Tetrahedron Letters, Vol.31, No.52, pp 7587-7590, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

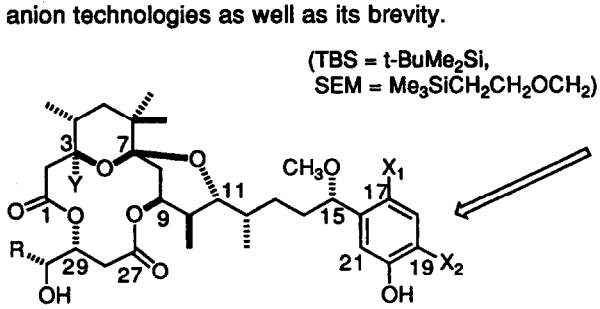
# Expeditious Synthesis of a Key $C_9$-$C_{21}$ Subunit of the Aplysiatoxins and Oscillatoxins

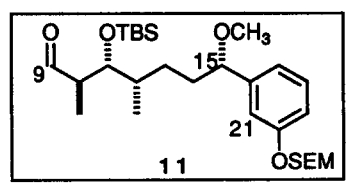
Robert D. Walkup,* Robert R. Kane, P. Douglas Boatman, Jr. and Raymond T. Cunningham

Department of Chemistry & Biochemistry, Texas Tech University, Lubbock, TX 79409-1061

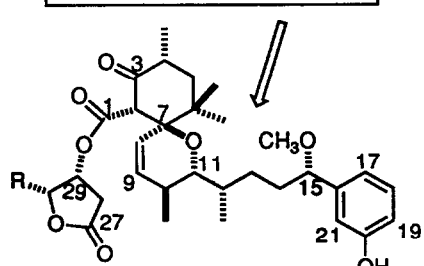
***Abstract:*** *The $C_9$-$C_{21}$ portion of the aplysiatoxin/oscillatoxin bluegreen algal metabolites was synthesized as the 9-aldehyde bearing a tert-butyldimethylsilyl ether group on the $C_{11}$ hydroxyl and a trimethylsilylethoxymethyl ether group on the $C_{20}$ hydroxyl. Featuring an asymmetric aldol and an asymmetric oxazaborolidine reduction, the synthesis proceeded with high (>90%) stereoselectivity in 13 steps and 5-7% overall yield from commercial starting material.*

The aplysiatoxins and the "A" oscillatoxins (**1** - **6**) are a class of natural products, known to be produced by three species of tropical marine bluegreen algae,[1] which are notable for their tumor promoting activity.[2] Oscillatoxin D (**7**) and 30-methyloscillatoxin D (**8**) are nontoxic co-metabolites of these organisms[3] which have been observed to possess antileukemic activity.[4] One synthesis of debromoaplysiatoxin (**2**)[5] and two syntheses of the nonnatural, albeit biologically active, 3-deoxyaplysiatoxins **9**[6] and **10**[7] have been reported. In conjunction with our current synthetic studies on the "D" oscillatoxins **7** and **8**, and our ongoing interest in the oscillatoxins in general,[8] we recognized that a general approach to all of these natural products could be made using the $C_8$-$C_9$ bond construction afforded by the aldol addition of a $C_8$ enolate to the $C_9$-$C_{21}$ aldehyde **11**.[9] This strategy differs from those utilized before for the assembly of the carbon skeleton of the aplysiatoxins,[5-7] and it has allowed us to design a more practical synthesis of the $C_9$-$C_{21}$ moiety --- as **11** --- than any previously reported. In this communication, we report the accomplishment of this design, which is notable for its timely utilizations of the "Evans aldol," the "Corey oxazaborolidine reduction," and imine anion technologies as well as its brevity.



