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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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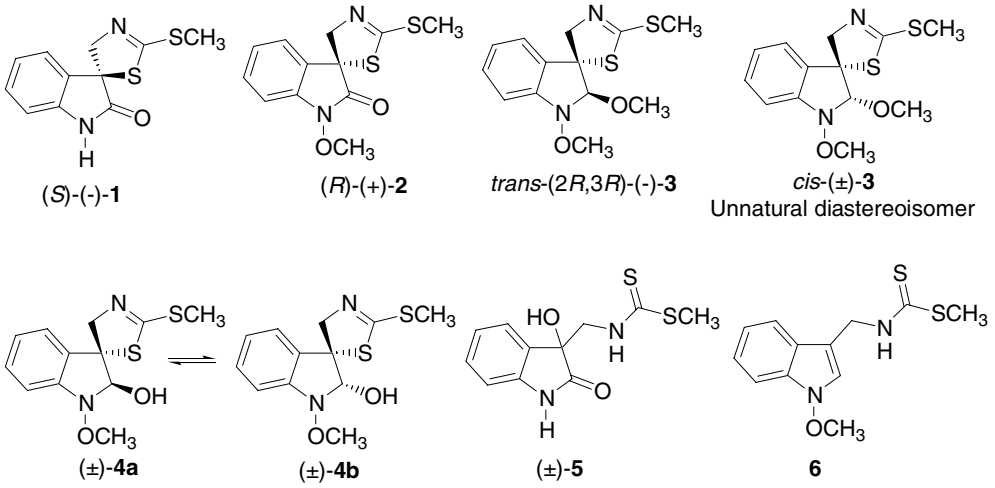


Figure 1.

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

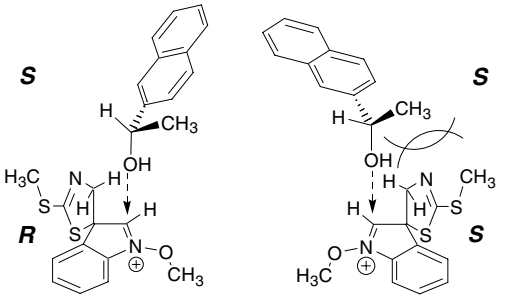
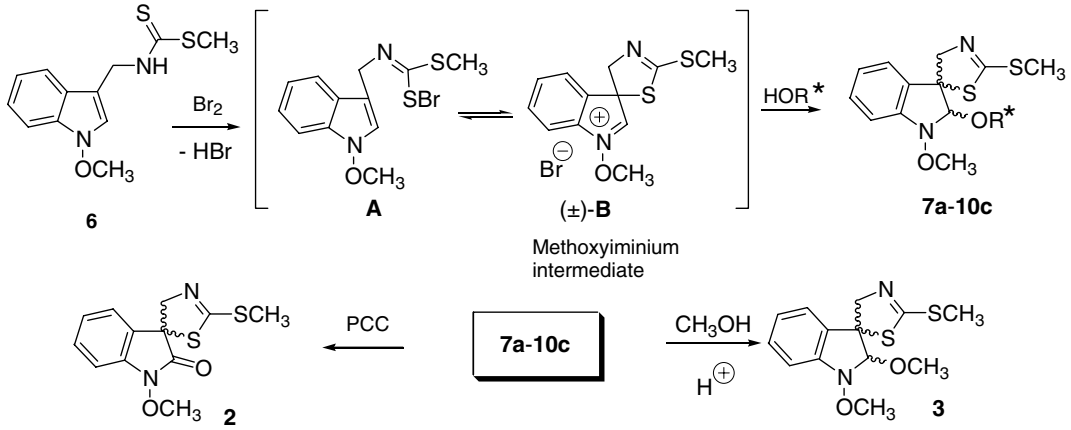


Figure 2.



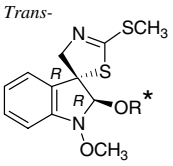
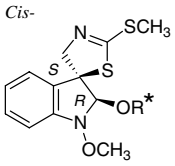
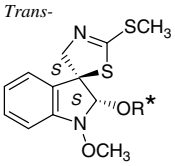
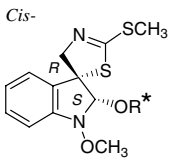
Scheme 1.

(*R*)-alcohol to (*R*)-methoxyiminium ion should be more favored from the sulfur side of thiazoline ring.

