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Synthetic Study on Oscillatoxin D: Construction of the C_1-C_{26} Spiroether Segment by Intramolecular Aldol Condensation and Michael-Type Addition

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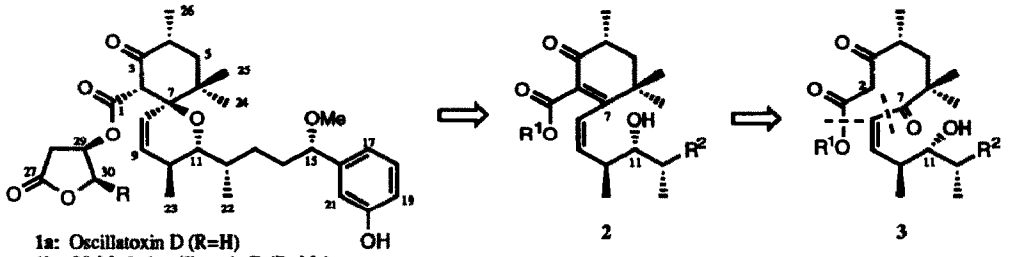
Abstract: The C_1-C_7 segment (**10**) and the C_8-C_{21} segment (**14**) of oscillatoxin D have been synthesized efficiently. The acyclic compound obtained by coupling of these two segments, has been converted into the C_1-C_{26} spiroether (**18**) possessing the same stereogenic centers of oscillatoxin D. The construction of the spiroether has been achieved by intramolecular aldol condensation and Michael-type addition as key steps.

Oscillatoxin D (**1a**) and 30-methyloscillatoxin D (**1b**) are natural products derived from β-polyketides. They occur with aplysiatoxins, potent tumor promoters, in the marine blue-green algae belonging to the Oscillatoriaceae: *Lyngbya majuscula*, *Schizothrix calcicola*, and *Oscillatoria nigroviridis*.[1] Oscillatoxin D displays antileukemic activity against the L 1210 cell line.[2] Aplysiatoxins and oscillatoxins have received much attention as attractive synthetic targets and several synthetic studies have recently been reported.[3] In connection with a series of our synthetic studies on aplysiatoxins,[4] we have succeeded to construct the unique spiroether of **1a** and **1b** which is absent in the structures of aplysiatoxins.

In retrosynthetic analysis (Scheme 1) , we adopted a possible biomimetic pathway for the cyclization of the spiroether ring. Intramolecular Michael-type addition of C_{11}-hydroxyl group to C_7 position in **2** and intramolecular aldol condensation-dehydration between C_2 and C_7 positions in **3**, are reasonably considered. Further division of **3** at the C_1 ester linkage and at the C_7-C_8 bond provides three fragments: the tricarbonyl moiety (C_1-C_7), (*Z*)-homoallyl alcohol equivalent (C_8-C_{21}), and β-hydoxy-γ-lactone (C_{27} -C_{30}). We describe herein the synthesis of the C_1-C_{26} segment whose all stereogenic centers are identical with those of natural **1a** and **1b**.



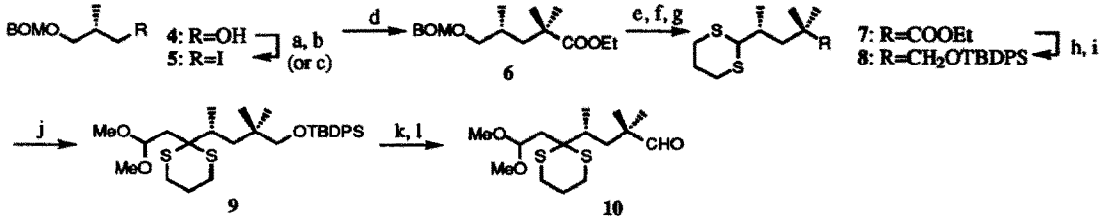
1a: Oscillatoxin D (R=H)
1b: 30-Methyloscillatoxin D (R=Me)

2 **3**

Scheme 1

The synthesis of the C_1-C_7 segment (Scheme 2) was started from methyl (*S*)-3-hydroxy-2-methylpropionate which was readily converted to the known alcohol **4** in two steps (93% yield).[5] Tosylation of **4** followed by substitution with iodide gave the alkyl iodide **5** (86% yield, 2 steps).[6] Treatment of **4** with iodine, triphenylphosphine, and imidazole in benzene also gave **5** directly in a good yield. Lithium enolate of ethyl