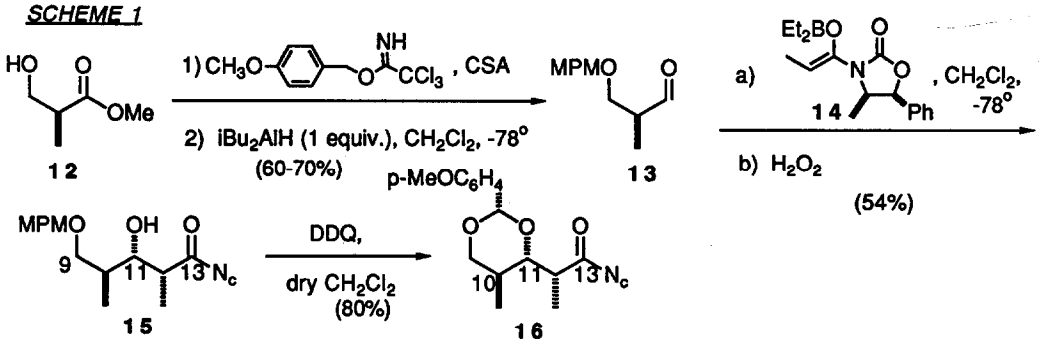

| | R | Y | $X_1$ | $X_2$ |
|---|---|---|---|---|
| **1**: Aplysiatoxin | $CH_3$ | OH | Br | H |
| **2**: Debromoaplysiatoxin | $CH_3$ | OH | H | H |
| **3**: 19-Bromoaplysiatoxin | $CH_3$ | OH | Br | Br |
| **4**: Oscillatoxin A | H | OH | H | H |
| **5**: 17-Bromooscillatoxin A | H | OH | Br | H |
| **6**: 17,19-Dibromooscillatoxin A | H | OH | Br | Br |
| **9**: 3-Deoxyaplysiatoxin | $CH_3$ | H | Br | H |
| **10**: 3-Deoxydebromoaplysiatoxin | $CH_3$ | H | H | H |




**7**: Oscillatoxin D: R = H
**8**: 30-Methyloscillatoxin D: R = $CH_3$

The stereogenic centers at $C_{10}$, $C_{11}$ and $C_{12}$ were established via synthesis of the $C_9$-$C_{13}$ subunit **15** as indicated in Scheme 1. Protection of the hydroxy group of (S)-methyl 3-hydroxy-2-methylpropanoate (**12**) as the para-methoxyphenylmethyl (MPM) ether,[10] then reduction yielded the aldehyde **13** in 60-70% overall yield.[11] Addition of the diethylboron enolate derivative (**14**) of (4R,5S)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one[12] to **13** yielded a 60-70% crude yield of a

