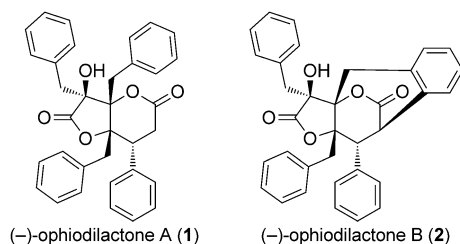


Total Synthesis of (–)-Ophiodilactone A and (–)-Ophiodilactone B**

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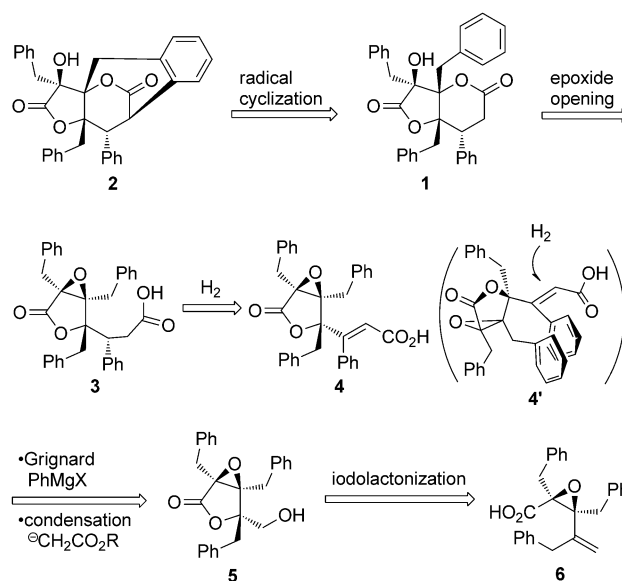
Abstract: The first asymmetric total synthesis of (–)-ophiodilactone A and (–)-ophiodilactone B, isolated from the ophiuroid (*Ophiocoma scolopendrina*), is reported. The key features of the synthesis include the highly stereocontrolled construction of the structurally congested γ -lactone/ δ -lactone skeleton through an asymmetric epoxidation, diastereoselective iodolactonization, and intramolecular epoxide-opening with a carboxylic acid, and biomimetic radical cyclization of ophiodilactone A to ophiodilactone B.

In 2009, Matsunaga and co-workers reported the isolation of ophiodilactones A (**1**) and B (**2**) from *Ophiocoma scolopendrina*, a tropical and subtropical ophiuroid widely distributed in the Indo-Pacific. These compounds exhibit moderate cytotoxic activity against P388 murine leukemia cells with IC_{50} values of 5.0 and 2.2 $\mu\text{g mL}^{-1}$, respectively.^[1] Intensive NMR studies led to the determination of their characteristic compact structures consisting of a fused γ -lactone/ δ -lactone skeleton with four phenyl groups and four or five contiguous stereogenic centers containing three quaternary centers. The absolute structures of **1** and **2** were tentatively determined based on the analysis of the CD-spectroscopic data of **1**.^[1]



Their unique highly substituted dilactone structures and biological activities prompted us to investigate the synthesis of ophiodilactones.^[2] Herein we describe the first total synthesis of (–)-ophiodilactone A (**1**) and (–)-ophiodilactone B (**2**), thereby unambiguously determining their absolute structures.

Matsunaga and co-workers proposed that ophiodilactone B (**2**) would be directly biosynthesized from ophiodilactone A (**1**) through a radical cyclization.^[1] Inspired by this hypothesis, we envisioned **1** as a precursor of **2** (Scheme 1). Since, to our knowledge, such an intramolecular radical



Scheme 1. Retrosynthetic analysis.

