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-vinylnaphtalene **2**. The key steps involve a Sharpless asymmetric dihydroxylation and reaction with an acetonylating pyridinium ylid.

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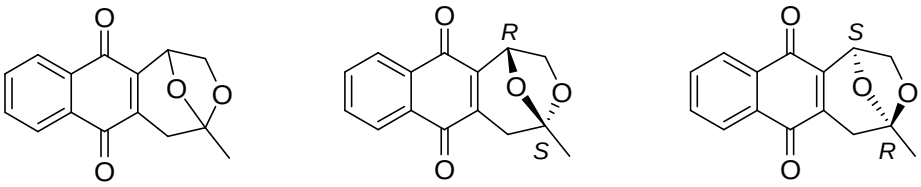
Keywords

Isagarin, *Pentas longiflora* Oliv., Sharpless asymmetric dihydroxylation.

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]



1 **1a** **1b**

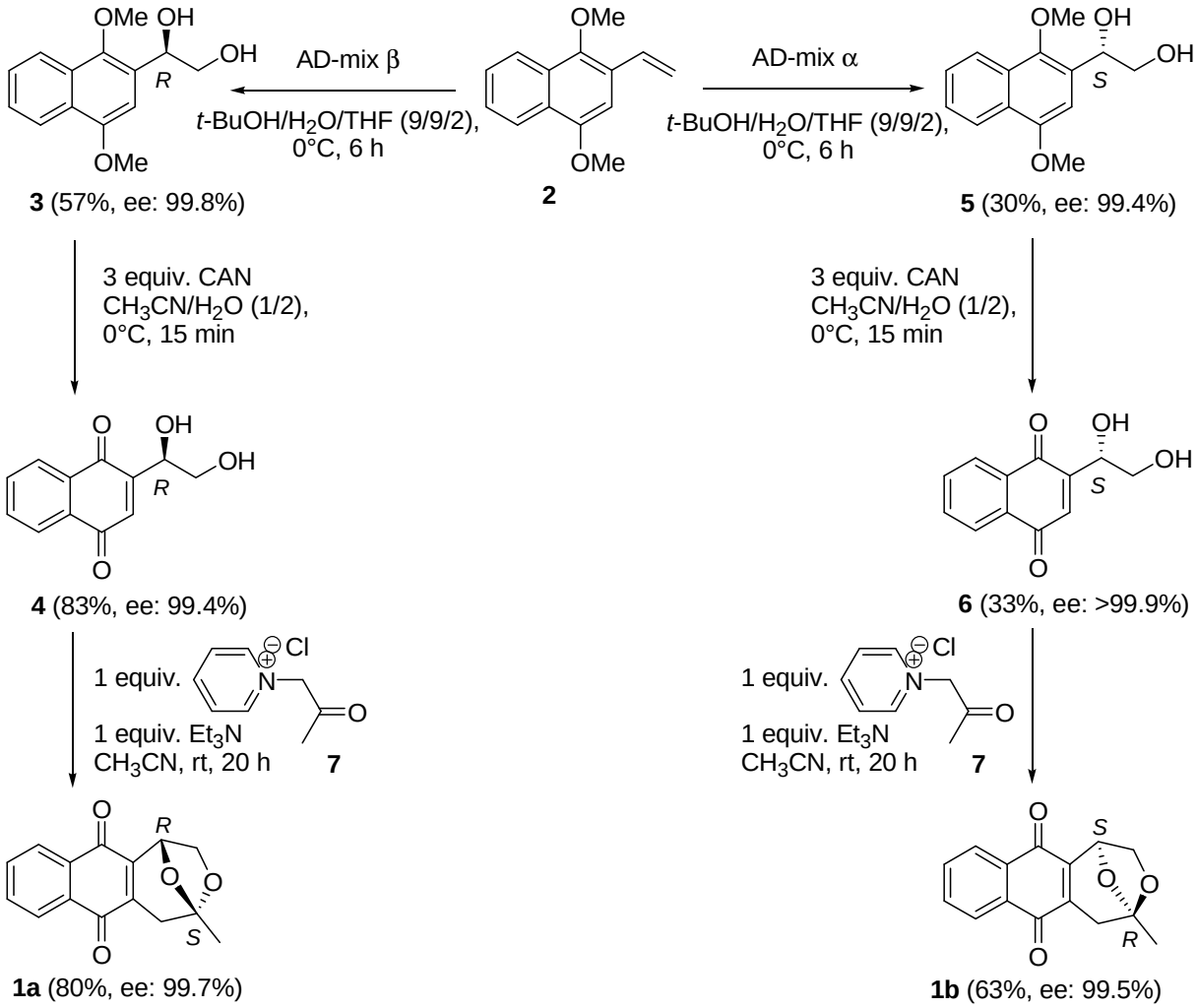
Due to its interesting architecture, isagarin is an attractive target for synthetic chemists, which resulted in a first racemic synthesis by our department.[3] Later, a total synthesis of isagarin **1** was reported in an overall yield of 24% using the Wacker cyclization in the key step.[4] However, isagarin **1** can exist as two different enantiomers: 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin, 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.

