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SYNTHESIS OF 6S,7S-ANHYDRO-SERRICORNINE.

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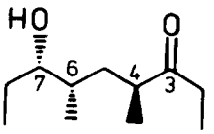
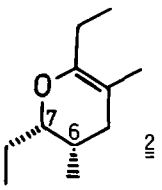
Summary: Diastereoselective and enantioselective reduction of the β-ketoester 3 by yeast to 4 provided the chiral starting material for a synthesis of 4RS,6S,7S-serricornine, having the same configuration as the natural product. This material was converted into optically active and diastereomerically pure 6S,7S-anhydro-serricornine (2).

The cigarette beetle, Lasioderma serricorne F [1] is a pest, feeding on tobacco leaves. Recently a sex pheromone, named serricornine, of this species has been identified as 4,6-dimethyl-7-hydroxy-3-nonanone (1). Following some nonselective syntheses of epimeric mixtures of 1 [2], stereoselective syntheses of the 4RS,6R,7R [3], 4RS,6R,7S [4] and 4S,6R,7R [5] -diastereomers were reported, establishing the natural material to have the 4S,6S,7S-configuration. Due to the lability of 1, identification and comparison of samples were performed with the acetate 11. More recently a second pheromone 2 for this species has been identified [6]. This material, which is significantly more active than 1, has been called anhydro-serricornine. Although its relative and absolute configuration is unknown, its cooccurrence with 1 in the same species suggests that 1 and 2 may have the same configuration at the related stereocenters.

We wish to report here a synthesis of the 4RS,6S,7S-epimers of 1 as well as of 6S,7S-anhydro-serricornine in an optical purity of ≥ 85 %.

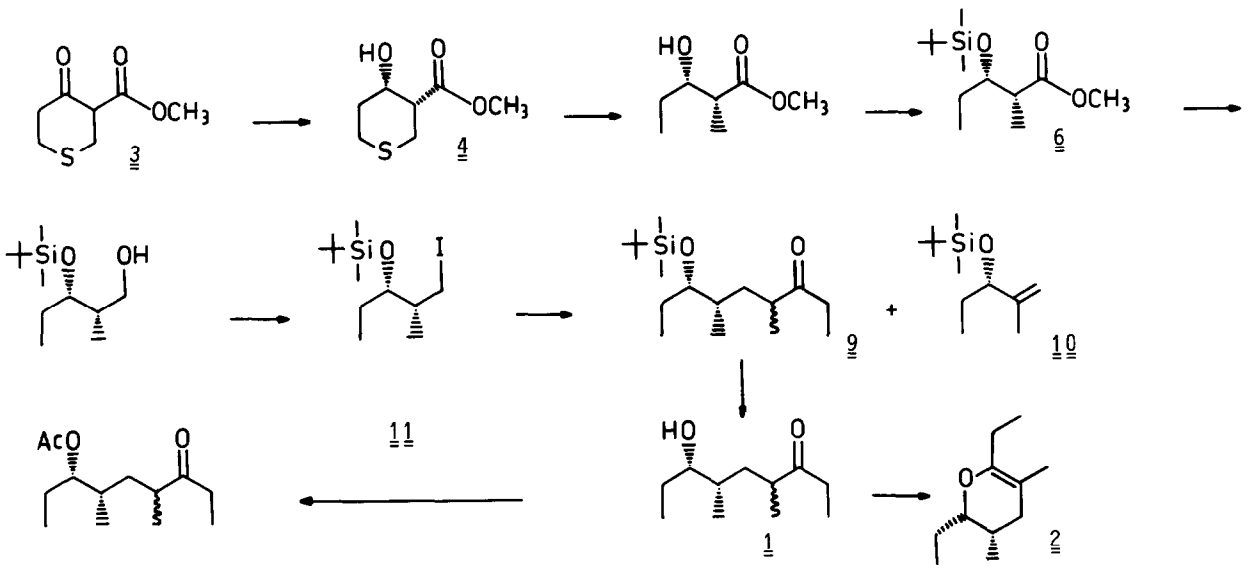




2

Key intermediate in our synthesis is the iodo-compound 8, the enantiomer of which served in one of Mori's syntheses [3] of 1. We envisaged a shorter route to this material by yeast reduction of a β-ketoester. Since the reduction of α-propionyl-=

