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A SHORT SYNTHESIS OF (-)-(4*R*,5*S*)-SITOPHILURE USING THE REGIO- AND STEREOSELECTIVE REDUCTION OF 3-ACYLTETRAHYDROTHIOPYRAN-4-ONES WITH BAKER'S YEAST

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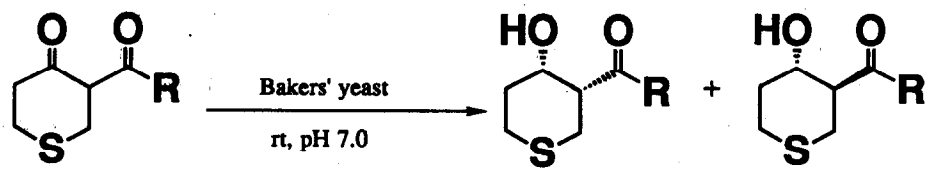
Summary: Bakers' yeast reduction of 3-acyltetrahydrothiopyran-4-ones is regio- and enantioselective, yielding predominantly (3*R*,4*S*)-3-acyl-4-hydroxytetrahydrothiopyranes with high optical purity. This reduction method coupled with the Raney-nickel desulfurization provides a ready access to the rice and maize weevils aggregation pheromone, (-)-(4*R*,5*S*)-sitophilure, in high optical purity.

Optically active β-hydroxyketones represent an important class of functionalized synthons useful in natural products synthesis,[1] and especially pheromones.[2] A simple and direct access to these invaluable synthons is provided by the regio-and stereoselective reduction of their parent dicarbonyl compounds with bakers' yeast. Whereas this method is well documented for acyclic β-diketones,[3] and for non-enolizable 1,3-cycloalkanediones,[1,4] little is known about the yeast-mediated reduction of enolizable cyclic 1,3-diketones bearing an endocyclic and an exocyclic carbonyl groups,[5] although selective epimerization at the α-carbon to the carbonyl followed by preferential reduction of a particular diketone would lead to the preparation of one of the several possible isomers in a stereospecific manner. In addition, stereocontrolled manipulation of the reduction products is expected to be much less difficult with the cyclic derivatives than their acyclic counterparts, and from the standpoint of the functional group transformation β-diketones possessing sulfur-containing heterocycles such as tetrahydrothiopyrane appear to be attractive substrates for the regio- and stereo-controlled construction of the natural products. Our ongoing interest in the reduction of sulfur-functionalized ketones [6] and particularly sulfur-containing heterocyclic ketones [7] led us to anticipate that regio- and stereocontrolled reduction of 3-propionyltetrahydrothiopyran-4-one **1b** with bakers' yeast coupled with the Raney-nickel desulfurization of the resulting β-hydroxyketones would provide a short synthesis of (-)-(4*R*,5*S*)-sitophilure, the aggregation pheromone of both the rice and maize weevils, which are responsible for serious economical losses of stored cereal grains.[8] We report herein that 3-acyltetrahydrothiopyran-4-ones **1**



1a-c **2a-c** **3a-c**

a: R = C_6H_5; **b**: R = C_2H_5; **c**: R = CH_3

Table 1. Bakers' yeast reduction of 3-acyltetrahydrothiopyran-4-ones

R	mmol	Yeast/g	Saccharose/g	Time/h	Yield/% [a]	*cis* : *trans*	%ee *cis*	%ee *trans*
C_6H_5	0.33	15.0	18.0	23	63	67 : 33[b]	85[c]	>99[c]
C_6H_5	0.33	15.0	-	23	77	68 : 32[b]	>99[c]	>99[c]
C_2H_5	0.66	5.0	6.0	24	63	100 : 0	93[d]	-
C_2H_5	0.66	5.0	-	24	66	100 : 0	97[d]	-
CH_3	0.55	4.2	5.0	24	32	100 : 0	93[d]	-
CH_3	0.66	5.0	-	24	40	100 : 0	95[d]	-

a) Isolated yield. b) Isolated by preparative TLC. c) Determined by chiral stationary phase HPLC analysis using CHIRACEL OB column. d) Determined by capillary GLC analysis of the corresponding (R)-MTPA esters.