The analysis of the reaction products (Table 1) confirmed the expected diastereoselectivity. Spirocyclization in the presence of (*S*)-(−)-1-(2-naphthyl)ethanol resulted in the formation of four diastereoisomers with the product of nucleophilic addition of this alcohol to (*R*)-methoxyiminium ion from the *Re*-face as the major product (**7a**), whereas (*R*)-(+)-1-(2-naphthyl)ethanol attacked the (*S*)-intermediate **B** mainly from the *Si*-face with the formation of diastereoisomer **8c** as the major product. The second most abundant isomers **7b** or **8d** correspond to the attack of the (*S*)-alcohol to (*S*)-ion and (*R*)-alcohol to (*R*)-ion from the sulfur side of the thiazolidine ring. Although the expected diastereoselectivity was achieved, isolated yields of major products of 1-methoxyspirobrassinol 1-(2-naphthyl)ethyl ethers were only 28% (**7a**) or 29% (**8c**) and their oxidation with PCC afforded moderate, 50–52% yields of (*R*)-(+)-**2** or (*S*)-(−)-**2**. Therefore, the application of the more common chiral auxiliary, (+)- and (−)-menthol, was studied with the aim of improving the yields. Stereoselection by menthol was expected to work on the basis of the same model as in the case of 1-(2-naphthyl)ethanol, with the large isopropyl group being the most remote from the reaction center during the approach of nucleophile to iminium ion. Reaction with (1*S*,2*R*,5*S*)-(+)- and (1*R*,2*S*,5*R*)-(−)-menthol proceeded with similar diastereoselectivity; however, the corresponding 1-methoxyspirobrassinol menthyl ethers **9a** (38%) or **10c** (40%) were obtained in higher isolated yields. Moreover the reaction time for their oxidation was shortened from 3 days in the case of 1-(2-naphthyl)ethyl ethers to 1 day and the yield of (*R*)-(+)-**2** or (*S*)-(−)-**2** increased to 68–70%. It is supposed that the cyclization of sulfenyl bromide **A** to iminium ion **B** (Scheme 1) is reversible. If the cyclization was not reversible, the maximum yields of the major diastereoisomers **7a**, **8c**, **9a**, and **10c** might not exceed 50%. Reversibility is supported by the findings that the yields calculated from the yields of chromatographically isolated mixtures with respect to the ratio of present isomers in all cases exceeded 50% (Table 1). Compounds **7a**–**10d** were prepared at room temperature. At lower temperatures (up to −70 °C) the stereoselectivity decreased, probably by participation of another mechanism, which will be the subject of our next studies. At higher temperatures (up to 50 °C in chloroform) decomposition was observed and therefore did not lead to higher stereoselectivity.

The structures of individual diastereoisomers of 1-(2-naphthyl) and menthyl ethers were determined by NMR studies, including 2D HSQC, HMBC, and NOESY or NOE-dif. experiments. Products **7b**, **8b**, **9b**, **10b**, **7d**, **8d**, **9d**, and **10d** exhibited in the NOESY spectra cross peaks between H-2 and H_b protons evidencing their structure as *cis*-diastereoisomers as shown for compound **9b** depicted in Fig. 3. The absolute configuration at C-3 was determined after oxidation to (*R*)- or (*S*)-1-methoxyspirobrassinin (**2**). Enantiomers of **2** were identified by comparison of their CD-spectra with already published data.[9] Taking into account the *cis*-diastereoisomeric structure, the configuration at C-2 of

Table 1. Stereochemistry, ratio of diastereoisomers and yields of 1-methoxyspirobrassinol 1-(2-naphthyl)ethyl and menthyl ethers

R*	Compound/ratio[a] (%)/yield[b] (%)			
	Trans- 	*Cis-* 	*Trans-* 	*Cis-* 
(*S*)-(−)-Np[c]	**7a**	**7b**	**7c**	**7d**
	69	22	2	7
	57	18	2	6
(*R*)-(+)-Np[c]	**8a**	**8b**	**8c**	**8d**
	7	7	68	18
	6	6	54	14
(1*S*,2*R*,5*S*)-(+)-Mt[d]	**9a**	**9b**	**9c**	**9d**
	57	18	20	5
	52	19	13	3
(1*R*,2*S*,5*R*)-(−)-Mt[d]	**10a**	**10b**	**10c**	**10d**
	17	3	60	20
	14	3	56	18

[a] The ratio of compounds **7** and their enantiomeric compounds **8** as well as **9** and their enantiomeric compounds **10** was determined by the integration of non-overlapping singlets of H-2 and the doublets of the H_b protons (see Fig. 3) in ^{1}H NMR spectra of crude product mixtures.

