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Total Syntheses of Isowondonins Based on a Biosynthetic Pathway

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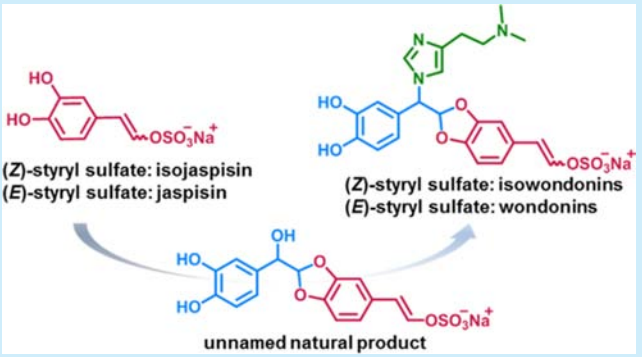
Supporting Information

ABSTRACT: The first total syntheses of (−)-isowondonin A and (−)-isowondonin B, which are unusual imidazole marine alkaloids, has been accomplished through the development of methods for the selective formation of styryl sulfate group and regioselective alkylation of the imidazole. Application of the Noyori asymmetric hydrogenation of ketones allows the asymmetric synthesis. These results in conjunction with ECD calculations led to the determination of the absolute configuration of isowondonins.



From an association of the sponges *Poecillatra wondoensis* and *Jaspis* sp., four bis(dihydroxystyrenyl)imidazole marine alkaloids (**1**−**4**, Figure 1) were isolated by one of us and named

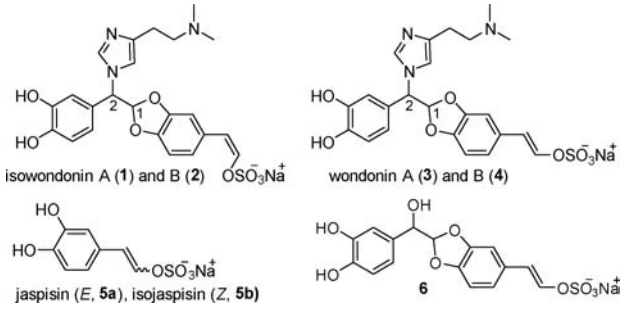


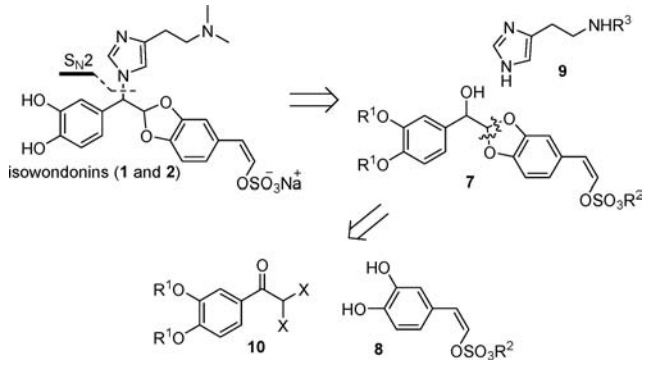
Figure 1. Structures of isowondonins (**1** and **2**), wondonins (**3** and **4**), and other styryl sulfate natural products.

wondonins and isowondonins according to the configuration of the styryl double bond.[1] These marine alkaloids are structurally unique by virtue of their dimeric dihydroxystyrenyl skeleton with a five-membered acetal ring and an embedded styryl sulfate moiety. The planar structure was determined by various spectroscopic methods. However, the relative and absolute stereochemistry of C1 and C2 could not be determined because of the lack of reliable NOE correlations.

The family of wondonins exhibit interesting biological activities, including antiangiogenic activity.[1,2] For example, wondonins inhibited the tube formation of human umbilical vein endothelial cells induced by bFGF or hypoxia without overt cytotoxicity,[1a,2] which are unique and useful characteristics for the development of new angiogenesis inhibitors with fewer side effects and less toxicity. Because of their unique biological and structural properties, wondonins have high potential to become a new class of antiangiogenic therapeutic agents. However, these natural products, like others, have many hurdles to clear. One challenge is the very restricted availability of the natural source. Chemical synthesis is the most likely solution for securing materials for further biological investigations. Herein we present the first total synthesis and determination of the relative and absolute stereochemistry of isowondonins (**1** and **2**).