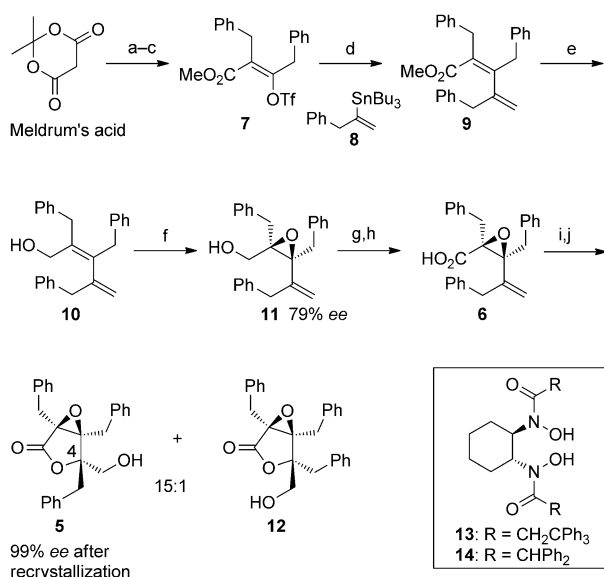
coupling between a benzene ring and a δ -lactone with site selectivity is unprecedented,^[3,4] it would be a very challenging goal to accomplish this radical process. From a retrosynthetic perspective, we assumed that ophiodilactone A (**1**) would be accessible from **3** by intramolecular epoxide opening with a carboxylic acid group with inversion of stereochemistry. To access **3** we envisioned hydrogenation of **4**, which was expected to preferentially proceed with desired diastereoselectivity as depicted in **4'**.^[5] We reasoned that compound **4** could be accessed from **6** via **5** by an approach involving diastereoselective iodolactonization and addition of phenyl and acetic acid units.

In our preliminary study,^[2] we have developed an eight-step synthesis of **6** from Meldrum's acid through Stille coupling^[6] of **7** with **8**^[7] and Katsuki–Sharpless asymmetric epoxidation^[8] of **10** (Scheme 2). Although the diastereoselectivity and overall yield of this synthesis were satisfying, its enantioselectivity was disappointingly low (35 % *ee*). Therefore, we first devoted our efforts to improving the asymmetric epoxidation step. After considerable experimentation,^[9] we eventually found that the method developed by Yamamoto and co-workers^[10] afforded epoxy alcohol **11** in acceptable enantioselectivity and yield although it proceeded very

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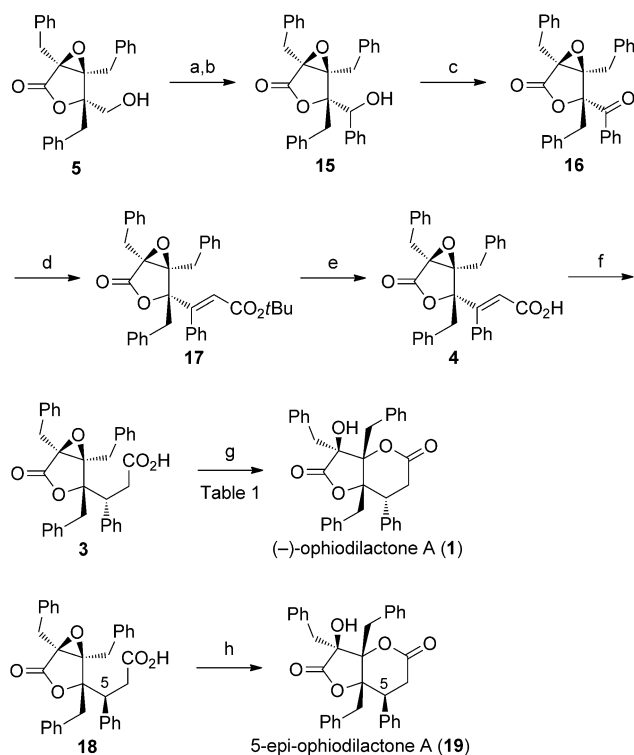
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201307835>.



