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Synthetic Route to Oscillatoxin D and Its Analogues

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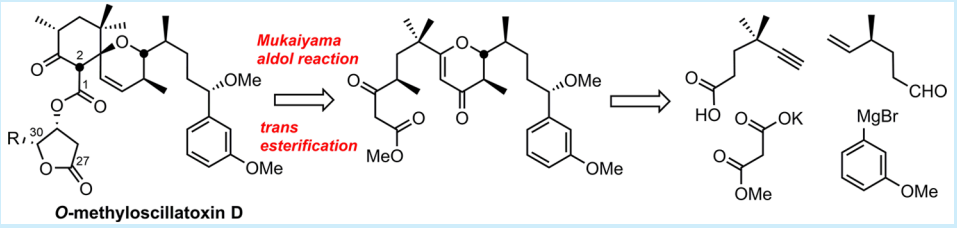
Supporting Information



ABSTRACT: *O*-Methyloscillatoxin D and its analogues were concisely synthesized by a bioinspired intramolecular Mukaiyama aldol reaction as a key step, which involves the construction of a novel spiro-ether moiety.

Oscillatoxin D (**1**) and 30-methyloscillatoxin D (**2**) are naturally occurring polyketides that were first isolated from marine cyanobacteria in the genus of *Oscillatoriacea* by Moore and co-workers in 1985.[1] Considering that these compounds were obtained from the same marine sources and found together with aplysiatoxin, which possesses a similar carbon skeleton, it seems feasible that the same, or similar, biosynthetic routes could be used to generate these natural products.[2]

The distinct structural features of aplysiatoxin include a macrodiolide that contains a spiro-ketal moiety with a hemiacetal, whereas oscillatoxin D possesses the novel spiro-ether moiety such as 1-oxaspiro[5.5]undec-4-en-8-one, which is connected to a β-hydroxy-γ-lactone through a β-keto ester linkage (Figure 1). Aplysiatoxin and debromoaplysiatoxin exhibit

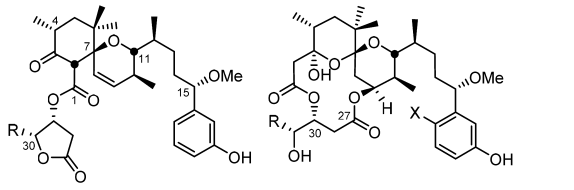


Figure 1. Structures of oscillatoxin D (**1**), aplysiatoxin (**3**), and their naturally occurring analogues.

a highly inflammatory activity and were identified as potent tumor promoters that operate through the activation of protein kinase C (PKC).[3] Inspired by the extensive work of Wender on brytostatin, a marine natural product that exhibits potent antitumor activity by activation of PKC,[4] Irie and co-workers have recently developed simplified analogues of aplysiatoxin that exhibit potent antitumor activity against several cancer cell lines with very weak tumor-promoting activity and no inflammatory activity.[5] These studies imply that a variety of aspects of the biological activity of aplysiatoxin might not simply be derived from the activation of PKC. On the other hand, oscillatoxin D showed antileukemic activity in the inhibition of the L-1210 cell line;[6] details of the aforementioned inhibition have not yet been clarified probably due to the limited amount of natural oscillatoxin D available. In this context, we hypothesized that the cytotoxicity of oscillatoxin D might not be derived from the activation of PKC but may arise from a yet unknown mechanism, as oscillatoxin D lacks a key structural motif to mimic diacyl glycerol (DAG), which is an endogenous activator of PKC.

The synthesis of aplysiatoxin and oscillatoxin D was extensively studied in the 1980s and 1990s,[7,8] immediately after the structures of these natural products had been determined. However, only one route for the total synthesis of aplysiatoxin was reported so far by Kishi in 1987.[9] Kishi and co-workers extensively investigated the structure−activity relationship of aplysiatoxin toward the promotion of PKC by synthesizing a variety of analogues and discovered that the essential structural feature for the activation of PKC is that C-27 to C-30 mimic DAG.[10] The total synthesis of oscillatoxin D and 30-methyloscillatoxin D was achieved in 1995 by Ichihara and Toshima,[11] although they did not carry out a biological evaluation.

We became interested in those marine natural products predominantly for two reasons: (i) from a biological perspective, these compounds exhibit a highly intriguing profile, and (ii) from a synthetic organic chemistry perspective, they exhibit unique structures. Herein, we disclose our synthetic efforts toward the development of a unified synthetic strategy for this class of marine natural products, which includes (i) a concise synthesis of a common intermediate for those two natural products and (ii) an expeditious synthesis of the methyl ethers of oscillatoxin D and 30-methyloscillatoxin D from this common intermediate.

