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Synthesis and structural characterization of the isomuscarines

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ABSTRACT

Four diastereomers of 2-[(trimethylammonium)-methyl]-5-methyltetrahydrofuran-3-ol, trivially named isomuscarine, *allo*-isomuscarine, *epi*-isomuscarine, and *epiallo*-isomuscarine, were prepared as bromide salts from 2,4-*like* and 2,4-*unlike* diastereomers of 3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione. The strategy for constructing the tetrahydrofuran nucleus of the isomuscarines uses alkenoxyl radical 5-*exo*-bromocyclization, occurring 2,3-cis-selectively for the 2,4-*like*-4-hydroxyhex-5-en-2-oxyl radical, and 2,3-trans-selectively for the 2,4-*unlike* diastereomer. A fraction of 4-hydroxyhex-5-en-2-oxyl radicals cyclizes 6-*endo*-selectively providing 5-bromo-2-methyltetrahydropyran-4-ols in yields between 3 and 15%. Substituting trimethylamine for bromide in 5-*exo*-bromocyclized products furnishes isomuscarine bromides, which were structurally characterized by X-ray diffraction and NMR-spectroscopy.

1. Introduction

Isomuscarines are tetrahydrofuran-derived quaternary ammonium cations structurally related to the muscarines,[1] by changing position of the hydroxyl substituent (Fig. 1).[2] In extension to the muscarines,[3,4] isomuscarine diastereomers are specified by prefices *allo*, *epi*, and *epiallo* for distinguishing relative configuration at the three stereocenters. The only isomuscarine prepared and structurally characterized so far is the *epiallo*-isomer, obtained by Joulliée and co-workers from a D-glucose-derived building block in nine synthetic steps.[2,5]

Our interest in muscarine- and isomuscarine-chemistry started with the quest for selectivity control in polar and free radical bromocyclizations.[6–9] From an enantioselective synthesis of (+)-muscarine we learned that the hydroxyl group in position 3 of (2*S*,3*R*)-hex-5-ene-2,3-diol directs polar 5-*exo*-bromocyclization by the *gauche* effect 2,5-cis-selectively.[10–13] Reversing this intrinsic stereoselectivity is feasible by changing the mechanism from polar to radical addition, converting the hydroxyl oxygen involved in C,O-bond formation into a radical oxygen. Oxygen radicals add to carbon–carbon double bonds via early transition states in kinetically controlled reactions with selectivity being controlled by orbital effects, torsional strain, temperature, and steric repulsion between the reaction centers.[14–17]

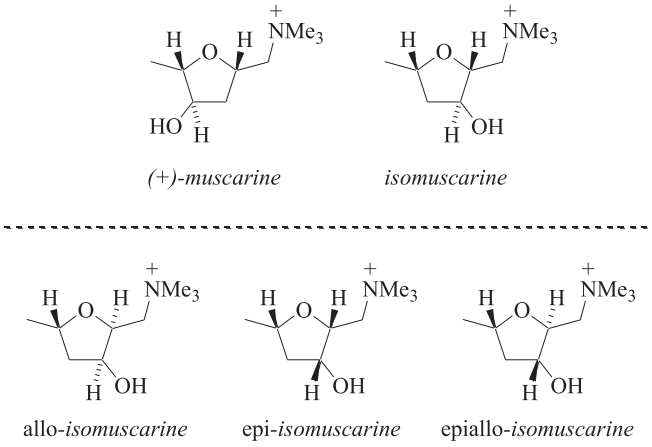

Fig. 1. Structure formulas of muscarine (top left) and isomuscarine (top right), and descriptors for specifying isomuscarine stereoisomers (bottom).

From a study on synthesis of *allo*-muscarine via 3-hydroxyhex-5-en-2-oxyl radical cyclization we learned that a hydroxyl group in β-position to the radical oxygen induces rapid β-fragmentation to

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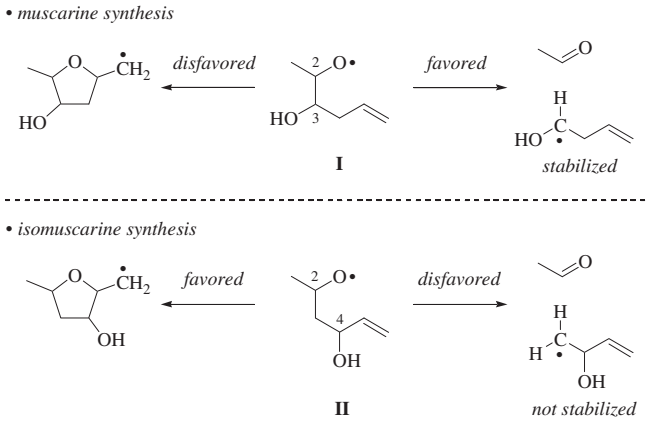
the aliphatic chain (Scheme 1, top).[18,19] Driving forces for breaking the β-carbon–carbon bond in alkenoxyl radical **I** are entropy, strength of the newly formed carbon–oxygen double bond, and stabilization of the liberated carbon radical by an α-hydroxyl substituent.



Scheme 1. Chemistry of the 3-hydroxyhex-5-en-2-oxyl radical (**I**) (top) and proposed selectivity of the 4-hydroxyhex-5-en-2-oxyl radical (**II**) (bottom).