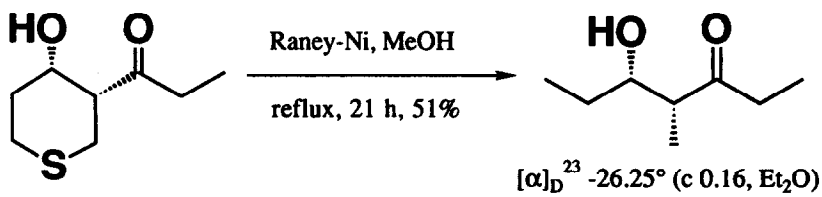
preferentially give upon bakers' yeast reduction (3*R*,4*S*)-3-acyl-4-hydroxytetrahydrothiopyranes **2** in high enantiomeric excess, and the subsequent sulfur functional group manipulation furnishes a simple synthesis of a pheromone in high optical purity.

Bakers' yeast reduction was conducted according to the following typical procedure: dry bakers' yeast (S. I. L. Lesaffre, 5g), saccharose (Wako, 6g) and a pH 7.0 aqueous phosphate buffer solution (KH_2PO_4-Na_2HPO_4) were mixed and stirred vigorously at rt for 30 min. In cases where no saccharose was used, dry bakers' yeast was simply stirred with the buffer solution until homogeneity. Then 3-propionyltetrahydrothiopyran-4-one **1b** [9] (0.66 mmol) dissolved in 5 ml of ethanol was added to the broth with constant stirring. Standard work-up followed by silica gel column chromatography allowed the isolation of pure (3*R*,4*S*)-3-propionyl-4-hydroxytetrahydrothiopyrane **2b** in 66% yield.[10] In the case of 3-benzoyltetrahydrothiopyran-4-one **1a**, the isomers were readily separated and isolated by preparative silica gel TLC. The relative configuration of 3-benzoyl-4-hydroxytetrahydrothiopyranes **2a** and **3a** were determined by ^{13}C NMR analysis: a substantial shielding was observed for the carbon bearing the hydroxyl group in the sterically congested *cis* isomer **2a**, which appears at δ 64.943 ppm whereas the corresponding carbon in the *trans* isomer **3a** appears at a lower field, δ 70.495 ppm.[11] Their optical purity was determined by chiral stationary phase HPLC analysis on a chiral column using the authentic β-hydroxyketone obtained by sodium borohydride reduction of the starting diketone **1a**.[12] The absolute configurations of **2a** and **3a** were established to be 3*R*,4*S* and 3*S*,4*S* forms, respectively, by an independent synthesis of (3*R*,4*S*)-3-benzoyl-4-hydroxytetrahydrothiopyrane **2a** starting from (3*R*,4*S*)-4-hydroxy-3-methoxycarbonyltetrahydrothiopyrane.[13] The optical purity of 3-propionyl- and 3-acetyl-4-hydroxytetrahydrothiopyranes **2b** and **2c** was determined by capillary GLC analysis of the corresponding crude (*R*)-MTPA esters and by comparison with the GLC behavior of authentic racemic (*R*)-MTPA esters.[14] The relative and absolute configurations of β-hydroxyketone **2b** were established by its conversion to the insect pheromone (-)-(4*R*,5*S*)-sitophilure. (vide infra)

As shown in Table 1, the reduction of the benzoyl derivative **1a** required high dilution conditions, but was regiospecific, providing exclusively the endocyclic carbonyl reduction products. This regioselectivity was confirmed by ^{1}HNMR analysis of the corresponding regioisomeric β-hydroxyketone obtained by the aldol reaction of tetrahydrothiopyran-4-one with benzaldehyde in diethyl ether, *i. e.*, the methine proton in the benzylic ketol appears at δ 4.960 ppm and δ 4.995 ppm which are much lower fields than that of 3-benzoyl-4-hydroxytetrahydrothiopyranes appearing at δ 5.43 ppm. This high regioselectivity may be rationalized by considering that the reactive species which is actually reduced by bakers' yeast is the phenyl-conjugated and stabilized enol possessing an exo-cyclic double bond rather than the free diketone **1a**, in which case concurrent

production of regioisomeric β-hydroxyketones would be possible. The observed diastereomeric ratio of 7 : 3 presumably reflects the selectivity of the proton migration during which *cis*-β-hydroxyketone **2a** forms faster than *trans* -β-hydroxyketones **3a**. It is of interest to note that under these reduction conditions, no diol product could be detected, which further substantiates the general tendency of 1,3-diketones to undergo reduction of a single carbonyl upon incubation with bakers' yeast.[2,3] In contrast, both of the carbonyl groups of 3-propionyl and 3-acetyl derivatives **1b** and **1c** were reduced to give regioisomeric β-hydroxyketones, with the endo-cyclic carbonyl reduction product as the major one for the propionyl derivative. However, the exo-cyclic carbonyl reduction products were very unstable under the reaction and work-up conditions, decomposing presumably *via* a retro-aldol pathway.[15] The high *cis* selectivity is consistent with previous observations made during the yeast reduction of other enolizable cyclic ketones and seems to be a consequence of the easy tautomeric interconversion between the enantiomers of the racemic substrates, followed by a preferential reduction of the (3*R*)-enantiomer which affords the *cis* isomer.[16]