[b] In the case of compounds **7a**–**7d** and enantiomeric **8a**–**8d**, the yields were calculated from the yield of chromatographically isolated mixture of all four diastereoisomers (83%), with respect to the ratio of diastereoisomers. In the case of **9a**–**9d** and enantiomeric **10a**–**10d**, the yields were calculated from the chromatographically isolated yields of the mixtures of *trans*-isomers **9a** and **9c** or **10a** and **10c**, (65% or 70%) and *cis*-isomers **9b** and **9d** or **10b** and **10d**, (20% or 21%), using the same observed ratio of diastereoisomers 80:20 for both mixtures of *trans*- and 85:15 for mixtures of *cis*-isomers.

[c] 1-(2-Naphthyl)ethyl.

[d] Menthyl.

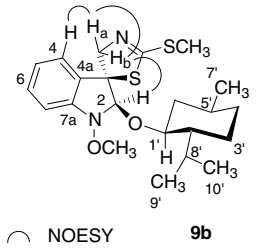


Figure 3.

cis-isomers was assigned (Table 1). In the case of compounds **7a**, **8a**, **9a**, **10a**, **7c**, **8c**, **9c**, and **10c** the NOESY and NOE-differential experiments did not show the interaction between H_b and H-1′ proton of secondary alcohol residue, which was expected to confirm their *trans*-diastereoisomeric configuration. However, the interaction between H-2 and H_b was also not observed and thus the structure of *trans*-diastereoisomers was assigned to these products. The absolute configuration at C-3 and C-2 was assigned as in the case of *cis*-diastereoisomers.

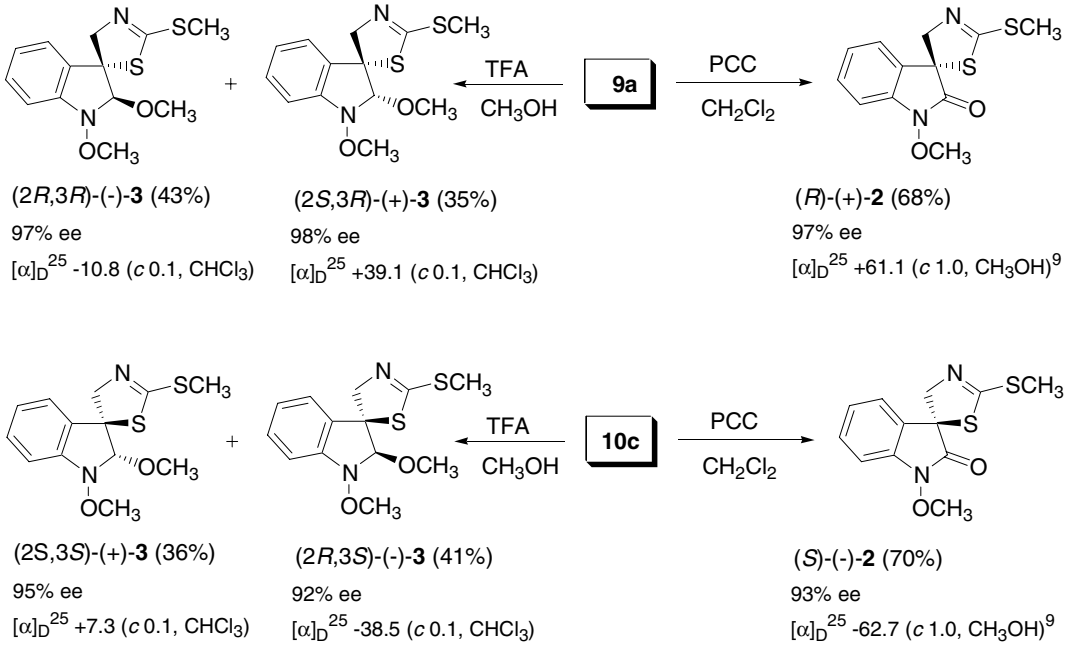
For the synthesis of targets, 1-methoxyspirobrassinol menthyl ethers **9a** and **10c**, as the major products of stereoselective spirocyclization, were used (Scheme 2). The oxidation of **9a** with PCC smoothly afforded the natural enantiomer of 1-methoxyspirobrassinin [(*R*)-(+)-**2**] whereas its unnatural enantiomer [(*S*)-(−)-**2**] was obtained by oxidation of **10c**. To prepare the natural (2*R*,3*R*)-(−)-1-methoxyspirobrassinol methyl ether [(2*R*,3*R*)-(−)-**3**], the methanolysis of **9a** was investigated. It was found that TFA-catalyzed methanolysis afforded a mixture of (2*R*,3*R*)-(−)-**3** and (2*S*,3*R*)-(+)-**3** in the ratio 1:1, easily separable by column chromatography. The analogous reaction of **10c** afforded the (2*S*,3*S*)-**3** and (2*R*,3*S*)-**3** isomers of 1-methoxyspirobrassinol methyl ether in the ratio 1:1 (Scheme 2). The enantiomeric excesses of synthesized enantiomers were determined by chiral HPLC, on the column CHIRACEL OD (ID 0.46 × 5 cm + 0.46 × 25 cm), using eluent hexane with 0.1% propan-2-ol at a flow rate 1.0 mL/min.