Scheme 2. Reagents and conditions: a) PhCH₂COCl, pyridine, CH₂Cl₂, then MeOH, reflux, 99%; b) PhCH₂Br, NaH, benzene/DMF, 85 °C, 82%; c) Tf₂O, 5 M LiOH, hexane, 0 °C, 93%; d) **8**, [Pd(PPh₃)₄] (0.1 equiv), CuCl, LiCl, DMSO, 80 °C, 94%; e) DIBAL-H, CH₂Cl₂, –78 °C, 97%; f) *t*BuOOH, **13** (0.1 equiv), VO(O*i*Pr)₃ (0.05 equiv), toluene, 0 °C, 89%; g) Dess–Martin periodinane, NaHCO₃, CH₂Cl₂; h) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*BuOH/H₂O, 0 °C; i) I₂, aq NaHCO₃, CH₂Cl₂, 0 °C; j) 20 M NaOH, THF, 50 °C, then H₂SO₄, 0 °C, 94% (15:1 mixture), 65% (enantiomerically pure **5** after recrystallization) from **11** (4 steps).

sluggishly. Thus, when compound **10** was reacted with *tert*-butyl hydroperoxide using **13** (0.1 equiv) and VO(O*i*Pr)₃ (0.05 equiv) in toluene at 0 °C for 6 days, **11** was obtained in 79% *ee*^[11] and 89% yield. The use of **14** in place of **13** resulted in comparable enantioselectivity (78% *ee*) albeit the yield became lower (60%). Compound **11** was then subjected to Dess–Martin oxidation followed by Pinnick–Kraus oxidation to provide carboxylic acid **6** cleanly. Upon successive iodolactonization, alkaline hydrolysis, and acidic lactonization, **6** afforded γ -lactones **5** and **12** in a ratio of 15:1 in 94% yield from **11**. Interestingly, the ratio turned out to be sensitive to the final acidic lactonization conditions. When this process was carried out at 80 °C rather than 0 °C, the ratio diminished to 6:1,^[2] implying the partial intervention of the C4 tertiary carbocation during lactonization of the corresponding dihydroxy carboxylic acid. At this stage enantiomerically pure **5** was obtained after recrystallization from benzene (65% from **11**). An X-ray structure^[12] of the mesylate derived from **5** allowed us to unambiguously determine the absolute configuration of **5** as depicted.

With the desired γ -lactone **5** in hand, we next investigated the synthesis of ophioidilactone A (**1**; Scheme 3). Compound **5** was subjected to Swern oxidation followed by Grignard reaction using phenylmagnesium chloride to give alcohol **15**, which was then oxidized to **16**. Peterson olefination^[13] of **16** proceeded smoothly to afford unsaturated ester **17** in 94% yield with excellent *E* selectivity, whereas either Horner–Wadsworth–Emmons or Wittig olefination did not produce **17** at all. As expected from the conformational analysis by



Scheme 3. Reagents and conditions: a) (COCl)₂, DMSO, CH₂Cl₂, –78 °C, then Et₃N; b) PhMgCl, THF, –40 °C, 81% (2 steps); c) Dess–Martin periodinane, NaHCO₃, CH₂Cl₂, 92%; d) Me₃SiCH₂CO₂*t*Bu, LHMDs, HMPA, –78 °C, 94%; e) TFA/CH₂Cl₂ (1:10), 60 °C; f) H₂, 20% Pd(OH)₂/C, AcOEt, 0 °C; g) HOCH₂CH₂OH, 150 °C, 55% from **17** (3 steps); h) H₂O, 150 °C, sealed tube, 40%.

molecular mechanics calculations, **17** did not undergo hydrogenation because of the steric bulkiness of the *tert*-butyl ester group. In fact, we successfully obtained the hydrogenated compound **3** from sterically less hindered carboxylic acid **4**. Notably, this hydrogenation took place with excellent diastereoselectivity at 0 °C and the corresponding C5-epimer **18** was not observed in the ¹H NMR, whereas the reaction at room temperature afforded a 7:1 mixture of **3** and **18**. To complete the total synthesis of ophioidilactone A (**1**), we explored the crucial intramolecular epoxide-opening reaction of **3** under various conditions (Table 1). Even acid-catalyzed conditions required higher temperatures, which caused the partial decomposition of **3** or **1** leading to the lower yield of