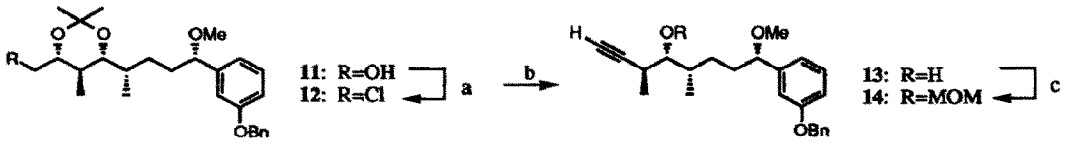
isobutyrate was alkylated with **5** to afford the ester **6** in a quantitative yield. Then **6** was converted to the 1,3-dithiane derivative **7** by the following three steps in 85% yield: (1) deprotection of benzyloxymethyl (BOM) ether, (2) Swern oxidation of the resulted alcohol, and (3) thioacetalization of the aldehyde with 1,3-propanedithiol. After reduction of **7** with lithium aluminum hydride ($LiAlH_4$), protection of the resulted alcohol as t-butyldiphenylsilyl (TBDPS) ether afforded **8** (91% yield, 2 steps). Further elongation of two carbons unit to **9** was achieved by treatment of lithiated **8** with 1-bromo-2,2-dimethoxyethane in 99% yield. Finally, **9** was transformed into the desired aldehyde **10** in two steps (86% yield): (1) deprotection of TBDPS ether and (2) oxidation of the primary alcohol. This segment **10**, which has one free aldehyde group and two masked carbonyl groups as 1,3-dithiane and dimethylacetal, would be the useful synthetic intermediate not only for **1a** and **1b** but also for the other aplysiatoxins.



a) TsCl, pyr./ CH_2Cl_2 (95%). b) NaI / acetone (91%). c) I_2 / Ph_3P, imidazole / benzene (82%). d) ethyl isobutyrate, LDA / THF (100%). e) H_2, Pd-black / EtOH (92%). f) $(COCl)_2$, DMSO, Et_3N / CH_2Cl_2. g) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$ / CH_2Cl_2 (92%, 2 steps). h) $LiAlH_4$ / Et_2O (93%). i) TBDPSCl, imidazole / DMF (98%). j) t-BuLi / HMPA-THF, then 1-bromo-2,2-dimethoxyethane (99%). k) n-Bu_4NF / THF (93%). l) SO_3-pyr., DMSO, Et_3N / CH_2Cl_2 (92%).

Scheme 2

For the synthesis of the C_8-C_{21} segment (Scheme 3), the alcohol **11** was employed as a versatile intermediate which has already been synthesized from D-glucose and 3-hydroxyacetophenone.[4] In order to introduce the C_8-C_9 (*Z*)-olefin *via* acetylene reduction, **11** was converted to **14**. The chloride **12** was prepared by treatment of **11** with triphenylphosphine in refluxing carbon tetrachloride in 99% yield. Then **12** was subjected to the base (lithium diisopropylamide) induced elimination to provide the acetylenic alcohol **13** in 72% yield.[7] The secondary hydroxyl group was protected as methoxymethyl (MOM) ether in 87% yield.[8]

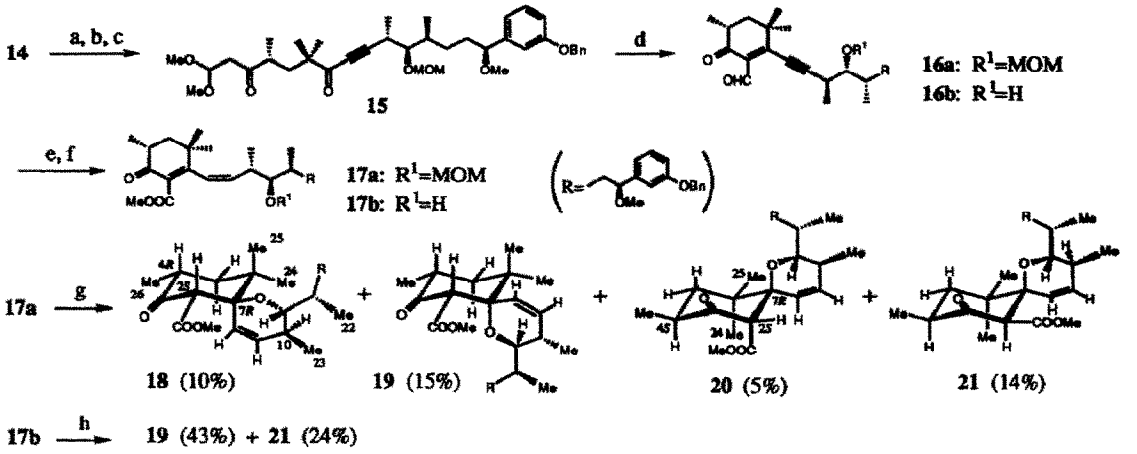


a) Ph_3P / CCl_4 (99%). b) LDA / THF (72%). c) MOMCl, i-Pr_2NEt / CH_2Cl_2 (87%).