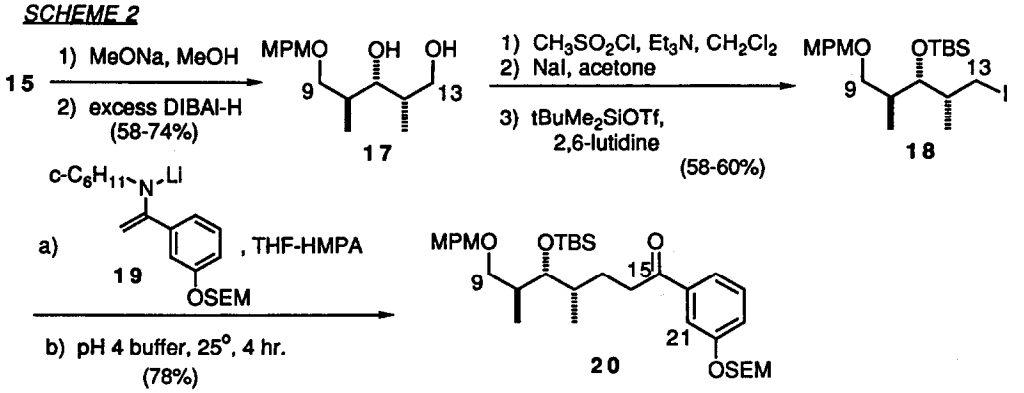
*SCHEME 1*




mixture of aldol products in which one diastereomer constituted greater than 90% of the mixture, according to NMR analysis. Crystallization of the crude mixture from ether/hexanes yielded the major diastereomer (**15**) in pure form, in 49% yield; chromatography of the mother liquor allowed the isolation of an additional 5% of **15**. The syn relationship between the $C_{11}$-hydroxyl and the $C_{12}$-methyl groups in **15** was indicated by the well-established precedents for syn-selectivity by boron enolates of N-acyloxazolidinones,[12] and by the observed vicinal coupling constant of 3.4 Hz for the $C_{11}$-$C_{12}$ hydrogens. The anti relationship between the $C_{11}$-hydroxyl and the $C_{10}$-methyl group in **15** was established by conversion of **15** to the acetal **16** (DDQ, $CH_2Cl_2$).[13] $^1$H-NMR analysis of **16** revealed a vicinal coupling constant of 11 Hz for the $C_{10}$-$C_{11}$ hydrogens, indicating an anti relationship. Thus, as noted for other cases by Evans,[12] the stereodirecting effect of the oxazolidinone moiety in **14** overrode the directing effect of the chirality resident in the aldehyde **13**.

The remainder of the $C_9$-$C_{21}$ skeleton of the aplysiatoxins/oscillatoxins was assembled as indicated in Scheme 2. Removal of the oxazolidinone moiety by esterification, then reduction cleanly afforded the diol **17** in 58-74% overall yield.[14] Selective mesylation, displacement using

*SCHEME 2*

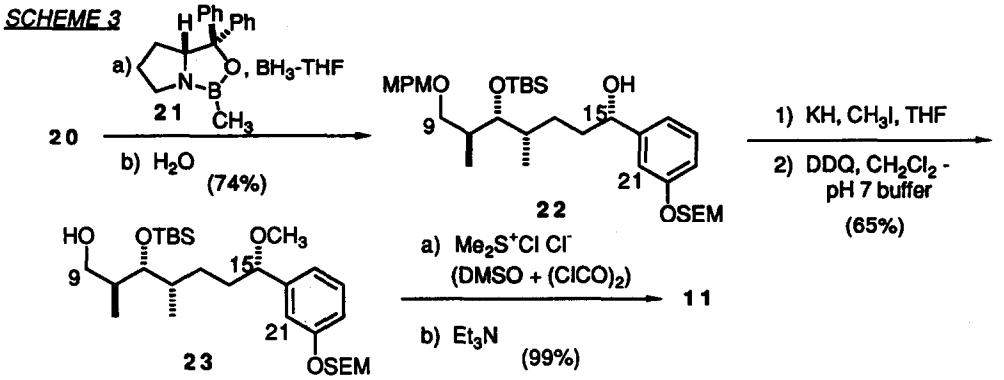



iodide, then protection of the 11-hydroxyl group yielded the iodide **18** in 58-60% overall yield.[15] Treatment of this iodide with the imine anion **19** (derived from the corresponding imine and LDA)[16]

in THF-HMPA, followed by hydrolysis of the imine functionality, resulted in the $C_9$-$C_{21}$ ketone **20** in 78% yield after purification.

