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First enantioselective synthesis of isagarin, a natural product isolated from *Pentas longiflora* Oliv.

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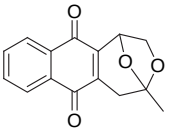
ABSTRACT

For the first time, an enantioselective synthesis of both 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b** was achieved starting from 1,4-dimethoxy-2-vinylnaphthalene **2**. The key steps involve a Sharpless asymmetric dihydroxylation and reaction with an acetonylating pyridinium ylid. The different optical rotations and melting points of the enantiopure 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b** with respect to the isolated natural product will be addressed.

1. Introduction

Isagarin **1**, a new type of tetracyclic naturally occurring 1,4-naphthoquinone, was isolated from the roots of *Pentas longiflora* Oliv. (Rubiaceae),[1] a woody herb from oriental intertropical Africa, also known as Isagara, which is used in African traditional medicine (Rwanda) to treat scabies and the skin mycosis *Pityriasis versicolor*.[2]



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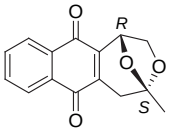
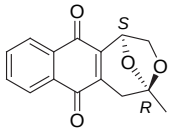


1a



1b

Due to its interesting architecture, isagarin is an attractive target for synthetic chemists, which resulted in a first racemic synthesis by our department.[3] Later, a total synthesis of isagarin **1** was reported in an overall yield of 24% using the Wacker cyclization in the key step.[4] However, isagarin **1** can exist as two different enantiomers: 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b**, and since the isolated natural product was reported to be optically active,[1] it does not concern a racemic mixture. Therefore it was decided to investigate the first enantioselective synthesis of both 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b** in order to determine the configuration of the isolated natural product as its biological activity may very well reside within a single enantiomer.

2. Results and discussion

The synthetic methodology used for the stereoselective synthesis of isagarin **1** is based on the former racemic synthesis developed by our department, which relied on the synthesis of 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone through osmium(VIII) tetraoxide mediated dihydroxylation of 1,4-dimethoxy-2-vinylnaphthalene **2** and subsequent oxidative demethylation.[3] In a following step, an acetonyl side chain was introduced on the 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone and racemic isagarin **1** was obtained after a spontaneous intramolecular condensation reaction. The Sharpless asymmetric dihydroxylation would be very suitable to introduce two hydroxy substituents on the vinylic double bound of compound **2** in a stereospecific way.[5] Although a possible racemization during the subsequent CAN-mediated oxidative demethylation may need further investigation, final reaction of the chiral 2-(1,2-dihydroxyethyl)-1,4-naphthoquinone **4** or **6** with acetylmethyl pyridinium ylid should give rise to the formation of a second chiral centre with one possible conformation, due to stereoinduction during the spontaneous intramolecular condensation reaction of the vicinal diol onto the added acetonyl side chain. In accordance with this rationale, 1*R*,4*S*-isagarin **1a** was synthesized starting from the precursor 1,4-dimethoxy-2-