Because jaspisins **5**[3] and the unnamed natural product **6** (Figure 1) were also identified during the process of isolating **1**−**4**,[1b] the wondonin family may originate biosynthetically from **6**, which in turn is formed from jaspisins **5**. According to this plausible biosynthetic pathway, our synthetic route to isowondonins was planned as shown in Scheme 1. with the preparation of dimeric dihydroxystyrene **7** from styryl sulfate **8** in the early stage of the synthesis, followed by its combination with histamine moiety **9**.

Scheme 1. Retrosynthetic Analysis of Isowondonins (1, 2)



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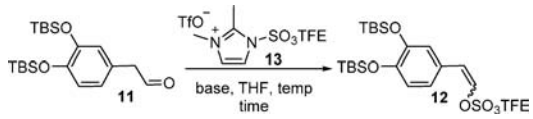
One of the major synthetic challenges afforded by members of the wondonin family includes the preparation of the styryl sulfate moiety. Although several natural products with a styryl or vinyl sulfate moiety have been reported,[3,4] synthetic methods to access these functional groups are very limited and suffer from low yields.[5] The available method for the preparation of vinyl sulfate is based on the use of an elimination reaction to form a vinyl residue from an α-chloro *O*-sulfated substrate[5c] or a cyclic sulfate.[5a,b] The application of this elimination method to the total synthesis would compel the introduction of the vinyl sulfate moiety at a late synthetic stage because of its instability and high polarity. This strategy may cause several difficulties during the total synthesis, including intensive and careful manipulation of protecting groups. Therefore, we chose an early-stage introduction of the styryl sulfate in a protected form followed by removal of the protecting group for sulfate at the end of the synthesis.

Our total synthesis started with an investigation of methods for the efficient and stereoselective formation of the styryl sulfate group. Inspired by the facile synthesis of vinyl tosylates or vinyl triflates from the corresponding carbonyl compounds via enol intermediates,[6] we envisioned that trapping of the enolate from α-aryl aldehyde **11** (Table 1) with a suitable

Table 1. Synthesis of Styryl Sulfate 12[a]



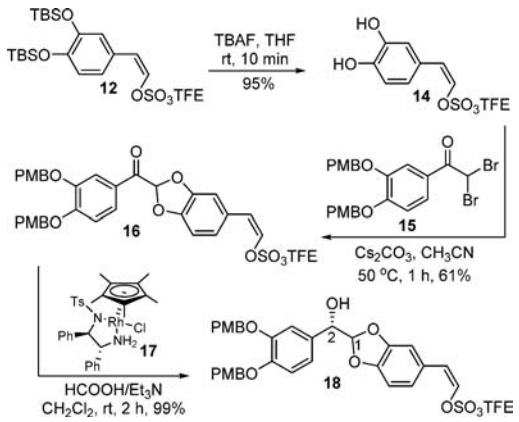
entry	base (equiv)	temp	time (h)	yield (%)[b]	*Z*:*E*
1	TEA (4)	rt	13	31	1:1
2	DIPEA (4)	rt	16	36	1:1
3	DBU (2)	rt	0.5	93	1:1
4	DBU (2)	0 °C	0.5	90	2:1
5	DBU (2)	−90 °C	0.5	92	6:1

[a]Reactions were run with **13** (4 equiv) at a substrate concentration of 0.1 M. [b]Isolated yields.

sulfating agent would afford the desired styryl sulfate in a protected form. As a protecting group for sulfate, we chose a 2,2,2-trifluoroethyl (TFE) group because sulfate esters with this protecting group are sufficiently stable under a variety of conditions to allow multistep synthesis with it.[7] Attempts at transforming α-aryl aldehyde **11** into styryl sulfate **12** were not successful[8] until sulfuryl imidazolium salt **13**[9] was employed as the sulfating agent. When DBU was used as a base in THF at −90 °C, the desired styryl sulfate **12** was obtained in high yield in a ratio of 6:1 favoring the *Z* isomer. The *Z*:*E* geometric selectivity was dependent on the reaction temperature, as summarized in Table 1.[8]

The obtained *cis*-styryl sulfate **12** was taken forward to the natural products. First, the silyl protecting groups of **12** were removed with TBAF to yield **14** (Scheme 2). For the asymmetric synthesis with catechol **14** or its monoprotected derivatives, we initially focused on the installation of the chiral center at the C1 acetal position during the formation of a dimeric dihydroxystyrenyl skeleton. However, because of the lack of availability of such asymmetric reactions, these attempts were not successful. Thus, dimeric dihydroxystyrene **16** was prepared in racemic form by condensation with α,α-dibromoketone **15** in the presence of Cs_2CO_3 at 50 °C.[10] It

Scheme 2. Synthesis of Dimeric Dihydroxystyrenyl Compound 18



is noteworthy that the vinyl sulfate group decomposed when the reaction temperature exceeded 50 °C.