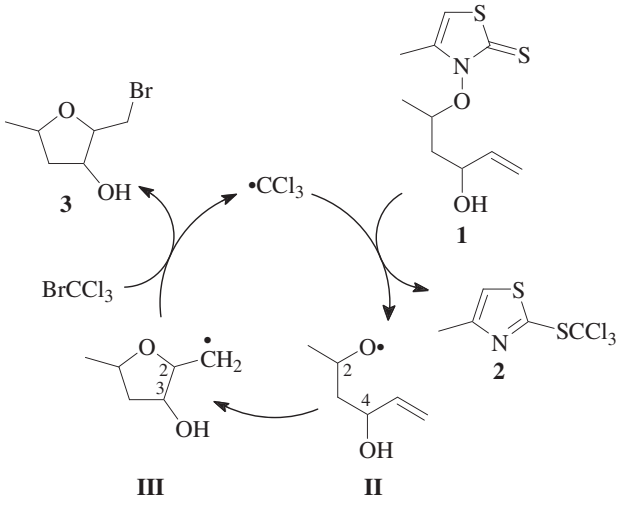
From the information gained by the *allo*-muscarine project we predicted that a hydroxyl substituent in γ-position to the radical oxygen exerts no similar rate enhancing effect for β-carbon–carbon breaking, as in regioisomer **I** (Scheme 1, bottom). We therefore reasoned that alkenoxyl radical **II** cyclizes 5-*exo*-selectively with stereoselectivity being guided by an interplay between polar and steric effects of the allylic hydroxyl group and the methyl substituent.[20,21]

The major result from the isomuscarine project shows that diastereomers of the 4-hydroxyhex-5-en-2-oxyl radical **II** undergo in solutions of bromotrichloromethane rapid, regio- and stereoselective 5-*exo*-bromocyclizations. The isomer described as *rel*-(2*S*,4*S*)-**II**, hereafter specified as *like*-**II**, cyclizes 2,3-cis-selectively, whereas the *rel*-(2*S*,4*R*)-stereoisomer of **II**, abbreviated as *unlike*-**II**, prefers the 2,3-trans mode of 5-*exo*-cyclization. Substituting trimethylamine for bromide in 5-*exo*-bromocyclized products gives the isomuscarines as bromide salts, which were structurally characterized by X-ray diffraction and NMR-spectroscopy.

2. Results and interpretation

2.1. Concept and general mechanistic considerations

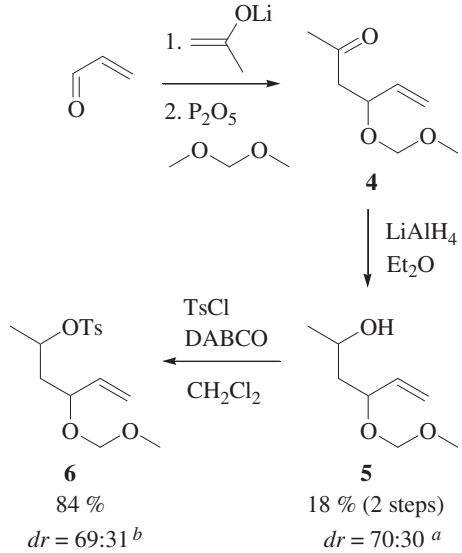
In extension to previous mechanistic and synthetic studies,[6,22,23] we used 3-alkenoxy-4-methylthiazole-2(3*H*)-thiones (MTTORs) **1** as progenitors for generating oxygen radicals under non-oxidative and pH-neutral conditions. Derivatives of compound **1** liberate alkenoxyl radicals in a propagating step of a radical chain reaction, by adding the trichloromethyl radical to the thione sulfur and subsequently breaking the nitrogen–oxygen bond homolytically (Scheme 2).[17] Alkenoxyl radical **II**, in extension to the general mechanism, cyclizes with a predicted 5-*exo*/6-*endo*-regioselectivity of 98:2, leading to carbon radical **III** as major product.[24] Nucleophilic carbon radicals similar to **III** homolytically displace bromine from bromotrichloromethane with bimolecular rate constants in the order of 10^8 M^{-1} s^{-1} at ambient temperature, providing 2-bromomethyl-5-methyltetrahydrofuran-3-ol (**3**) presumably as mixture of 2,3-cis/trans-stereoisomers. Bromine atom abstraction from the mediator gives the trichloromethyl radical for continuing the chain reaction.



Scheme 2. Strategy for constructing the isomuscarine nucleus from 3-alkenoxythiazole-2(3*H*)-thione **1** and bromotrichloromethane in a radical chain reaction.

2.2. Stereoisomers of 3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione (1)

For preparing *like* and *unlike* stereoisomers of 3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione (**1**) we devised a six-step synthesis beginning with a mixed aldol addition of lithium propenolate to 2-propenal. The aldol addition yields 4-hydroxyhex-5-en-2-one.[25] The product rapidly eliminates water on standing and was therefore immediately converted into methoxymethyl derivative **4**.[26] Reducing the carbonyl group of *O*-protected hydroxyketone **4** by lithium aluminum hydride afforded a 30:70-mixture of *like*/*unlike*-4-methoxymethyloxyhex-5-en-2-ol (**5**), which was esterified by *p*-toluenesulfonyl chloride in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to furnish derived tosylate **6**. Treating *O*-alkenyl tosylate **6** in a solution of dimethylformamide with *N*-hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt gives after acid-catalyzed methanolysis of the methoxymethyl protecting group and chromatographic purification MTTORs *like*- and *unlike*-**1** as single diastereomers (Schemes 3 and 4).[27,28]



Scheme 3. Synthesis of 4-(methoxymethyloxy)-hex-5-en-2-yl tosylate (**6**) from 2-propenal. [a] Diastereomeric ratio (dr) derived from intensities of carbon-13 NMR-resonances. [b] dr derived from proton-NMR-integrals.