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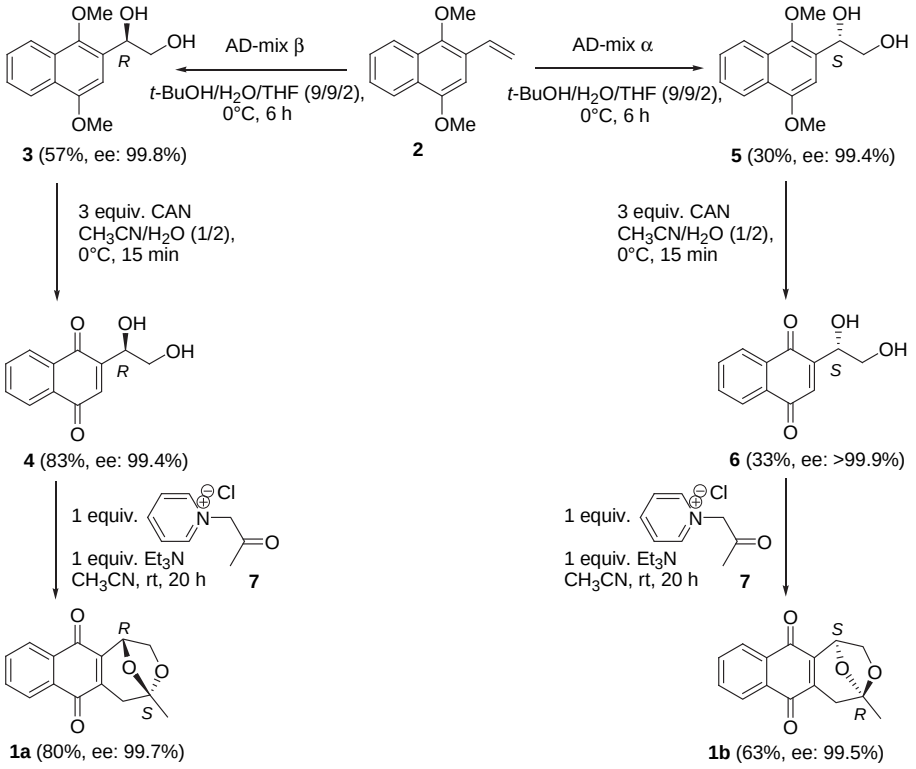
vinylnaphthalene **2**,[3] which was subjected to a Sharpless asymmetric dihydroxylation using the AD-mix β catalyst and resulted in the formation of 2-(1*R*,2-dihydroxyethyl)-1,4-dimethoxynaphthalene **3** in 57% yield (Scheme 1). Then, cerium(IV) ammonium nitrate (CAN) was used in aqueous acetonitrile to oxidize the 1,4-dimethoxynaphthalene **3** to 2-(1*R*,2-dihydroxyethyl)-1,4-naphthoquinone **4** in 83% yield via oxidative demethylation. Analogous results were obtained for 1*S*,4*R*-isagarin **1b** using AD-mix α catalyst instead of AD-mix β (Scheme 1). Introduction of the acetonyl group and formation of the final isagarins **1a** and **1b** was performed as described previously.[3]

a single enantiomer as a difference of 29° and 5° could be witnessed, respectively (Table 1). Finally, the melting points of the different enantiomers were found to be similar and a difference in the melting points of both the synthesized enantiomers with the corresponding racemate can be witnessed (Table 2). Different melting points between pure enantiomers and a racemate are common in literature,[6] which can be ascribed to a different crystalline structure.

Finally, the activity of the synthesized 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b** was tested *in vitro* against *Mycobacterium tuberculosis* H37Rv, in a luciferase screening assay.[7] Two concentration



Scheme 1.

The enantiomeric excess (ee) of the different synthesized compounds was determined by high performance liquid chromatography on an immobilized amylose derivative chiral column (Chiralpak® IA column) (Table 1). Interestingly, a comparison of the optical rotation of the synthesized 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b** with the reported α_D value of the naturally occurring isagarin **1**[1] suggests that the natural product does not occur as

Table 1
Enantiomeric excess (ee) and optical rotation of the synthesized compounds

Compound	Solvent mixture HPLC	ee (%)	Solvent	Concentration (g/100 ml)	α_D(°)
3	Heptane/*i*-PrOH 4/1	99.8	$CHCl_3$	0.17	−31
5	Heptane/*i*-PrOH 4/1	99.4	$CHCl_3$	0.34	+32
4	MTBE/EtOH 49/1[a]	99.4	*i*-PrOH	0.17	−37
6	MTBE/EtOH 49/1[a]	>99.9	*i*-PrOH	0.24	+39
1a	MTBE/EtOH 49/1[a]	99.7	$CHCl_3$	0.51	+17
1b	MTBE/EtOH 49/1[a]	99.5	$CHCl_3$	0.33	−17
natural isagarin (Ref. 1)	Not determined		$CHCl_3$	0.25	−12

[a] MTBE=Methyl *tert*-butyl ether.

levels (10 μM and 1 μM) were tested on their ability to stop or slow down growing the luminescent *M. tuberculosis* and Streptomycin, which has a strong bactericidal activity, was used as a negative control. However, both the synthesized target compounds **1a** and **1b** were found to be inactive against *M. tuberculosis*.

