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# A Stereoselective Route to the Spirobicyclic Ring System of Oscillatoxin D

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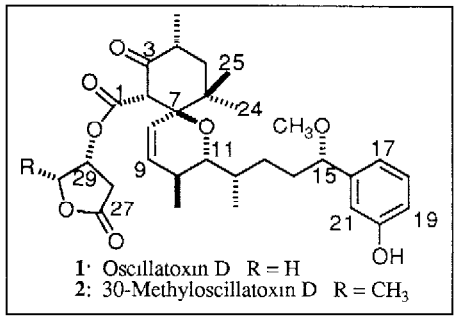
*Key Words.* Oscillatoxin D; 1-oxaspiro[5.5]undec-4-ene-8-one; β-ketoester, Cyclization; 2,3-dihydro-4-pyranone

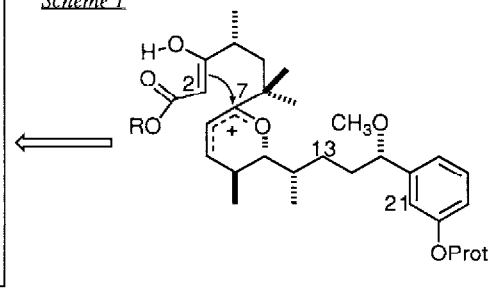
***Abstract:*** *Using a model system, a stereoselective assembly of the 1-oxaspiro[5.5]undec-4-ene-8-one ring system of the antileukemic natural products oscillatoxin D and 30-methyloscillatoxin D was demonstrated. A key step was an intramolecular attack of the $C_1$-$C_3$ β-ketoester enol on a silyl-activated 2,3-dihydro-4-pyranone to create a silyloxy analogue of the natural products' spirobicyclic ring system*

Oscillatoxin D (**1**) and 30-methyloscillatoxin D (**2**) are nontoxic natural products found in three species of tropical marine bluegreen algae of the class Oscillatoriaeceae [1] They co-occur with the toxic polyacetate tumor promotors of the aplysiatoxin/oscillatoxin A class,[2,3] and are remarkable for their antileukemic activity.[4] We have been involved in synthetic studies of the oscillatoxins and aplysiatoxins,[5] and are particularly interested in the "D" oscillatoxins because of the synthetic challenge posed by their unique 1-oxaspiro[5.5]undec-4-ene-8-one ring system, which encompasses sensitive β-ketoester and tertiary allylic ether moieties. A synthetic route to this ring system which features an attack of the $C_1$-$C_3$ β-ketoester on a cyclic "oxadienyl cation" (Scheme 1) seemed reasonable for selectively producing the $C_2$ and $C_7$ stereogenic centers This communication reports the successful demonstration of this strategy in a model system which produces a 9-oxygenated analogue of the otherwise authentic spirobicycloundecenone ring system of the "D" oscillatoxins.




**1**: Oscillatoxin D R = H
**2**: 30-Methyloscillatoxin D R = $CH_3$

*Scheme 1*

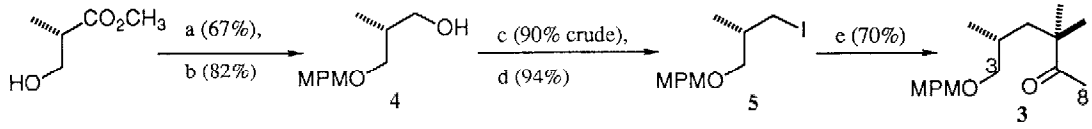



For our model study we used a methyl group at $C_{13}$, reasoning that the isopropyl group attached to the pyran ring would faithfully mimic steric effects of the natural product's $C_{13}$-$C_{21}$ moiety.

The $C_3$-$C_8$ (oscillatoxin numbering) intermediate **3** was synthesized from (S)-methyl 3-hydroxy-2-methylpropanoate in five steps (Scheme 2). Hydroxyl protection,[6] reduction (to **4**), and functional group manipulation produced the iodide **5**, which was added to the thermodynamic enoxyborate derivative of 3-methyl-2-butanone[7] to yield **3** in 40% overall yield.[8] This ketone can be used as a starting material for the synthesis of any of the aplysiatoxin/oscillatoxin natural products.