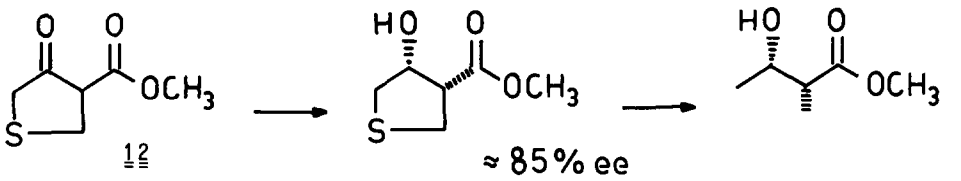
acetate produces the R-enantiomer of low enantiomeric purity [7], the related reduction of α-propionyl-propionate would probably not lead to the alcohol 5 with S-configuration. However, the S-enantio- and diastereoselective reduction of cyclohexanone-2-carboxylate by yeast [8] suggested that 3 [9] could be an appropriate substrate. Its reduction by fermenting yeast furnished 71 % of 4, the diastereomeric purity of which was evident from the ^{13}C-NMR-spectrum. The relative and absolute configuration of the product was assumed to be that shown in 4, by analogy to the yeast reduction of cyclohexanone-2-carboxylate [8]. This assignment was substantiated eventually by the conversion of 4 into 1.



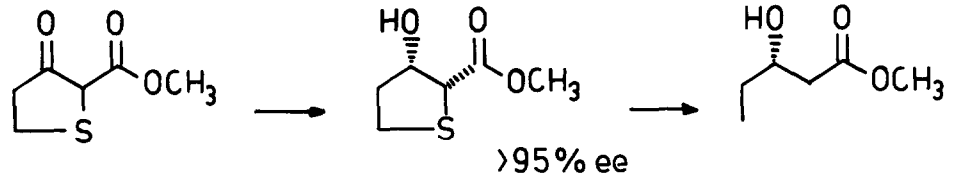
Raney-Ni-desulfurisation of 4 proceeded without epimerization [10] to give 86 % of 5, with a diastereomeric purity of 98 %. The enantiomeric purity of 5 was estimated to be ≥ 85 % by ^{19}F-NMR-analysis of the MTPA-esters [11]. Since the carboxylic acid derived from 4 (KOH/CH_3OH, 96 %) is crystalline, this opens the opportunity to generate optically pure material. In this preliminary study, however, we used 4 as obtained. Its further conversion via 5 to 8 posed no problems: Treatment with tBu-$SiMe_2Cl$/imidazole/DMF furnished 85 % of 6, $[\alpha]_D^{20}$ = + 1.8 (c = 3.78, $CHCl_3$). Subsequent reduction with DIBAH in Et_2O/hexane, yielded 81 % of 7, $[\alpha]_D^{20}$ = -2.6 (c = 1.9, $CHCl_3$). Conversion to the iodo compound 8 (70 %) was accomplished with N-methyl-dicyclohexyl-carbodiimidium iodide [12], in THF, 8: $[\alpha]_D^{20}$ = + 11.7 (c = 3.75, $CHCl_3$).

The elaboration of 8 into 10 followed Mori's [3, 4] route: However, on reaction of 8 with the lithium enolate of diethyl ketone in THF/HMPA we encountered a competing elimination of 8 to 10, which decreased the yield of 9 to 37 %. Deprotection with $(n\text{-Bu})_4N^{\oplus}F^{\ominus}$ in THF and acetylation with Ac_2O/pyridine led to the acetate 11, which was purified by preparative VPC (SE 30, 130 °C). The ^{13}C-NMR spectrum revealed it to be a 1 : 1 mixture of the 4S,6S,7S- and the 4R,6S,7S-isomers, based on the ^{13}C-NMR data documented by Mori [3, 4, 5]. The rotation of $[\alpha]_D^{20}$ = - 18,5 ° (c = 1.08, MeOH) demonstrated that the configuration of our synthetic material corresponds to that of the natural product [1, 3].