In order to establish the absolute configuration at C2, the ketone of **16** was subjected to the action of Noyori's (*R*,*R*)-RhTsDPEN catalyst **17** under transfer hydrogenation conditions.[11] The corresponding alcohol **18** was obtained in 99% yield in a ratio of 19:1 in favor of the *S* configuration at C2.[12] At this stage, the two diastereomers resulting from mixed stereochemistry at C1 were inseparable. Therefore, we proceeded with the mixture of diastereomers.

Having obtained the dimeric dihydroxystyrenyl skeleton, we next explored the introduction of the histamine moiety at C2 (Scheme 3). The C2 hydroxyl group of **18** was converted to a bromide under Appel conditions[13] to yield **19**. The substitution reaction of **19** with *N*-Boc-protected histamine **20** in CH_3CN at 40 °C afforded a mixture of regioisomeric products in a 1:1 ratio due to the tautomeric equilibrium of the imidazole ring.[8] Addition of base to the reaction mixture caused the decomposition of **19**. To overcome the regioselectivity problem, we investigated directing groups that could differentiate the two nitrogen atoms in the imidazole ring and could be easily removed after the reaction. After some efforts, we determined that an iodine group at the 5′-position was suitable for this purpose. When the substitution reaction was performed with iodinated histamine **21**[14] in CH_3CN at 40 °C for 60 h, compound **22** was obtained as the only detectable regioisomer (31% yield, 83% brsm). At a higher temperature, the vinyl sulfate moiety decomposed, and a complex mixture was obtained. To understand the obtained regioselectivity, a DFT study was performed. The calculated "relative nucleophilicity"[15] values of the two nitrogens in **21** differed considerably (N1′ = 3.5, N3′ = 0.7) compared with those of the two nitrogens in **20** (N1′ = 0.3, N3′ = 0.5).[16]

Separation of the diastereomers of **22** was possible using Prep-HPLC. The separated diastereomers **22a** and **22b** both showed a negative optical rotation. The enantiomeric purities of **22a** and **22b**, as determined by chiral HPLC analysis, were found to be 87 and 86% ee, respectively. These percentages correspond to a ratio of 19:1, which indicated the conservation of the enantiomeric purity at C2 in the two successive substitution reactions (**18** → **22**).

To finish the total synthesis with **22a**, the iodine-directing group was removed with $NaBH_4$, and the *N*-Boc and PMB protecting groups were simultaneously removed using trifluoroacetic acid to afford **23a** in 74% yield over the two steps. The

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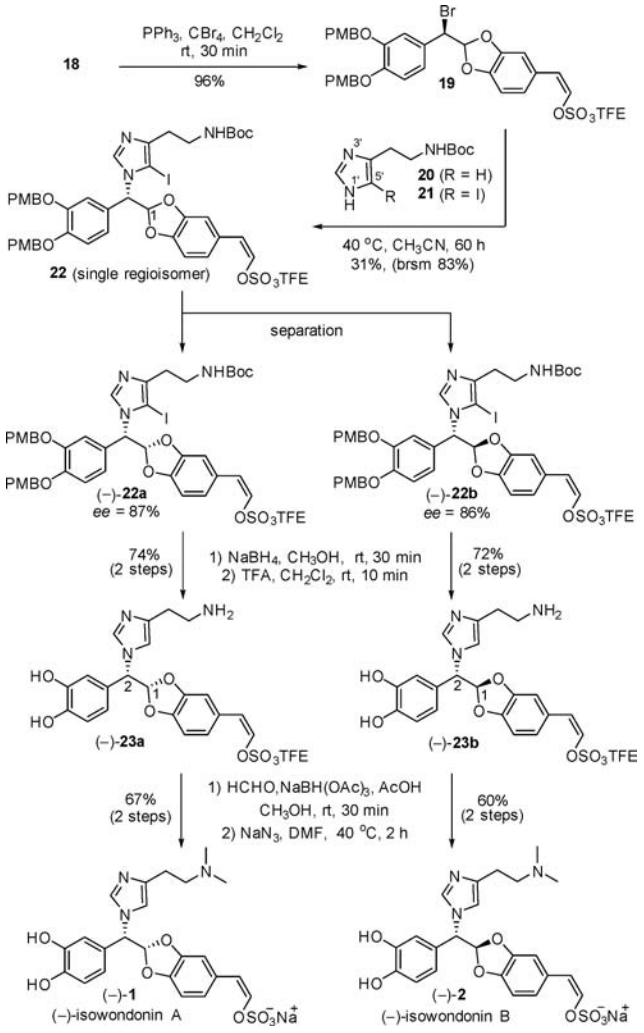
Scheme 3. Completion of the Syntheses of (−)-Isowondonin A (1) and (−)-Isowondonin B (2)