2. Experimental procedure for (*R*)-(+)-1-methoxyspirobrassinin and (2*R*,3*R*)-(−)-1-methoxyspirobrassinol methyl ether

2.1. (2*R*,3*R*)-1-Methoxyspirobrassinol (1*S*,2*R*,5*S*)-menthyl ether 9a

To a stirred mixture of 1-methoxybrassinin **6** (133 mg, 0.5 mmol) and powdered molecular sieves (3 Å) in dry CH_2Cl_2 (7 mL) at room temperature was added freshly prepared solution of Br_2 (0.028 mL, 88 mg, 0.55 mmol) in dry CH_2Cl_2 (1.25 mL). After stirring for 1 min, a suspension of (1*S*,2*R*,5*S*)-(+)-menthol (86 mg, 0.55 mmol), triethylamine (509 mg, 0.702 mL, 5 mmol) and powdered molecular sieves (3 Å) in dry CH_2Cl_2 (7 mL) was added. Stirring was continued for 20 min, and the reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with 1 M HCl (13 mL) and water (20 mL). The organic layer was dried over anhydrous Na_2SO_4. The residue obtained after evaporation of solvent was subjected to chromatography on silica gel (13 g, petroleum ether/diethyl ether 4:1), affording 137 mg (65%) of the mixture of *trans*-diastereoisomers (**9a**, **9c**) and 46 mg (22%) of the mixture of *cis*-diastereoisomers (**9b**, **9d**). Subsequent chromatography of the mixture of *trans*-diastereoisomers **9a** and **9c** on silica gel (20 g, CH_2Cl_2) gave **9a** [79 mg (38%)] as a colorless oil, $[\alpha]_D^{25}$ −8.9 (*c* 0.74, $CHCl_3$), >99% ee.[11]

Enantiomeric product **10c** (40%), $[\alpha]_D^{25}$ +11.0 (*c* 0.88, $CHCl_3$), >99% ee was prepared by the same procedure using (1*R*,2*S*,5*R*)-(−)-menthol.



Scheme 2.

2.2. (*R*)-(+)-1-Methoxyspirobrassinin 2

To a vigorously stirred slurry of pyridinium chlorochromate (138 mg, 0.642 mmol) and anhydrous magnesium sulfate (116 mg, 0.936 mmol) in dry CH_2Cl_2 (0.45 mL), a solution of **9a** (90 mg, 0.214 mmol) in dry CH_2Cl_2 (1.8 mL) was added. The reaction mixture was stirred for 24 h at room temperature and then diluted with CH_2Cl_2 (2 mL). After adding a small amount of silica gel, the solvent was evaporated and the residue preabsorbed on silica gel was purified by silica gel column chromatography (4 g, petroleum ether/diethyl ether 4:1) to give 43 mg (68%) of (*R*)-(+)-1-methoxyspirobrassinin [(*R*)-(+)-**2**] as colorless needles, mp 129–131 °C (EtOAc/hexane). The spectral data were fully identical with those of natural product.[4] The absolute configuration was determined by direct comparison of ECD spectra with published data.[9]