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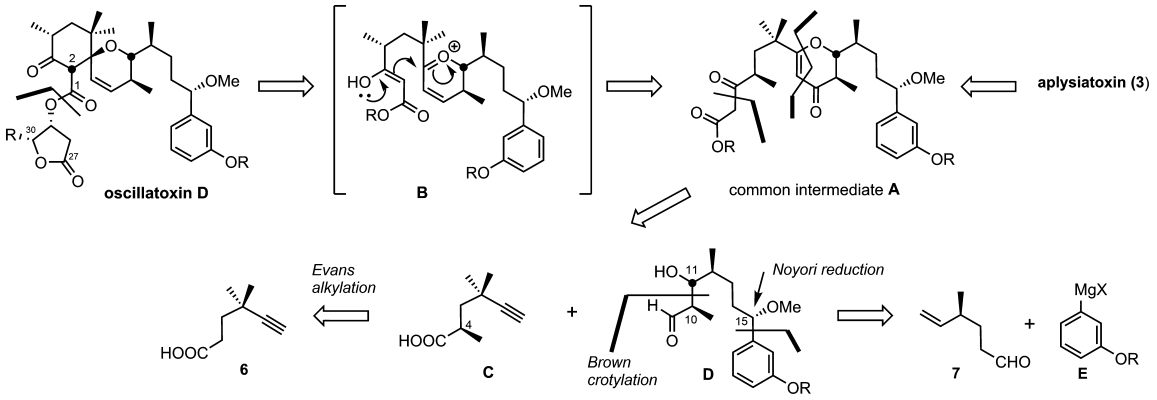
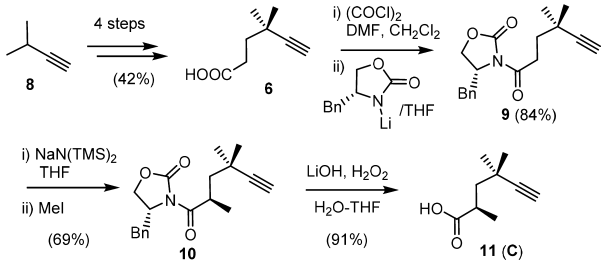
Scheme 1. Retrosynthetic Analysis of Oscillatoxin D



The retrosynthetic analysis of oscillatoxin D is shown in Scheme 1. We planned to synthesize oscillatoxin D, aplysiatoxin, and their analogues from intermediate **A**, which includes all carbon atoms of these natural products except for those of the β,γ-dihydroxycarboxylic acid moiety. We envisioned that the cyclohexanone moiety of the spiro-ether moiety might be biosynthetically constructed by addition of an enol of the β-keto ester to an oxonium ion of the hypothetical intermediate **B**, which might be generated via a Ferrier rearrangement from **A**,[12,13] and that this key reaction might be emulated by an intramolecular Mukaiyama aldol reaction.[14] The β-keto ester moiety of **A** could be prepared by addition of an acetate to the corresponding carboxylic acid, and the dihydropyrone of **A** could be constructed by an intramolecular conjugate addition of a β-hydroxy ynone. This retrosynthetic analysis led us to find two segments of alkyne **C** and aldehyde **D**. Alkyne **C** could be prepared by Evans's asymmetric alkylation of previously reported **6**,[15] whereas aldehyde **D** could be synthesized from previously reported aldehyde **7**[16] and 3-alkoxyphenyl Grignard reagent **E**, in which Brown's crotylation and Noyori's asymmetric hydrogenation would be employed for crucial introduction of asymmetry.

The synthesis of **C** started with the preparation of carboxylic acid **6** from commercially available 3-methyl-1-butyne (**8**) in four steps according to literature procedures (Scheme 2).[15] After the

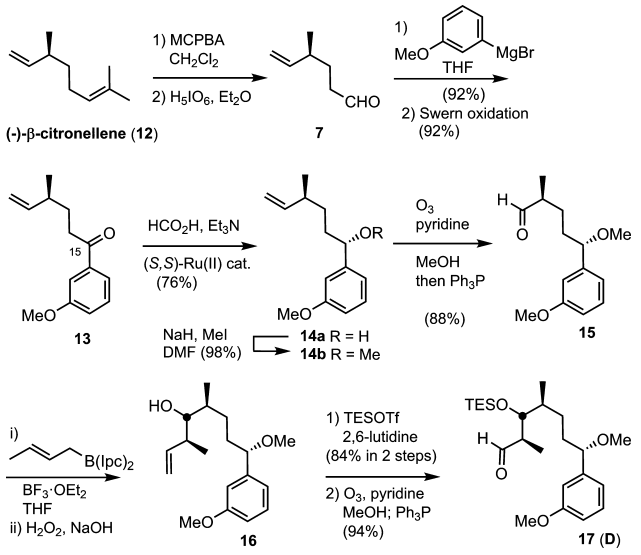
Scheme 2. Synthesis of 11 as the Alkyne Segment C



coupling with the D-phenylalanine-derived Evans chiral auxiliary, the resulting **9** was methylated under conventional conditions to afford **10** as a single diastereomer.[17] A subsequent alkaline hydrolysis furnished **11** as the alkyne segment **C** in good yield.[18]