N,*N*-dimethylation of the primary amine function in **23a** was achieved by treatment with formalin and $NaBH(OAc)_3$. Finally, the TFE protecting group of the sulfate was removed using NaN_3 in DMF[9] to afford isowondonin in 67% yield over the two steps. The synthetic isowondonin obtained from **22a** exhibited a negative optical rotation $\{[\alpha]_D^{20}$ −4.2 (*c* 0.72, $CH_3OH)\}$, and its NMR spectra were in good agreement with those of isowondonin A (**1**). For the synthesis of isowondonin from **22b**, we used the same sequence of reactions as applied to the synthesis of **1** from **22a**. The isowondonin obtained from **22b** also exhibited a negative rotation $\{[\alpha]_D^{20}$ −4.5 (*c* 0.65, $CH_3OH)\}$, and the spectra were identical to those of isowondonin B (**2**). The reported optical rotations of isowondonins A and B are both negative ($\{[\alpha]_D^{20}$ −4.0 (*c* 0.72, $CH_3OH)\}$ and $\{[\alpha]_D^{20}$ −3.7 (*c* 0.65, $CH_3OH)\}$). These observations suggested that isowondonins A and B possess an *S* configuration at C2 and are epimers at the C1 acetal position.

After determining the C2 configuration of the isowondonins, electronic circular dichroism (ECD) spectroscopy was used to define the configuration of C1.[17] Because the experimental ECD spectrum of isowondonins was not suitable, the ECD analysis was performed using compound **23**. Theoretical calculations of the ECD spectrum were conducted for all four possible enantiomers of **23a** and **23b** using time-dependent DFT at the B3LYP/SVP level in methanol. As shown in Figure 2, the calculated ECD spectrum of the (1*S*,2*S*) isomer exhibited

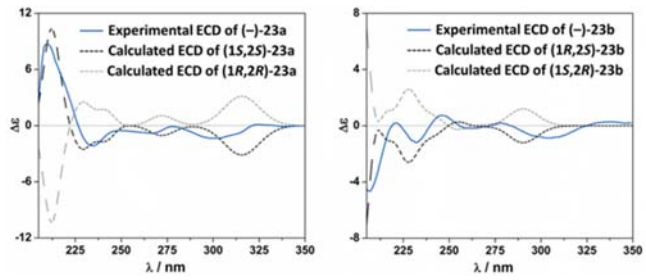


Figure 2. Experimental and calculated ECD spectra of (−)-**23a** and (−)-**23b**.

good agreement with the experimental spectrum of (−)-**23a** in methanol, and the spectrum of the (1*R*,2*S*) isomer was in good agreement with the experimental curve of (−)-**23b**.[18] Therefore, the stereochemistry of isowondonins A and B was assigned as shown in Scheme 3.

In summary, we have completed the first total synthesis of bis(dihydroxystyrenyl)imidazole marine alkaloids. The biomimetic synthesis of isowondonins was achieved using a convergent strategy. Key aspects of the synthesis include the selective formation of styryl sulfate in a protected form and the regioselective alkylation of the iodinated imidazole. Noyori's asymmetric hydrogenation was employed to install the stereocenter at C2. In combination with the asymmetric synthesis, ECD calculations enabled us to determine the stereochemistry of the isowondonins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01336.

Copies of ^1H and ^{13}C NMR spectra of all new compounds and preparation of starting materials (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Shin, J.; Rho, J.-R.; Seo, Y.; Lee, H.-S.; Cho, K. W.; Kwon, H. J.; Sim, C. J. *Tetrahedron Lett.* **2001**, *42*, 1965. (b) Chang, Y. H.; Shin, D.; Na, Z.; Lee, H.-S.; Kim, D.-D.; Oh, K. B.; Shin, J. *J. Nat. Prod.* **2008**, *71*, 779.

