si N N
CH2Cl2
OSi O
OCH3
4
79%
O O
e e
THF
NH4Cl
H2O
OH O O O
5
H2SO4
CH3OH
O O
O
6
+
O O
O
7
O
2 6
3 4 5
7
O
8
O
Stegobinone

yield of the boronate ester, which was immediately reacted with acetaldehyde. The erythro 3-methyl-pent-1-en-4-ol obtained was contaminated by 2 % of the threo isomer. The enantiomeric purity of 2 could be estimated to be 60 to 70 % by either using Mosher's reagent [7] or $Eu(TFC)_3$ [8] as shift reagent.

In order to convert 2 to the β-hydroxybutyrate 3, the hydroxy group was acetylated first. Subsequent ozonolysis , oxidation and esterification followed by removal of the acetate group gave a high yield of the methyl 3-hydroxy-2-=methyl-butyrate (3) having $[\alpha]_D^{25} = + 9.23°$ (c = 5.2, CH_3OH). This value corresponded to an optical purity of 64 % [9] and substantiated the expected absolute configuration of the obtained 3 as 2S,3R.

Condensation with the dianion of 4-methyl-3,5-heptanedione [10] required prior conversion of 3 to the trimethylsilylether 4. This was treated with two equivalents of the dianion and quenched with aqueous NH_4Cl in order to cleave the silyl ether. After excess diketone was removed under vacuum the residue containing 5 was cyclised with 5 % methanolic H_2SO_4 over night as in the previously reported syntheses. This led to a 2:1 mixture of 6 and 7. The crude mixture was purified by vpc (190° C, 1,8 m column with 5 % SE 30 on chromosorb G-AW-DMCS, 60 to 80 mesh) and medium pressure liquid chromatography on silica gel with CH_2Cl_2 + 3 % Et_2O as eluant, resulting in 16 % (based on 4) of 6 and 11 % of its C-3-epimer 7. The structural assignments rest on the comparison of the 100-MHz-^{1}H-NMR-spectra and the ^{13}C-NMR-spectra with those of the natural product [2] and of the synthetic racemic materials [3,4]. As in the previous syntheses each 6 and 7 were obtained as a 1:1 mixture of epimers at C-7.

Our results show that the stereochemistry at C-3 is lost either during the hydrolytic removal of the trimethylsilyl-group or more likely during the cyclization step. Moreover our samples of 6 and 7 tended to equilibrate even on prolonged storage in a freezer. The obtained 6 was optically active showing $[\alpha]_D^{25}$ + 79.8° (c = 19.8, $CDCl_3$). This mitigates against the mechanism recently proposed for the cyclization of 5 [4].

A comparison of the CD-spectra (in n-hexane) of natural stegobinone and of 6 is given in the table. The maxima due to the enone n-π^* chromophore in the 350 nm region show that our 2R,3S-material 6 is the antipode of natural

stegobinone 8. In the 260 to 280 nm region, characteristic of the π-π^* absorption of the conjugated enone, the CD spectra of synthetic 6 and of natural stegobinone differ considerably both in sign and magnitude of the maxima. This is probably because in the 1:1 mixture of C-7 epimers the expected exciton couplets should compensate, whereas stegobinone appears to be stereochemically homogenous at C-7.

		CD of 6[x)]	CD of Stegobinone[2)]	
358.8 nm	$\Delta\varepsilon$ =	+ 0.49	360	- 0.42
343.4		+ 1.03	345	- 0.87
331.8		+ 1.06		
284.4		- 0.23	285	-13.0
260.8		+ 0.69	260	+ 9.1

x) optical purity $\leq$ 65 %

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