Compound **D** was synthesized from previously reported **7**, which is easily prepared by the selective cleavage of the trisubstituted alkene of (−)-β-citronellene (**12**) (Scheme 3).[16] Subsequently, **7** reacted with 3-methoxyphenylmagnesium bromide in THF to provide an adduct, which was obtained as

Scheme 3. Synthesis of 17, Aldehyde Segment D



a 1:1 diastereomeric mixture at the C-15 position. The *S*-configuration at the C-15 position could be installed by an asymmetric reduction of ketone **13** obtained from a Swern oxidation of the corresponding alcohol. A Noyori asymmetric transfer hydrogenation, using RuCl[(*S*,*S*)-Tsden](*p*-cymene) as a catalyst,[19] proceeded in a highly stereoselective manner to provide **14a**,[20] which was methylated to furnish **14b** in good overall yield. However, ozonolysis of **14b** under conventional conditions proved to be problematic (12−59% yield), probably due to the oxidation of the phenol moiety under these conditions. An extensive examination revealed that the addition of pyridine[21] and reduction of the reaction time of ozonization increased the yield of aldehyde **15** to 88%. Asymmetric crotylation of **15**, using the Brown reagent derived from (−)-$(Ipc)_2$BOMe,[22] yielded **16** in a highly stereoselective manner.[23] Protection of the resulting hydroxy group with TES followed by ozonolysis under the aforementioned conditions afforded **17** as aldehyde segment **D**.

Subsequently, we investigated the coupling of aldehyde **17** with alkyne **11** (Scheme 4). To avoid a protection/deprotection sequence of the carboxylic acid moiety of **11**, the dianion generated by treatment of **11** with *n*-BuLi in THF was treated with aldehyde **17** to give a ∼3:1 diastereomeric mixture of adducts, which were oxidized with Dess-Martin periodinane to provide ynone **18**. We discovered that cyclization of **18** was best

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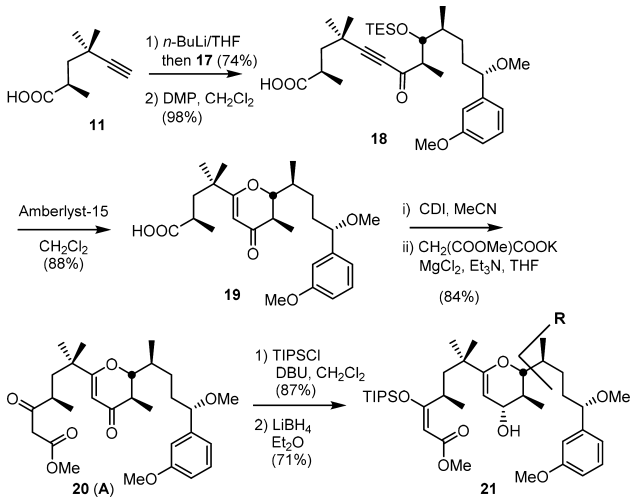
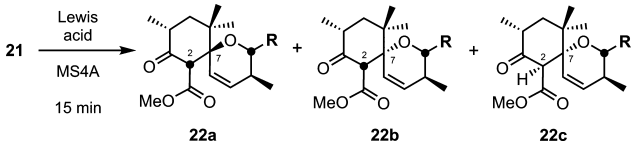
Scheme 4. Synthesis of Common Intermediate 20 (A) and Precursor 21 for the Intramolecular Mukaiyama Aldol Reaction



carried out by treatment with an ion-exchange resin (H^+),[24] which furnished dihydropyrone **19** in good yield. Then, an acetate moiety was introduced by using the Masamune procedure,[25] which afforded β-keto ester **20** as common intermediate **A**.