Subsequent assembly of the model $C_1$-$C_{13}$ moiety of the "D" oscillatoxins as the diketopyranone **6** is indicated in Scheme 3. Oxidation of **4** followed by the chelation-controlled addition of an isopropyl group yielded the alcohol **7**.[9] Protection of the 11-hydroxyl group followed by deprotection/oxidation at $C_9$ yielded

*Scheme 2*

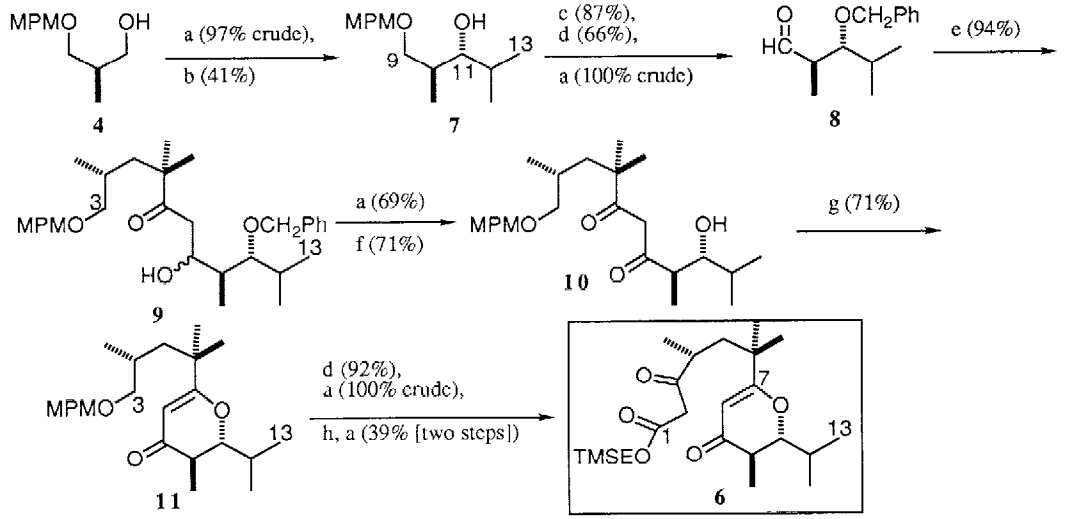



*a) p-CH3O-C6H4-CH2OC(=NH)CCl3, camphorsulfonic acid, CH2Cl2, 25°, 18 hr. b) 1 LiAlH4, THF, 0°; 2. H2O. c) CH3SO2Cl, Et3N, CH2Cl2, 0°, 30 min. d) NaI, acetone reflux, 4 hr e) 1 KH + 3-methyl-2-butanone, THF, 25°, 40 min., 2. add BEt3 (~1 eq.), 25°, 15 min., 3. add 5, 0°, 2.5 hr.*

the aldehyde **8**. Addition of the lithium enolate derivative of **3** to **8** resulted in the C3-C13 aldol product **9** as a 4:1 mixture of diastereomers whose relative configurations were not determined.[10] Oxidation to the β-diketone followed by hydrogenolytic deprotection[11] yielded hydroxydiketone **10**, which underwent intramolecular ketalization/dehydration to **11** under acid catalysis Conversion of the C3-hydroxymethyl group to the aldehyde, then addition of the lithium enolate of trimethylsilylethyl acetate produced the C1-C13 β-hydroxyester as a 2:1 mixture of diastereomers. Oxidation using Swern's oxalyl chloride/DMSO recipe yielded the desired β-ketoester **6** plus a significant amount (18%) of a β-chloroester byproduct. We are confident that a change in oxidation conditions can prevent the production of the byproduct [12]

Treatment of **6** with an excess of tert-butyldimethylsilyl trifluoromethanesulfonate in the presence of an amine resulted in the rapid formation of the four diastereomeric spirobicyclic products **12-15**, in a 70:6:12:12 ratio, in 72% yield (Scheme 4). The labile diastereomers were separated by HPLC.[13,8] Nuclear Overhauser effect (NOE) difference spectra of **12-14** allowed the indicated structural assignments to be made.[14] A few of

