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STEREOSELECTIVE SYNTHESIS OF THE FUSED γ-LACTONE/ δ-LACTONE CORE OF OPHIODILACTONES

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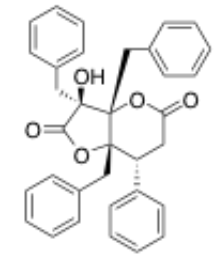
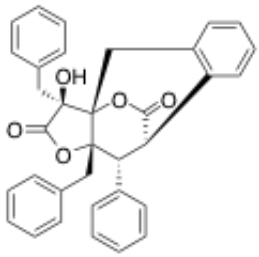
Abstract – A promising precursor of ophiodilactones A and B, tetrameric phenyl propanoids isolated form the ophiuroid *Ophiocoma scolopendrina*, has been synthesized stereoselectively employing a halolactonization and an intramolecular epoxide-opening with a carboxylic acid as key reactions.

Ophiodilactones A (**1**) and B (**2**), isolated form the ophiuroid *Ophiocoma scolopendrina*, exhibit moderate cytotoxic activity against P388 murine leukemia cells with IC_{50} values of 5.0 and 2.2 μg/mL, respectively.[1] These compounds possess characteristic 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 configuration of **1** was tentatively determined by its CD spectrum; however that of **2** has not been elucidated yet.[1] Their unique highly substituted dilactone structures and intriguing biological activities prompted us to investigate the synthesis of ophiodiactones. We report here the highly stereoselective synthesis of the fused γ-lactone/δ-lactone core **3**, a promising precursor of ophiodilactones.



ophiodilactone A (**1**)

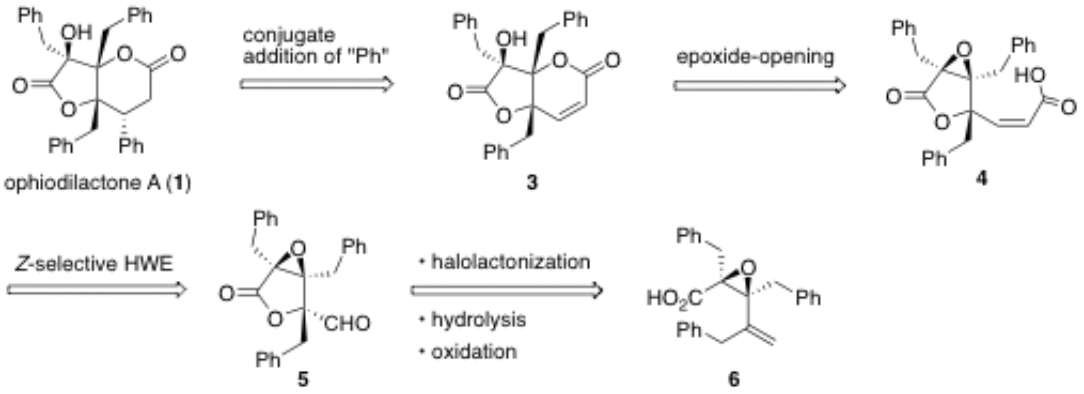


ophiodilactone B (**2**)

Since ophiodilactone B (**2**) could be accessible from ophiodilactone A (**1**) by, for example, Oikawa's method involving α-sulfinylation, Pummerer reaction accompanied by cyclization of a phenyl group, and desulfurization,[2] we focused on the synthesis of **1**. Scheme 1 illustrates our retrosynthetic analysis of **1**.

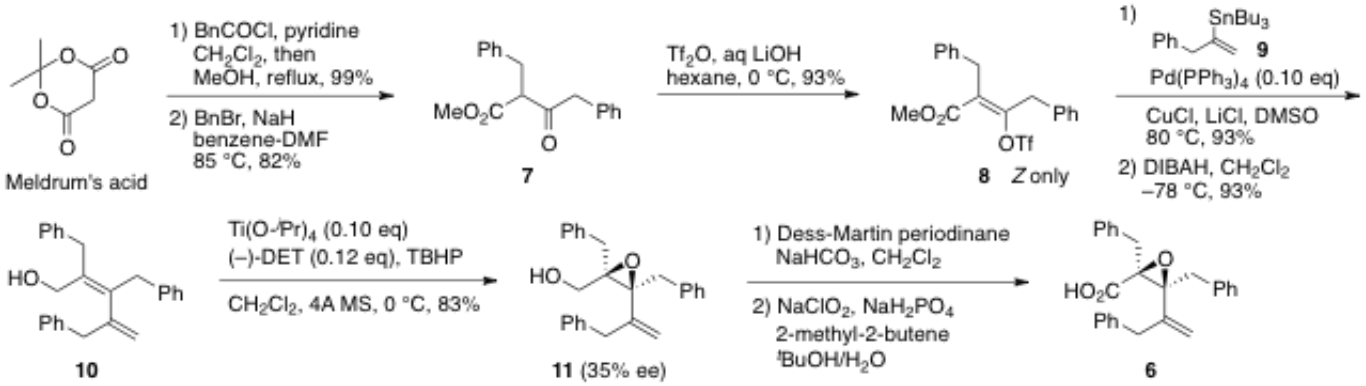
Dedicated to Prof. Ei-ichi Negishi on the occasion of his 77th birthday.

