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Diastereo- and Enantioselective Syntheses of 2-Methyl-Tetrahydrofuran-3-Thiol

ANDREAS GOEKE

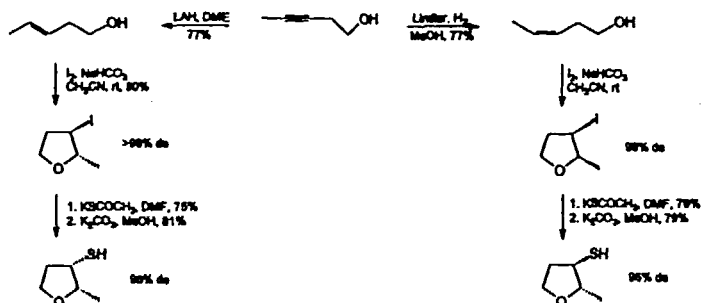
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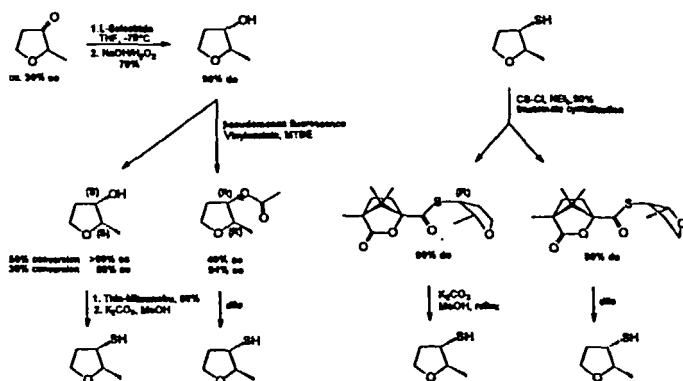
The sensory properties of diastereomeric as well as enantiomeric forms of flavor compounds frequently differ. 2-Methyl-tetrahydrofuran-3-thiol is a well-known flavor chemical possessing an intense meatlike odor and flavor enhancing properties. The compound was first described in a patent by Unilever [1] which was followed by several others [2], all in the area of meat flavors. Generally, the compound is used as a mixture of isomers, although recently, the *trans*-thiol was mentioned to be the stronger meat-like compound [3]. However, there is no information about the olfactive properties of the four possible enantiomers.



To provide efficient diastereoselective and EPC-syntheses for 2,3-disubstituted tetrahydrofurans, different strategies have been applied: An iodocyclization approach leading to diastereomerically pure 2-methyl-3-mercapto-furanes is depicted in scheme 1. The diastereoselectivity depended on the isomeric purities of the (*E*)- and (*Z*)-3-pentenols and on the substitution of the iodo-tetrahydrofurans by thioacetates.

Scheme 1. Iodocyclizations leading to 2-methyl-tetrahydrofuran-3-thiol.



Scheme 2. Resolution of *cis*-configured tetrahydrofuran-3-ol and -thiol.

The enantiomers of the *trans*-configured thiol were obtained via enzymatic resolution of the corresponding *cis*-alcohol using the lipase *pseudomonas fluorescens* with ee's up to >99% (scheme 2). The absolute configuration was assigned based on a correlation with lactic acid. However, the enzymatic approach failed in the case of the *trans*-alcohol. Therefore, the *cis*-thiol was resolved classically via the camphoric acid thioesters (scheme 2). The relative configuration was elucidated by X-ray crystallography.

Finally, the odor and taste properties were evaluated by a panel of five flavorists. Clearly, the *trans*-isomers possessed stronger meaty and roasted notes while the *cis*-thiols were weaker and had more sulfurous and musty notes. However, the *cis/trans*-mixture combines both notes to a harmonic full-body meat flavor.

Table 1. Odor properties of the enantiomeric tetrahydrofuran-thiols.

config.	odor	odor th.	$[\alpha]_D^{25}$ (CHCl ₃)	% ee
(2 <i>S</i> ,3 <i>R</i>)	sulfurous, burnt, meaty, roasted, green, strong	2 pg	-45.1	96
(2 <i>R</i> ,3 <i>S</i>)	sulfurous, musty, cabbage, onion, strong	12 pg	+42.0	94
(2 <i>R</i> ,3 <i>R</i>)	sulfurous, rotten, meaty, weaker	13 pg	-7.3	>99
(2 <i>S</i> ,3 <i>S</i>)	sulfurous, roasted meaty, burnt, weaker	4 pg	+8.9	97

References

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