Scheme 3

The coupling of two segments (**10** and **14**) and construction of the spiroether ring system were next examined as follows (Scheme 4). The lithium acetylide of **14** was successfully coupled with the aldehyde **10** to give the diastereomeric alcohol (93% yield, diastereoselectivity: ca. 1:1). The diketone **15** was prepared from

the alcohol in two steps: (1) oxidation of the secondary hydroxyl group in 87% yield and (2) hydrolysis of the dithioacetal with N-chlorosuccinimide in 85% yield. When **15** was treated with 50% aq. TFA-$CHCl_3$ (1:5), hydrolysis of the dimethylacetal and the intramolecular aldol condensation-dehydration took place giving cyclohexenones **16a** and **16b** in 56 and 27% yields, respectively. Oxidation of the aldehyde **16a** to the corresponding carboxylic acid followed by treatment with diazomethane afforded the methyl ester in 64% yield. Then partial hydrogenation of the acetylenic linkage in the presence of Lindlar catalyst in ethyl acetate gave the (Z)-olefin **17a** in 77% yield. The hydroxyaldehyde **16b** was also subjected to the same three steps sequence (54% yield) to give **17b** as the direct precursor for intramolecular Michael-type addition.[9]



a) n-BuLi / THF, then **10** (93%). b) SO_3·pyr., DMSO, Et_3N / CH_2Cl_2 (87%). c) NCS, $AgNO_3$ / 10% aq. CH_3CN (85%). d) 50% aq. TFA-$CHCl_3$ (1: 5) (**16a**: 56%, **16b**: 27%). e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene / t-BuOH-H_2O, then CH_2N_2 / Et_2O (R^1=MOM: 64%, R^1=H: 76%). f) H_2, Lindlar catalyst / EtOAc (**17a**: 77%, **17b**: 71%). g) conc. HCl / MeOH. h) t-BuOK / THF.

Scheme 4

Deprotection and acid catalyzed intramolecular Michael-type addition of the MOM ether **17a** proceeded successively in conc. HCl-MeOH to give the four diastereomeric spiroethers: **18**, **19**, **20**, and **21** in 10, 15, 5, and 14% yields, respectively. In addition, these spiroethers were obtained from the hydroxyl compound **17b** under the same acidic condition. Under the basic condition (t-BuOK / THF), **17b** was converted into **19** and **21** in 43 and 24% yields, respectively. The stereochemistries of the four diastereomers (**18** - **21**) were elucidated through detailed analysis of their NOE difference spectra.[10] The NOE enhancements of **18** were similar to those of natural **1a** and **1b**.[1] Irradiation of the C_{25} axial methyl group and the C_{24} equatorial methyl group of **18** gave positive NOEs for H_2, H_4, and H_{24} protons and for H_{10} and H_{25} protons, respectively. These indicate that H_2 and H_4 protons have to be located in axial positions and the ether oxygen has to be attached equatorially to the cyclohexanone ring. The stereostructures of **19**, **20**, and **21** were clearly assigned as indicated in Scheme 4. In diastereomers **20** and **21**, conformation of cyclohexanone ring flipped in contrast to that of **18** and **19**, and the C_4 configuration epimerized to stabilize thermodynamically. Thus we have synthesized a very important intermediate toward total synthesis of **1a** and **1b**. Now, optimization of

diastereoselectivity on intramolecular Michael-type addition, isomerization to the desired spiroether **18**,[11] and conversion into **1a** and **1b**, have been investigating.

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6. Satisfactory spectroscopic data were obtained for all new compounds.
7. Yadav, J. S.; Deshpande, P.K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033-7046.
8. t-Butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP) ethers could be introduced as protective groups of the C_{11}-hydroxyl group (see NOTE 9).
9. Without difficulty, **22** and **23** were converted into **24** and **17b**, respectively, by the same sequence as described in Scheme 4. Especially, **23** acted as a versatile intermediate because deprotection of THP ether and dimethylacetal and intramolecular aldol condensation-dehydration proceeded successively to give **16b**. Deprotection of TBDMS ether **24** was unsuccessful under many conditions.

10. NOE data for spiroethers: for **18**: (i) H_{25} (irradiated proton) → H_2, H_4, and H_{24} (enhanced protons); (ii) H_{24} → H_{10} and H_{25}; (iii) H_{10} → H_{22}, H_{23}, and H_{24}. for **19**: (i) H_{25} → H_2, H_4, $H_{5eq.}$, H_8, and H_{24}; (ii) H_2 → H_4, H_8, and H_{25}; (iii) H_4 → H_2, H_{25}, and H_{26}; (iv) H_{11} → H_{24}. for **20**: (i) H_{24} → H_4, H_8, H_{25}, and COOMe; (ii) H_{11} → H_2. for **21**: (i) H_{24} → H_2, H_4, H_8, and H_{25}; (ii) H_8 → H_2, H_9, and H_{24}; (iii) H_{25} → H_{10} and H_{24}.
11. Formation of **18**, **20**, and **21** was observed chromatographically when a small amount of **19** was treated in conc. HCl-MeOH. Since undesired isomers **20** and **21** still have the correct *7R* configuration, they can be isomerized to **18** under acidic or basic condition.

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