We envisaged dilactone **3** as a precursor of **1**, which could be accessed from **4** by intramolecular epoxide-opening with a carboxylic acid group. To access **4** we envisioned an approach starting with halolactonization of **6** via *Z*-selective Horner-Wadsworth-Emmons olefination of aldehyde **5**. The key issue of this approach is the diastereoselectivity of the halolactonization step as well as the feasibility of the δ-lactone formation.



Scheme 1. Retrosynthetic analysis of ophiodilactone A

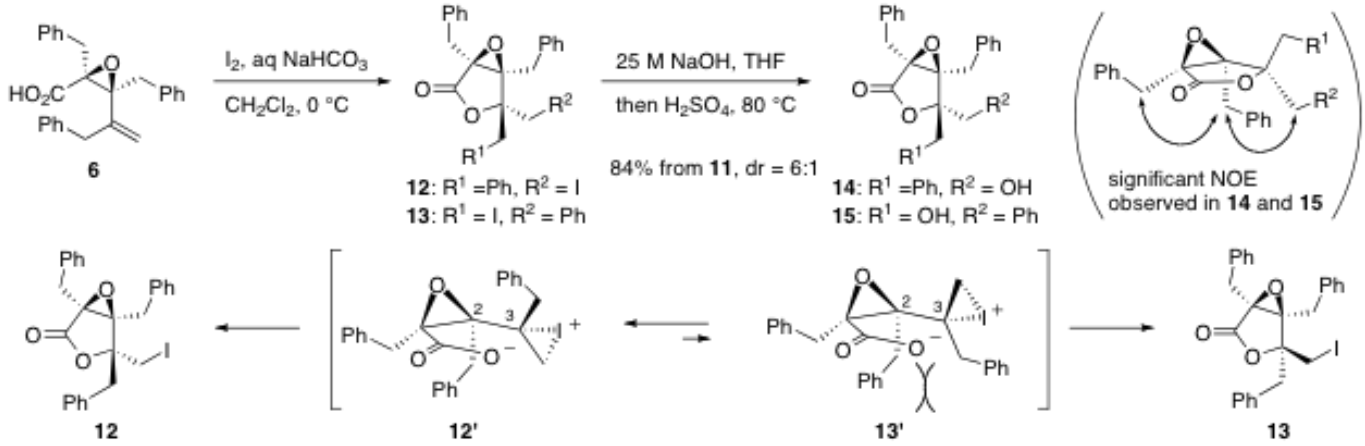
Our synthesis of the key dilactone **3** thus commenced with the enantio- and stereoselective preparation of epoxy carboxylic acid **6** (Scheme 2). Meldrum's acid was converted to β-ketoester **7**[3] in 81% yield by acylation with phenylacetyl chloride followed by methanolysis and benzylation. Upon treatment of **7** with triflic anhydride under alkaline conditions according to Frantz's method,[4] the enol triflation took place with complete *Z*-selectivity[5] to afford triflate **8** as the sole product in 93% yield. Stille coupling[6] of **8** with stannane **9**,[7-9] and subsequent DIBAH reduction gave alcohol **10** in 87% yield. Katsuki-Sharpless asymmetric epoxidation[10] of **10** afforded epoxy alcohol **11** in 83% yield but the enantioselectivity was disappointingly low.[11] Compound **11** thus obtained was then subjected to Dess-Martin oxidation and Lindgren-Kraus oxidation to provide carboxylic acid **6** which was used for the next reaction without purification.



Scheme 2. Synthesis of carboxylic acid **6**

The crucial iodolactonization of **6** was conducted under the conditions using iodine and aqueous $NaHCO_3$ in CH_2Cl_2 at room temperature to give a diastereoisomeric mixture of **12** and **13**, which was directly

hydrolyzed to afford epoxy γ-lactones **14** and **15** as a 6:1 mixture in 84% yield from **11** (Scheme 3). The relative configurations of **14** and **15** are determined by their NOESY and HMBC spectra. The observed diastereoselectivity can be rationalized by considering intermediates **12'** and **13'**. Thus, intermediate **13'** experiences a severe steric repulsion between the C-2 and C-3 benzyl groups. On the other hand, another intermediate **12'** does not undergo such a significant steric repulsion, so that **12'** becomes thermodynamically more stable than **13'**. Since intermediates **12'** and **13'** exist under equilibration, compound **12** is produced as a major product.



