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Stereoselective synthesis of (*R*)-(+)-1-methoxyspirobrassinin, (2*R*,3*R*)-(−)-1-methoxyspirobrassinol methyl ether and their enantiomers or diastereoisomers

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Abstract—Stereoselective synthesis of cruciferous indole phytoalexin (*R*)-(+)-1-methoxyspirobrassinin and its unnatural (*S*)-(−)-enantiomer was achieved by spirocyclization of 1-methoxybrassinin in the presence of (+)- and (−)-menthol and subsequent oxidation of the obtained menthyl ethers. Methanolysis of menthyl ethers in the presence of TFA afforded (2*R*,3*R*)-(−)-1-methoxyspirobrassinol methyl ether as well its unnatural (2*S*,3*S*)-, (2*R*,3*S*)-, and (2*S*,3*R*)-isomers.

1. Introduction

Phytoalexins are defined as antimicrobial low molecular weight secondary metabolites, produced by plants after their exposure to physical, biological, or chemical stress.[1] About 40 indole phytoalexins have been isolated from economically and dietary important plants of the family *Cruciferae*, cultivated worldwide.[2] Among them, several spiroindoline[3,5′]thiazolidine-type phytoalexins, such as (*S*)-(−)-spirobrassinin [**1**, from Japanese radish (*Raphanus sativus*)],[3] (*R*)-(+)-1-methoxyspirobrassinin [**2**, from kohlrabi (*Brassica oleracea* var. *gongylodes*)],[4] or (2*R*,3*R*)-(−)-1-methoxyspirobrassinol methyl ether [**3**, from Japanese radish (*R. sativus*)][5] have been described. Compounds **1**–**3** were previously synthesized as racemates. (±)-Spirobrassinin was prepared by cyclization of (±)-dioxibrassinin (**5**) with $SOCl_2$ or MsCl, enantioresolved by (*S*)-(−)-1-phenylethyl isocyanate and the absolute configuration of (*S*)-(−)-spirobrassinin was determined by X-ray analysis after derivatization with (−)-camphanoyl chloride.[6] (±)-1-Methoxyspirobrassinin [(±)-**2**] and (±)-1-methoxyspirobrassinol methyl ether [(±)-**3**] were synthesized by dioxane dibromide-mediated spirocyclization of 1-methoxybrassinin (**6**) in dioxane.[7] The reaction probably proceeds via sulfenyl bromide (**A**), which cyclizes to indoleninium ion (**B**, Scheme 1). In the presence of methanol as a nucleophile attacking the intermediate methoxyiminium ion (**B**), a mixture of racemic *trans*- and unnatural *cis*-diastereoisomer[8] of **3** was obtained, from which the natural *trans*-diastereoisomer was isolated by flash chromatography. In the presence of water, another spiroindoline phytoalexin 1-methoxyspirobrassinol (**4**), with as yet unknown absolute stereochemistry, was prepared.[7] This compound exists in solution as a mixture of two diastereoisomers, owing to its unstable hemiaminal structure.[5] Oxidation of the mixture of isomers **4a** and **4b** with CrO_3 afforded racemic **2**.[7] (±)-1-Methoxyspirobrassinin and *trans*-(±)-1-methoxyspirobrassinol methyl ether were enantioresolved by chiral HPLC and the absolute configurations of natural (*R*)-(+)-**2** and (2*R*,3*R*)-(−)-**3** were determined by ECD, VCD, and chemical correlation.[9]

In the present Letter we wish to report the diastereoselective synthesis of (*R*)-(+)-**2** and (2*R*,3*R*)-(−)-**3** as well as their unnatural isomers. For this purpose we investigated spirocyclization of 1-methoxybrassinin in the presence of chiral secondary alcohols as nucleophiles

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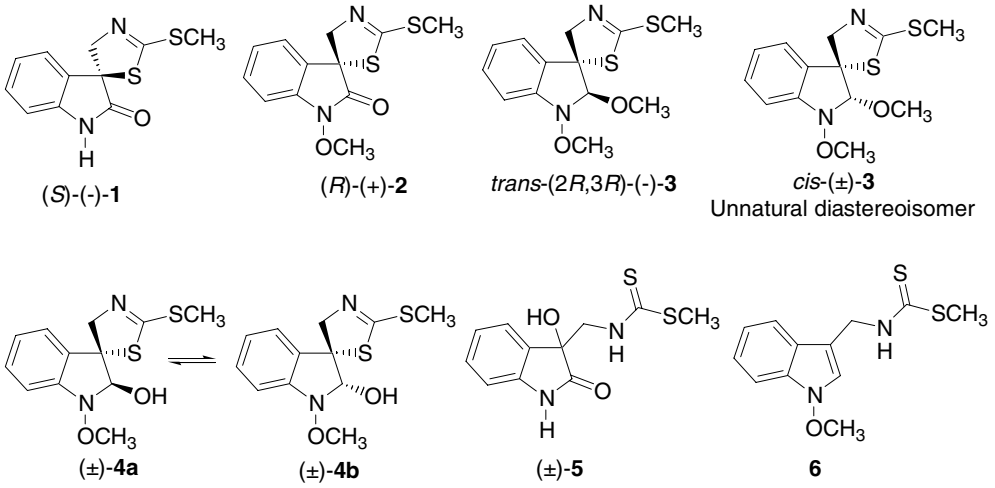