The synthesis of 9 opened an access as well to the 6S,7S-isomer of anhydro-= serricornine 2: After deprotection of 9 as above the crude 1 was heated with a catalytic amount of p-toluenesulfonic acid. Crude 2 was distilled at 20 Torr and purified by preparative VPC. (SE 30, 80 °C). It gave a correct elemental analysis and displayed the following data:
^1H-NMR, $CDCl_3$, 400 MHz: 0,841 (d, J = 7,0 Hz, 3H); 0,944 (t, J = 7,4 Hz, 3H); 0,99 (t, J = 7,4 Hz, 3H); 1,31 - 1,38 (m, 2H); 1,48 - 1,60 (m, 1H); 1,549 (s, 3H); 1,88 - 2,14 (m, 4H); 3,54 - 3,58 (m, 1H).
^{13}C-NMR, $CDCl_3$: 148,103; 98,844; 79,007; 35,288; 29,773; 23,544; 23,495; 17,412; 13,548; 12,127; 10,441. $[\alpha]_D^{23}$ = - 61.5 ± 0.5 ° (c = 2.28, $CHCl_3$).



12 ≈ 85% ee



>95% ee

The diastereo- and enantioselective reduction of 3 illustrates how the yeast can be outwitted by offering a cyclic substrate in lieu of an open chain one. We have applied this principle advantageously for the reduction of the tetrahydro-thiophene-derivatives 12 [13] and 13 [14]. The resulting β-hydroxy-esters have been converted by Raney-Ni-desulfurisation into highly useful

chiral building blocks, that are not available in similar diastereomeric [15] or enantiomeric [7] purity by yeast reduction of open chain β-ketoesters.

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References:

1) T. Chuman, M. Kohno, K. Kato and M. Noguchi, Tetrahedron Lett. 1979, 2361.

2) T. Chuman, K. Kato and M. Noguchi, Agr. Biol. Chem. 43, 2005 (1979); M. Ohne, T. Onishi, T. Chuman, M. Kohno and K. Kato, ibid 44, 2259 (1980).

3) K. Mori and H. Nomi, Tetrahedron Lett. 1981, 1127.

4) T. Chuman, M. Kohno, K. Kato, M. Noguchi, H. Nomi and K. Mori, Agr. Biol. Chem. 45, 2019 (1981).

5) M. Mori, T. Chuman, M. Kohno, K. Kato, M. Noguchi, H. Nomi and K. Mori, Tetrahedron Lett. 1982, 667.

6) H. Z. Levinson, A. R. Levinson, W. Francke, W. Mackenroth and V. Heemann, Naturwiss. 68, 148 (1981).

7) F. Fråter, Helv. Chim. Acta 62, 2829 (1979) and references quoted.

8) B. S. Deol, D. D. Ridley and G. W. Simpson, Austr. J. Chem. 29, 2459 (1976).

9) E. A. Fehnel and M. Carmack, J. Am. Chem. Soc. 70, 1813 (1948).

10) cf. R. E. Ireland and F. R. Brown, jr., J. Org. Chem. 45, 1868 (1980).

11) J. A. Dale, D. L. Dull and H. S. Mosher, J. Org. Chem. 34, 2543 (1969).

12) R. Scheffold and E. Saladin, Angew. Chem. 84, 158 (1972); Angew. Chem., Int. Ed. Engl. 11, 229 (1972).

13) P. A. Rossy, W. Hoffmann and N. Müller, J. Org. Chem. 45, 617 (1980).

14) V. E. Kolchin, N. S. Vulfson, Zh. Obshch. Khim 32, 3659 (1962); Chem. Abstr. 58, 13888c (1963).

15) R. W. Hoffmann, W. Ladner, K. Steinbach, W. Massa, R. Schmidt and G. Snatzke, Chem. Ber. 114, 2786 (1981).

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