In conclusion, an enantioselective synthesis of both 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b** was achieved with excellent enantiomeric excesses, after a Sharpless asymmetric dihydroxylation of 1,4-dimethoxy-2-vinylnaphthalene **2**, oxidative demethylation and subsequent reaction with an acetylmethyl pyridinium ylid. In addition, a comparison of the optical rotation of the chiral isagarins **1a** and **1b** with the reported α_D value of the naturally occurring isagarin **1** suggests that the natural product does not occur as a single enantiomer.

3. Experimental section

3.1. General experimental methods

Spectroscopic data were recorded as follows: ^{1}H NMR spectra were recorded at 400 MHz or 300 MHz, ^{13}C NMR spectra were recorded at 100 MHz or 75 MHz. Melting points (mp) were

Table 2
Melting points of the synthesized compounds

Compound	Solvent of crystallization*	Mp (°C)	Racemate (Ref. 3)	
			Solvent of crystallization	Mp (°C)
3	–[a]	122.0–122.8	–[b]	79–81
5	–[a]	123.4–124.0		
4	EtOAc	161.2–162.5	CH_2Cl_2	143
6	EtOAc	160.7–161.3		
1a	EtOH	180.1–180.8	EtOH	165.1–165.4
1b	EtOH	179.7–180.2		
natural isagarin (Ref. 1)	MeOH	160.9–161.4	—	—

[a] The crystals were obtained pure directly after flash chromatography on silica gel (petroleum ether/EtOAc 1/9).
[b] The crystals were obtained pure directly after flash chromatography on silica gel (hexane/EtOAc 1/4).

determined on a Büchi B540 melting point apparatus with a temperature gradient of 1 °C/min. The reported melting points are not corrected. Infrared spectra were recorded with a Perkin–Elmer Spectrum BX FT-IR apparatus using the attenuated total reflection (ATR) technology. Mass spectra were recorded using a direct inlet system (70 eV) with a VL detector (ES, 4000 V). For the chiral HPLC a Chiralpak® IA column was used. Elemental analyses were executed with Perkin–Elmer Series II CHNS/O Analyzer 2400. Flash chromatography was carried out using a glass column with silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis.

The recorded experimental properties of all the synthesized compounds were found to be identical to literature data.[3]

3.2. General procedure for the Sharpless asymmetric dihydroxylation of 1,4-dimethoxy-2-vinylnaphthalene 2

To a round bottomed flask was added 10 ml of *t*-BuOH, 10 ml of water and AD mix-α or β (2.80 g, 1.4 g/mmol), which was purchased commercially. The mixture was stirred at room temperature for 5 min and then cooled to 0 °C. To this solution was added 1,4-dimethoxy-2-vinylnaphthalene **2** (2 mmol, 0.43 g), dissolved in THF (2.2 ml), and the reaction mixture was stirred vigorously at 0 °C for 6 h. The reaction was quenched with saturated aqueous sodium sulfite at room temperature. Ethyl acetate (15 ml) was added to the reaction mixture and after separation of the layers, the aqueous phase was extracted two more times with ethyl acetate. The combined organic layers were washed with brine and dried (Na_2SO_4). Flash chromatography on silica gel with petroleum ether/ethyl acetate 1/9 as eluent gave 2-(1,2-dihydroxyethyl)-1,4-dimethoxynaphthalenes **3** or **5**. The spectral data of compounds were in accordance with data reported in literature,[3] and the optical rotation along with the melting points are shown in Tables 1 and 2, respectively.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.04.105. These data include MOL files and InchIkeys of the most important compounds described in the article

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