Figure 1.

reacting with a methoxyiminium ion (see Fig. 1). The dioxane dibromide-mediated spirocyclization in dioxane used previously[7] appeared to be inconvenient, since it is difficult to dry and store the dried dioxane. Any trace of water results in the formation of **4** as the unwanted side product. Therefore spirocyclization was performed with bromine in dry dichloromethane. It was assumed that in the chiral-alkyl containing ethers **7**–**10**, one of the four possible diastereoisomers would be major. Oxidation with pyridinium chlorochromate (PCC)[9] should afford an enantiomer of 1-methoxyspirobrassinin (**2**), and acid-catalyzed methanolysis should lead to a 1:1 mixture of the optically active *trans*- and *cis*-diastereoisomers of 1-methoxyspirobrassinol methyl ether (**3**), epimeric at C-2 (**B**, Scheme 1).

For the first experiments, we selected the (*S*)-(−)- and (*R*)-(+)-1-(2-naphthyl)ethanol because it possesses the large naphthyl moiety. The prediction of diastereoselectivity was based on stereoelectronic considerations. It was supposed, that the chiral secondary alcohol would approach methoxyiminium ion **B** from the less hindered CH_2-side of thiazoline ring in the direction of Bürgi–Dunitz trajectory[10] with the naphthyl substituent being the most remote from the reaction center. In this model, the (*R*)-methoxyiminium intermediate should be preferably attacked by the (*S*)-enantiomer of the alcohol from the less hindered CH_2-side of thiazoline ring (Fig. 2), whereas in the case of (*S*)-methoxyiminium intermediate the analogous attack of (*S*)-alcohol will be unfavored. With the (*R*)-enantiomer of alcohol the situation was expected to be opposite. By analogy the approach of the (*S*)-alcohol to the (*S*)-methoxyiminium ion and

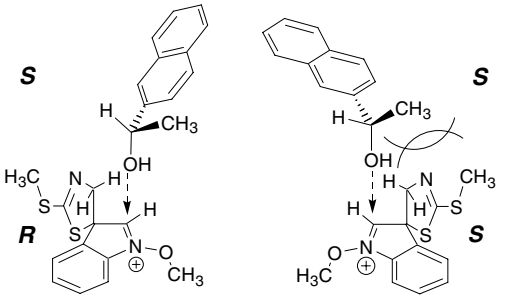
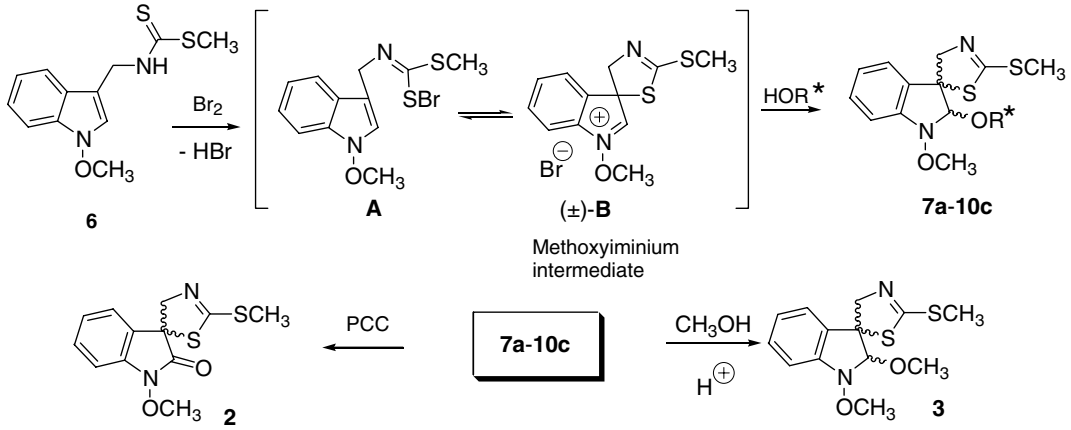


Figure 2.



Scheme 1.