The present highly regio- and stereoselective yeast reduction of 3-propionyltetrahydrothiopyran-4-one **1b** was applied to a short and stereocontrolled synthesis of the insect pheromone (-)-(4*R*,5*S*)-sitophilure [17] as illustrated below. The synthesized pheromone was determined to be of 98% ee by comparison of the magnitude



(3*R*,4*S*)

$[\alpha]_D^{23}$ -26.25° (c 0.16, Et_2O)
lit.[8b] $[\alpha]_D^{20}$ -26.7° (c 1.52, Et_2O)

of its optical rotation with the one reported by Mori and Ebata for the optically pure material.[8b] This pheromone synthesis also established the absolute configuration of the yeast reduction product **2b** to be 3*R*,4*S* configuration.

In conclusion, 3-acyltetrahydrothiopyran-4-ones, which can be readily synthesized from commercially available starting materials have been shown to undergo a highly regio- and stereoselective reduction with bakers' yeast, providing 3-acyl-4-hydroxytetrahydrothiopyranes of high optical purity. These chiral synthons are potentially useful in the field of natural products synthesis as exemplified by a short and concise synthesis of the rice and maize weevils aggregation pheromone, (-)-(4*R*,5*S*)-sitophilure.

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9. The starting diketones were prepared according to the following procedures: 3-Benzoyltetrahydrothiopyran-4-one **1a** was synthesized in 67% yield by the benzoylation of tetrahydrothiopyran-4-one with phenyl benzoate under the action of sodium amide according to the method of Hauser et al.[10] The propionyl derivative **1b** was available in two steps by the coupling of the commercially available methyl 3-mercapto-propionate with 1-chloro-3-pentanone (76%) followed by the Dieckmann-type cyclization of the resulting ketoester in THF at rt under the action of sodium hydride (56%). The acetyl derivative **1c** was prepared in 25% yield in a one-pot Michael addition of methyl 3-mercaptopropionate to methylvinylketone under the action of sodium hydride followed by the Dieckmann-type cyclization of the resulting adduct. All the spectral properties of **1a-c** were consistent with the assigned structures.
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12. HPLC (Chiracel OB , 4.6 mm x 250 mm, mobile phase hexane/2-propanol 12/1, flow rate 0.7 ml/min); *cis* isomer **2a**: RT = 21.598 min (4*S*) and RT = 25.873 min (4*R*); *trans* isomer **3a**: RT = 32.683 min (4*S*) and 44.870 min (4*R*).
13. a) For the bakers' yeast reduction of 3-methoxycarbonyltetrahydrothiopyran-4-one, see R. W. Hoffmann, W. Helbig, and W. Ladner, *Tetrahedron Lett.*, **23**, 3479 (1982); b) 4-Hydroxy-3-methoxycabonyl-tetrahydrothiopyrane obtained by bakers' yeast reduction, $[\alpha]_D^{23}$ +35.7° (c 4.36, benzene), was first hydrolyzed with aqueous methanolic KOH, then coupled with phenyllithium in ether to produce (+)-(3*R*,4*S*)-3-benzoyl-4-hydroxytetrahydrothiopyrane; $[\alpha]_D^{23}$ +77.3° (c 0.044, $CDCl_3$).
14. GLC (SE-30, 0.25 mmx 50 m, at 230 °C constant temperature); (*R*)-MTPA ester of **2b**: RT = 32.490 min (4*R*) and 34.176 min (4*S*); (*R*)-MTPA ester of **2c**: RT = 27.043 min (4*R*) and 28.523 min (4*S*).
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17. Spectral properties of (-)-(4*R*,5*S*)-sitophilure: NMR ($CDCl_3$, 270 MHz) δ 0.95 (t, *J* = 22.5, 3H), 1.06 (t, J = 22.0, 3H), 1.13 (d, *J* = 22.0,3H), 1.25-1.58 (m, 2H), 2.44-2.66 (m, 3), 2.7 (br s, 1H), 3.77-3.88 (m, 1H). IR (neat) 3450, 2990, 1700, 1470, and 740 cm^{-1}.

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