*Scheme 3*

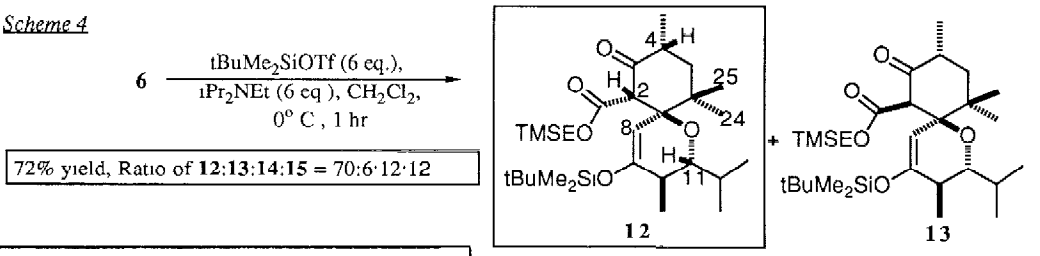



*a) 1 Me2SCl+ Cl-, -78°, CH2Cl2; 2 Et3N b) 1 iPrMgCl / CuBr-SMe2, THF, -78°, 1.5 hr.; 2. H2O. c) 1 KH, THF, 0°, 10 min.; 2 PhCH2Br, 0°, 1 hr d) DDQ, 5 1 CH2Cl2 pH 7 buffer, 25°, 10 min e) 1 3 + LDA, THF, -78°, 5 min ; 2 add 8, -78°, 30 min., 3 H2O f) H2 (40 psi), W-2 Raney Ni, EtOH, 9 hr g) ~1% camphorsulfonic acid, CH2Cl2, 25°, 18 hr. h) 1 H2C=C(OLi)OCH2CH2SiMe3, THF, -78°, 30 min.; 2. H2O*

the salient NOE's which were observed for **12-14** are indicated in Scheme 4. For each diastereomer, the NOE's between 2-H and 4-H and/or 25-H allowed the relative configuration at $C_2$ to be assigned, and the NOE's

between 11-H and 2-H -- or between 2-H and 8-H -- allowed the relative configuration of $C_7$ to be assigned The NOE's observed for the major product **12** corresponded best with the 2S,7S structure, which corresponds with the configuration of the "D" oscillatoxins [15] Furthermore, the product **12** exhibited a long-range coupling (J = 1.0 Hz) between the two hydrogens on $C_2$ and $C_4$, as observed in the natural products **1** and **2**, and **12** was observed to epimerize to its $C_2$ epimer, **13**, upon standing, just as the "D" oscillatoxins were reported to epimerize.[1]

*Scheme 4*

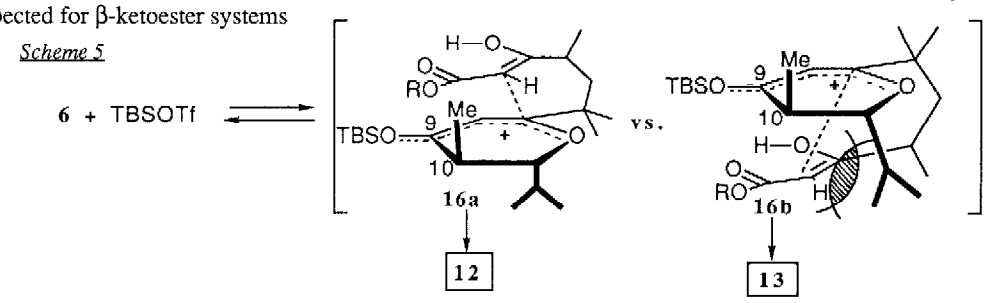



| *Signal Irradiated* | *Signal Scrutinized* | *NOE Observed?*[a] *12* | *13* | *14* |
|---|---|---|---|---|
| *11-H* | *2-H* | *yes (3 3)* | *-b-* | *no* |
| *11-H* | *10-H* | *yes (3.3)* | *-b-* | *no* |
| *11-H* | *24-H* | *no* | *-b-* | *yes (1 9)* |
| *2-H* | *4-H* | *yes (1 9)* | *no* | *-b-* |
| *2-H* | *11-H* | *yes (3 3)* | *no* | *-b-* |
| *2-H* | *25-H* | *yes (1 9)* | *no* | *yes (1 9)* |
| *2-H* | *24-H* | *no* | *yes (2 2)* | *no* |
| *2-H* | *8-H* | *no* | *yes (3.1)* | *yes (2 3)* |
| *2-H* | *tBuSi* | *no* | *yes (~1)* | *-b-* |
| *2-H* | *$Me_2Si$* | *no* | *yes (~1)* | *-b-* |