(2) Jun, H.-O.; Kim, Y.; Kwon, Y.-W.; Hong, S.-S.; Kim, K.-W.; Shin, J.; Kim, T.-Y. *FEBS Lett.* **2007**, *581*, 4977.

DOI: 10.1021/acs.orglett.6b01336
Org. Lett. 2016, 18, 2986−2989

(3) (a) Ohta, S.; Kobayashi, H.; Ikegami, S. *Biosci., Biotechnol., Biochem.* **1994**, *58*, 1752. (b) Ohta, S.; Kobayashi, H.; Ikegami, S. *Tetrahedron Lett.* **1994**, *35*, 4579.
(4) (a) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *Tetrahedron Lett.* **1994**, *35*, 5873. (b) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *Tetrahedron* **1994**, *50*, 13583. (c) Musman, M.; Ohtani, I. I.; Nagaoka, D.; Tanaka, J.; Higa, T. *J. Nat. Prod.* **2001**, *64*, 350. (d) Pereira, A. R.; Byrum, T.; Shibuya, G. M.; Vanderwal, C. D.; Gerwick, W. H. *J. Nat. Prod.* **2010**, *73*, 279.
(5) (a) Dagron, F.; Lubineau, A. *J. Carbohydr. Chem.* **2000**, *19*, 311. (b) Zeitouni, J.; Norsikian, S.; Merlet, D.; Lubineau, A. *Adv. Synth. Catal.* **2006**, *348*, 1662. (c) Bedke, D. K.; Shibuya, G. M.; Pereira, A. R.; Gerwick, W. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2010**, *132*, 2542.
(6) (a) Ritter, K. *Synthesis* **1993**, *1993*, 735. (b) Chassaing, S.; Specklin, S.; Weibel, J. M.; Pale, P. *Curr. Org. Synth.* **2012**, *9*, 806. (c) Chassaing, S.; Specklin, S.; Weibel, J.-M.; Pale, P. *Tetrahedron* **2012**, *68*, 7245.
(7) (a) Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett.* **1997**, *38*, 7243. (b) Karst, N. A.; Islam, T. F.; Avci, F. Y.; Linhardt, R. J. *Tetrahedron Lett.* **2004**, *45*, 6433. (c) Miller, S. C. *J. Org. Chem.* **2010**, *75*, 4632.
(8) See the Supporting Information for details.
(9) Desoky, A. Y.; Hendel, J.; Ingram, L.; Taylor, S. D. *Tetrahedron* **2011**, *67*, 1281.
(10) (a) Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Monopoli, A.; Ongini, E.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2002**, *45*, 115. (b) Stack, D. E.; Hill, A. L.; Diffendaffer, C. B.; Burns, N. M. *Org. Lett.* **2002**, *4*, 4487. (c) Kim, B.-H.; Lee, J.; Choi, J.-S.; Park, D. Y.; Song, H. Y.; Park, T. K.; Cho, C.-H.; Ye, S.-K.; Joo, C.-K; Koh, G. Y.; Kim, T.-Y. *Br. J. Pharmacol.* **2015**, *172*, 3875.
(11) (a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393. (b) Ikariya, T.; Blacker, J. *Acc. Chem. Res.* **2007**, *40*, 1300.
(12) The configuration of C2−OH of **18** was assigned by Mosher analysis. See the Supporting Information for details.
(13) (a) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801. (b) de Andrade, V. S. C.; de Mattos, M. C. S. *Curr. Org. Synth.* **2015**, *12*, 309.
(14) Jain, R.; Avramovitch, B.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 3235.
(15) Roy, R. K.; Krishnamurti, S.; Geerlings, P.; Pal, S. *J. Phys. Chem. A* **1998**, *102*, 3746.
(16) DFT computations were performed using Material Studio 2016 and Gaussian 09. See the computational study section in the Supporting Information for details.
(17) (a) Berova, N.; Di Bari, L.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914. (b) Nugroho, A. E.; Morita, H. *J. Nat. Med.* **2014**, *68*, 1.
(18) The calculated ECD spectra of the (1*R*,2*R*) and (1*S*,2*R*) isomers were in agreement with the experimental spectra of the enantiomers prepared from **16** using Noyori's (*S*,*S*)-RhTsDPEN catalyst. See the Supporting Information for details.

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