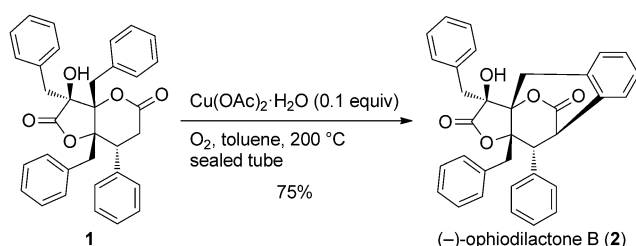
Table 1: Synthesis of ophioidilactone A from **3**.

Entry	Conditions	Yield [%] ^[a]
1 ^[b]	CSA (1 equiv), TFA (5equiv), CH ₂ Cl ₂ , 160 °C, 4 h, sealed tube	0 ^[c]
2	TFA, 100 °C, 3 days, sealed tube	15
3	TFA, 150 °C, 4 h, sealed tube	38
4	H ₂ O, 150 °C, 12 h, sealed tube	50
5	HOCH ₂ CH ₂ OH, 150 °C, 5 h	55

[a] Overall yield from **17** (3 steps). [b] Conditions reported by Trost and Kriche for the similar cyclization.^[17] [c] Compound **3** was recovered in 50% yield. CSA = camphorsulfonic acid.

1 (Table 1, entries 1–3). However, we gratifyingly found that the epoxide-opening reaction proceeded under neutral conditions when **3** was simply heated at 150 °C in a protic solvent such as water and ethylene glycol (Table 1, entries 4, 5).^[14,15] The best result was obtained under the conditions listed in entry 5, which produced (–)-ophiodilactone A (**1**) in 55 % yield from **17**. The spectral data of the synthetic ophiodilactone A were identical to those of the natural specimen^[1] in all respects. It is important to add that upon exposure of **18**^[16] to the conditions listed in entry 4, the cyclization took place sluggishly to produce 5-epi-ophiodilactone (**19**). The comparison of the spectral data of **1** and **19** allowed us to further confirm that hydrogenation of **4** occurred with desired diastereofacial selectivity.

To achieve biomimetic transformation of ophiodilactone A (**1**) to ophiodilactone B (**2**), we focused on direct oxidative coupling reactions of C–H and Ar–H bonds. Although such reactions have been widely investigated, they were mostly executed under basic conditions.^[4] However, owing to the extreme instability of **1** under basic conditions, we had to intensively seek appropriate neutral or weakly acidic conditions for our endgame. As a result, we found that when a solution of **1** in toluene was heated with Cu(OAc)₂·H₂O (0.1 equiv) at 200 °C under oxygen by modifying the procedure reported by Taylor and co-workers,^[4b,18] the radical cyclization cleanly took place to furnish (–)-ophiodilactone B (**2**) in 75 % yield (Scheme 4). The reaction



Scheme 4. Synthesis of ophiodilactone B.

proceeded with excellent site selectivity and no other cyclized products were observed. Note that when the reaction was conducted at 170 °C, the yield was dramatically diminished to 6 % and the unreacted **1** was recovered in 91 % yield. The synthetic ophiodilactone B exhibited spectral properties identical in all respects to those reported for the natural product.^[1]

In conclusion, we have accomplished the first total synthesis of (–)-ophiodilactone A (**1**) and (–)-ophiodilactone B (**2**) in enantiomerically pure forms in 14 % (17 steps) and 10 % (18 steps) overall yields from Meldrum's acid, respectively. The present work illustrates the prowess of the copper-catalyzed radical cyclization to enable biomimetic transformation of **1** to **2**.

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