We investigated the intramolecular Mukaiyama aldol reaction as a key reaction for the synthesis of the spiro-ether moiety of oscillatoxin D. Precursor **21** was easily prepared by silylation of β-keto ester **20** with TIPSCl and DBU, followed by reduction with $LiBH_4$ in diethyl ether (Scheme 4). When **21** was treated with $TiCl_4$ as a Lewis acid in dichloromethane at −78 °C, that is, conventional Mukaiyama aldol reaction conditions,[14] a complex mixture of unidentified products was obtained (entry 1 in Table 1). Carrying out the reaction with $SnCl_4$ afforded a mixture of the

Table 1. Intramolecular Mukaiyama Aldol Reaction of 21

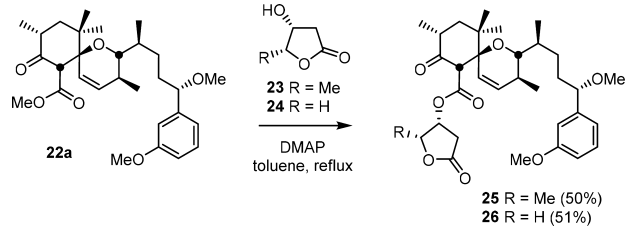


	conditions			product yield (%)		
entry	Lewis acid	solvent	temp (°C)	**22a** (desired)	**22b**	**22c**
1	$TiCl_4$	CH_2Cl_2	−78	0	0	0
2	$SnCl_4$	CH_2Cl_2	−78	44	32	8
3	TMSOTf	CH_2Cl_2	−78	41	18	4
4	TIPSOTf	CH_2Cl_2	−78	63	25	6
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	60	28	4
6	$BF_3{\cdot}OEt_2$	CH_3CN	−40	0	0	96

desired product **22a** and its diastereomers **22b** and **22c** in 44, 32, and 8% yield, respectively (entry 2). The stereochemistry of these products (Table 1) was determined by extensive analysis of the corresponding COSY and NOESY spectra.[26] Encouraged by this result, several other Lewis acids, including trialkylsilyl triflates and $BF_3{\cdot}OEt_2$, were screened. Among these, TIPSOTf and $BF_3{\cdot}OEt_2$ afforded the best results, generating **22a** in 63 and 60% yield, respectively (entries 4 and 5). Reactions using these Lewis acids afforded similar ratios for **22a**, **22b**, and **22c**. Interestingly, when acetonitrile was used as a solvent for the reaction with $BF_3{\cdot}OEt_2$, **22c** was obtained exclusively and in high yield (entry 6). To obtain better insight into the nature of the stereocontrolling element, **22a**, **22b**, and **22c** were exposed separately to the optimal conditions (entry 5; $BF_3{\cdot}OEt_2/CH_2Cl_2/-78$ °C), which afforded ratios of the mixture of **22a**, **22b**, and **22c** that are similar to that of entry 5 in Table 1.[26] These experiments suggest that the intramolecular aldol reaction should be reversible under the applied conditions, and that the desired product **22a** should be thermodynamically the most stable. The solvent effect of acetonitrile might be rationalized in terms of a coordination of the solvent to the oxocarbenium intermediate;[27] that is, acetonitrile might coordinate to the oxonium ion from the less hindered β-face by an axial attack, whereupon the enolate could attack from the α-face, which would result in the exclusive formation of **22c**. These conditions could potentially be used for the synthesis of stereoisomeric analogues of oscillatoxin D in future structure−activity relationship studies.

Toward the synthesis of 30-methyloscillatoxin D, the transformation of the methyl ester of **22a** into the ester with the γ-lactone **23** was examined (Scheme 5). During our

Scheme 5. Synthesis of the Methyl Ethers of 30-Methyloscillatoxin D and Oscillatoxin D



preliminary experiments, the hydrolysis of the ester followed by re-esterification with **23** was unsuccessful, as the resulting β-keto acid readily decarboxylated to afford the corresponding ketone. Thus, we attempted the direct transesterification of the β-keto ester, which has been reported by Taber.[28] To our delight, 30-methyloscillatoxin D methyl ether (**25**) was obtained in moderate yield upon heating a toluene solution of **22a** and lactone **23**[29] to reflux in the presence of DMAP. The NMR spectra of **25** were in good agreement with those of the natural product, except for the methyl group at the phenolic position. The structure of **25**, including its stereochemistry was unambiguously determined by a single-crystal X-ray diffraction analysis.[30] Under similar conditions, the methyl ether of oscillatoxin D (**26**) was obtained from the reaction with **24**[31] in comparable yield.

In summary, we have developed a concise and highly stereocontrolled route to **20** (**A**), which is a common intermediate for the synthesis of the methyl ether of oscillatoxin D and aplysiatoxin (in 14 steps from **12**). Common intermediate **A** was efficiently transformed into the methyl ethers of oscillatoxin D and 30-methyloscillatoxin D in four steps, which includes an intramolecular Mukaiyama aldol reaction that is based on considerations of the biosynthesis of the natural products. The synthetic route developed in this study should provide access to a wide range of analogues of oscillatoxin D, which could be used in future biological investigations. Synthesis of aplysiatoxin from common intermediate **A** and the evaluation of its biological activity, including the activation of PKC, of the

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synthesized oscillatoxin D and its analogues are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03032.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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