2.3. (2*R*,3*R*)-(−)-1-Methoxyspirobrassinol methyl ether 3

To a solution of **9a** (49 mg, 0.117 mmol) in dry methanol (1 mL) was added TFA (15 mg, 0.01 mL, 0.13 mmol). The reaction mixture was stirred for 12 h, solvent evaporated and the residue obtained subjected to chromatography on silica gel (10 g, cyclohexane/diethyl ether 2:1) affording 15 mg (43%) of (2*R*,3*R*)-(−)-**3**; R_f (cyclohexane/diethyl ether 2:1) 0.51 as a colorless oil, and 12 mg (35%) of (2*S*,3*R*)-(+)-**3**; R_f (cyclohexane/diethyl ether 2:1) 0.31 as colorless crystals, mp 77–79 °C (hexane). The spectral data for (2*R*,3*R*)-(−)-**3** were fully identical with those of natural product,[5] whereas the data for (2*S*,3*R*)-(+)-**3** were fully identical with those of corresponding racemate.[9]

In summary, the diastereoselective synthesis of spiroindoline[3,5′]thiazolidine-type phytoalexins was achieved by the spirocyclization of 1-methoxybrassinin in the presence of (+)- and (−)-menthol as the chiral nucleophile with the formation of chiral 1-methoxyspirobrassinol menthyl ethers. Oxidation of menthyl ethers with PCC afforded (*R*)-(+)-1-methoxyspirobrassinin and its unnatural (*S*)-(−)-isomer in 26% and 28% overall yields and enantiomeric excesses 97% and 93%. Natural (1*R*,2*R*)-(−)-1-methoxyspirobrassinol methyl ether (97% ee) and its other three unnatural stereoisomers (92–98% ee) were synthesized by TFA-catalyzed methanolysis of chiral 1-methoxyspirobrassinol menthyl ethers.

Acknowledgments

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11. *Data for* **9a**: Anal. Calcd for $C_{22}H_{32}N_2O_2S_2$ requires: C, 62.82; H, 7.67; N, 6.66. Found: C, 62.5; H, 7.9; N, 6.4. ν_{max} ($CHCl_3$) 2953, 2893, 2863, 1567, 1453, 1120, 1033, 987, 933 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29 (dd, 1H, *J* 7.5, 1.2 Hz, H-4), 7.23 (dt, 1H, *J* 1.2, 7.7 Hz, H-6); 7.01 (dt, 1H, *J* 1.0, 7.5 Hz, H-5), 6.95 (dd, 1H, *J* 7.9, 0.6 Hz, H-7), 5.16 (s, 1H, H-2); 5.02 (d, 1H, *J* 15.3 Hz, H_b), 3.93 (s, 3H, OCH_3), 3.91 (d, 1H, *J* 15.3 Hz, H_a), 3.59 (dt, 1H, *J* 4.3, 10.5 Hz, H-1′), 2.56 (s, 3H, SCH_3); 2.41 (quinted, 1H, *J* 6.8, 2.0 Hz, H-8′), 2.24–2.19 (m, 1H, H-6′), 1.68–1.63 (m, 2H, H-3′, H-4′), 1.42–1.26 (m, 2H, H-2′, H-5′), 1.06–0.86 (m, 3H, H-3′, H-4′, H-6′), 0.94 (d, 3H, *J* 6.9 Hz, H-7′), 0.92 (d, 3H, *J* 6.9 Hz), and 0.83 (d, 3H, *J* 6.9 Hz) [H-9′ and H-10′]; NOESY correlations H_a/H-4, H_b: OCH_3/H-7: H-2/H-1′, H-6′; δ_C (100 MHz, $CDCl_3$) 163.3 (C=N), 148.5 (C-7a), 129.4 (C-6), 128.7 (C-4a), 124.0 (C-4), 123.8 (C-5), 112.8 (C-7), 104.1 (C-2), 79.5 (C-1′), 70.1 (CH_2), 69.3 (C_{spiro}), 63.7 (OCH_3), 48.7 (C-5′), 41.6 (C-6′), 34.3 (C-4′), 31.5 (C-2′), 24.8 (C-8′), 23.1 (C-3′), 22.4 (C-7′), 21.4 and 16.3 (C-9′ and C-10′), 15.0 (SCH_3); MALDI-TOF MS, *m*/*z* (%): 420.9 $[M+H]^+$ (94); CD (CH_3OH, nm) λ_{ext} ($\Delta\varepsilon$): 214 (−39.2), 238 (+8.1), 264 (−2,8), 293 (+4.6).