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-vinylnaphtalene **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-vinylnaphtalene **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).[6] Then, cerium(IV) ammonium nitrate (CAN) was used in aqueous acetonitrile to oxideze the 1,4-dimethoxynaphthalene **3** to 2-(1*R*,2-dihydroxyethyl)-1,4-naphthoquinone **4** in 83% yield via oxidative demethylation. Analogously, 1*S*,4*R*-isagarin **1b** was prepared starting from vinylnaphthalene **2** by treatment with AD-mix α catalyst to afford 2-(1*S*,2-dihydroxyethyl)-1,4-dimethoxynaphthalene **5** in 30% yield by means of a Sharpless asymmetric dihydroxylation (Scheme 1). Cerium(IV) ammonium nitrate mediated oxidation of the 1,4-dimethoxtynaphthalene **5** provided 2-(1*S*,2-dihydroxyethyl)-1,4-naphthoquinone **6** in a 33% yield. In a last step an acetonyl group was introduced across 1,4-naphthoquinones **4** and **6** by Michael addition of acetylmethyl pyridinium ylid, which was generated *in situ* by treatment of acetylmethyl pyridinium chloride **7** with one equivalent of triethylamine in

acetonitrile, to furnish 1*R*,4*S*-isagarin **1a** and 1*S*,4*R*-isagarin **1b** after spontaneous intramolecular condensation in a yield of 80% and 63%, respectively.



Scheme 1

The enantiomeric excess (e.e.) 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 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). Although different melting points between pure enantiomers and a racemate are common in literature,[7] it can be ascribed to a different crystalline structure.

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

Compound	Solvent mixture HPLC	e.e. (%)	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

Table 2. Melting points of the synthesized compounds

Compound	Solvent of crystallization*	mp (°C)	Racemate (ref. 3) Solvent of crystallization	mp (°C)
3	—[1]	122.0-122.8	—[2]	79-81
5	—[1]	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	—	—

[1] The crystals were obtained pure directly after flash chromatography on silicagel (petroleum ether/EtOAc 1/9)

[2] The crystals were obtained pure directly after flash chromatography on silicagel (hexane/EtOAc 1/4)

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-vinylnaphtalene **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.

Acknowledgement

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[6] **General procedure for the Sharpless asymmetric dihydroxylation of 1,4-dimethoxy-2-vinylnaphtalene 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 minutes 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 was stirred vigorously at 0°C for 6 hours. 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 Table 1 and 2, respectively.

[7] Examples can be found in: Levkin, P.A., Strelenko, Y.A., Lyssenko, K.A., Schurig, V., Kostyanovsky, R.G. *Tetrahedron Asymm.*, **2003**, *14*, 2059-2066.

Graphical Abstract

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