Scheme 3. Synthesis of epoxy γ-lactone **14**

With the desired epoxy γ-lactone **14** in hand, we next investigated the construction of the fused γ-lactone/δ-lactone core structure (Scheme 4). Swern oxidation of **14** gave aldehyde **5**, which was then subjected to Horner-Wadsworth-Emmons reaction following Ando's protocol[12] to afford *Z*-α,β-unsaturated ester **16** quantitatively. Then, we examined the key δ-lactone formation under various conditions (Table 1). As a result, when **16** was heated at 80 °C in TFA using a sealed tube, the cleavage of the *tert*-butyl ester and the concomitant epoxide-opening took place cleanly to give dilactone **3**[13] having a fused γ-lactone/δ-lactone skeleton in 94% yield (entry 1). This TFA-promoted reaction turned out to be very sluggish at refluxing temperature (entry 2). Among Lewis acids searched, $ZnBr_2$ was found to effectively promote the cyclization (entries 3, 4, and 5) and dilactone **3** was obtained in 83% yield under the conditions listed in entry 5. The stereochemistry of **3** was confirmed by its NOESY spectra.

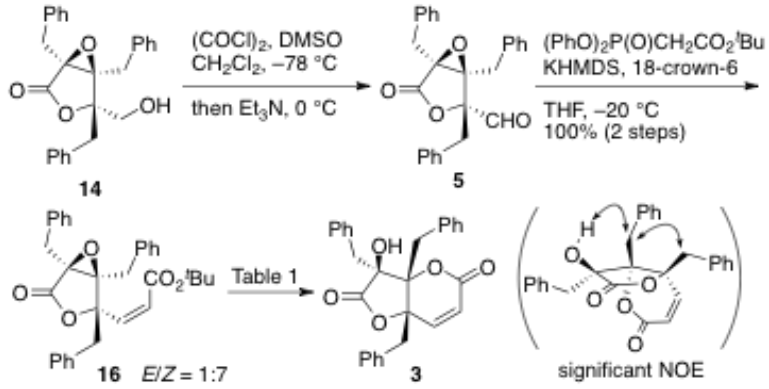


Table1. Acid-promoted reactions of **16** giving **3**

Entry	Conditions	Yield of **3**
1	TFA, 80 °C, 6 h	94%
2	TFA, reflux, 2.5 days	45%
3	$ZnBr_2$ (5.0 eq), $ClCH_2CH_2Cl$, 120 °C, 14 h	41%
4	$ZnBr_2$ (5.0 eq), dioxane, 160 °C, 15 h	62%
5	$ZnBr_2$ (5.0 eq), THP, 120 °C, 12 h	83%

Scheme 4. Synthesis of dilactone **3**

In conclusion, we have developed an effective method for the stereoselecive construction of the fused γ-lactone/δ-lactone core structure of ophiodilactones. The remaining task towards the total synthesis of ophiodilactone A (**1**) is the stereoselective introduction of a phenyl group to **3** which is currently under investigation.

ACKNOWLEDGEMENTS

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5. Triflation of **7** using Tf_2O and aqueous 25 % Me_4NOH in hexane at 5 °C gave the corresponding *E*-isomer exclusively in 93% yield. See ref 4.
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11. The enantiomeric purity was determined by ^{1}H NMR analysis of the corresponding *R*- and *S*-MTPA esters although the absolute configuration was not determined.
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13. Dilactone **3**: a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.24 (m, 15H), 6.56 (d, J = 10.1 Hz, 1H), 5.91 (d, J = 10.1 Hz, 1H), 4.07 (d, J = 14.2 Hz, 1H), 3.27 (d, J = 14.6 Hz, 1H), 3.24 (d, J = 14.7 Hz, 1H), 3.19 (d, J = 14.6 Hz, 1H), 3.05 (d, J = 14.2 Hz, 1H), 2.95 (d, J = 14.7 Hz, 1H), 2.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 160.0, 139.5, 132.9, 132.8, 132.5, 132.1, 131.4, 131.3, 128.7, 128.6, 127.9, 127.7, 127.6, 123.1, 91.0, 78.4, 77.1, 41.2, 37.7, 35.3, 29.7, 18.4; FTIR (neat) 3420, 3031, 1783, 1741, 1495, 1452, 1279, 1181, 1087, 1038 cm^{-1}; MS (EI) *m/z* 91 (100), 185, 276, 305, 440 (M^+); HRMS (EI) calcd for $C_{28}H_{24}O_5$ (M^+) 440.1622, found 440.1625.