[a] *NOE's (approximate percentages) given in parentheses.*[14]
[b] *Results obscured or ambiguous due to overlapping signals*

A justification for the stereoselectivity of the Lewis acid-mediated cyclization of **6** to produce **12-15** is offered in a simplistic form in Scheme 5. Silylation of the 9-keto oxygen would produce the oxadienyl cation **16** which is activated for nucleophilic attack by the enol (or silyl enol ether) form of the $C_1$-$C_3$ β-ketoester. Attack on the si face of $C_7$ (**16a**) suffers less steric interference (the incoming nucleophile being 1,4-cis to the 10-methyl group) than attack on the re face (**16b**, where the incoming nucleophile is 1,3-cis to the 11-isopropyl group). The selectivity for the 2S product depends upon the enol (or enol ether) favoring the Z configuration, as expected for β-ketoester systems

*Scheme 5*




These results justify a synthetic design for the "D" oscillatoxins which features a Lewis acid-mediated "$C_2$ enol to $C_7$ oxadienyl cation" cyclization. Synthetic efforts which will follow such a design and improve the **6** ⇒ **12** stereoselectivity are currently underway. It should be noted that a $C_9$-$C_{21}$ aldehyde which can substitute for the $C_9$-$C_{13}$ model **8** in the synthesis described above is already in hand.[5b]

*These findings were taken from the Ph.D dissertation (Texas Tech University, 1990) of P Douglas Boatman, Jr This research was made possible by funding from the Robert A Welch Foundation, the donors of the Petroleum Research Fund administered by the American Chemical Society, and by donations graciously provided by Lubbock Oncology Associates (David R Close, M D ) and Lubbock Oncology Clinic (Benny P Phillips, M D , Ali A El-Domeiri, M.D ) The NMR spectrometers employed were purchased using funds provided by the NSF (#CHE-851404) The assistance of Mr David W Purkiss with the measurement of NOE difference spectra is gratefully acknowledged*

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4. Personal communication from professor Richard E. Moore, University of Hawaii The activity noted was based on an assay using a limited amount of oscillatoxin D against the L1210 cell line

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8. All new compounds exhibited spectroscopic and analytical properties commensurate with their identities and purities. This data will be reported in a forthcoming full account of this research, but until then is available from the authors upon request.

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10. If this aldol addition proceeded via chelation control (Masamune, S., Ellingboe, J.W., Choy, W. *J. Am. Chem Soc* **1982**, *104,* 5526) then the major diastereomer should have the 9S (oscillatoxin numbering) configuration common to the 9-hydroxylated aplysiatoxins and "A" oscillatoxins.[2,3]

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13. DuPont Zorbax-Sil column (5m silica gel, 0.4 mm id X 25 cm), 98 2 hexanes : ethyl acetate eluent at 1.0 mL/min. retention times: **12**. 5.1 min, **13**: 7.0 min; **14**: 6.5 min; **15**: 4.7 min.

14. Compound **15** decomposed in storage before its NOE difference spectrum could be measured.

15. The report by Moore et al. (reference 1) did not list the values of the NOE enhancements that they observed, and their NOE experiments differed from ours: irradiation of 25-H ⇒ NOE at 2-H and 4-H; irradiation of 24-H ⇒ NOE at 10-H and 5-H; irradiation of 10-$CH_3$ ⇒ NOE at 11-H and 12-H; irradiation of 12-$CH_3$ ⇒ NOE at 10-H. We were unable to perform these experiments with our model compounds because the proximity of the NMR signals for the methyl groups did not allow for their selective irradiation.

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