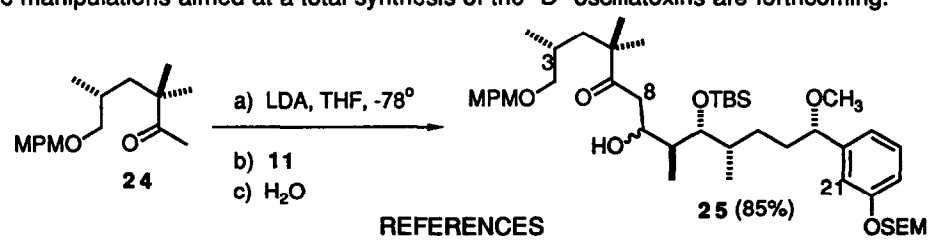
Completion of the synthesis of **11** is indicated in Scheme 3. Reduction of the ketone **20** by borane in the presence of 30-40 mole percent of the R-oxazaborolidine reagent **21**[17] yielded the alcohol **22** in 74% yield after purification. NMR analysis of the crude product (in comparison with a 50:50 mixture of diastereomers prepared by sodium borohydride reduction of **20**) indicated a diastereomeric ratio of >95:<5. The major diastereomer **22** was assigned the 15S configuration on the basis of the precedents for similar asymmetric reductions,[17] and on the basis of the CD spectrum of **23** (in ethanol), which exhibited positive Cotton effects for the absorbances at 268 nm and 271 nm, in agreement with the Cotton effects observed for aplysiatoxin and other benzylic ethers having the S configuration at the benzylic center.[1b] The Ireland and Yamamura groups, during their separate syntheses of 3-deoxyaplysiatoxin,[6,7] used Noyori's chiral binaphthol-$LiAlH_4$ reagent[18] and Brown's diisocampheylchloroborane reagent,[19] respectively, to achieve a similar asymmetric reduction of a 15-keto precursor.

*SCHEME 3*




Straightforward O-methylation followed by deprotection of the 9-hydroxyl group yielded the alcohol **23** in 65% overall yield after purification. Swern oxidation converted **23** into the aldehyde **11** in 99% yield. Thus the $C_9$-$C_{21}$ moiety of the aplysiatoxins and oscillatoxins was produced in 13 steps and 5-7% overall yield from the commercially available ester **12**.

To demonstrate the utility of **11**, it was treated with the lithium enolate derivative of the methyl ketone **24**. This resulted in the formation of the alcohol **25** --- a $C_3$-$C_{21}$ subunit of the aplysiatoxins/oscillatoxins --in 85% yield as a mixture of diastereomers. Further details of this and subsequent synthetic manipulations aimed at a total synthesis of the "D" oscillatoxins are forthcoming.[20]




## REFERENCES

1) a) Moore, R.E. *Pure Appl. Chem.* **1982**, *54*, 1919; b) Moore, R.E., Blackman, A.J., Cheuk, C.E.,

Mynderse, J.S., Matsumoto, G.K., Clardy, J., Woodard, R.W., Craig, J.C. *J. Org. Chem.* **1984**, *49*, 2484.

2) a) Fujiki, H., Sugimura, T., Moore, R.E. *Env. Health Persp.* **1983**, *50*, 85; b) Fujiki, H., Tanaka, Y., Miyake, R., Kikkawa, U., Nishizuka, Y., Sugimura, T. *Biochem. Biophys. Res. Commun.* **1984**, *120*, 339; c) Arcoleo, J.P., Weinstein, I.B. *Carcinogenesis* **1985**, *6*, 213 and references therein.

3) Entzeroth, M., Blackman, A.J., Mynderse, J.S., Moore, R.E. *J. Org. Chem.* **1985**, *50*, 1255.

4) Personal communication from professor Richard E. Moore, University of Hawaii. The activity noted was based on an assay using the L1210 cell line.

5) Park, P.-U., Broka, C.A., Johnson, B.F., Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205.

6) Ireland, R.E., Thaisrivongs, S., Dussault, P.H. *J. Am. Chem. Soc.* **1988**, *110*, 5768.

7) a) Toshima, H., Yoshida, S.-i., Suzuki, T., Nishiyama, S., Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6721; b) Toshima, H., Suzuki, T., Nishiyama, S., Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6725.

8) Walkup, R.D., Cunningham, R.T. *Tetrahedron Lett.* **1987**, *28* , 4019.

9) Moore has shown that bromination of the non-halogenated natural product **2** under buffered conditions yields the brominated natural products **1** and **3** (ref. 1b). This precedent suggests that we need not worry about having the $C_{17}$ and $C_{19}$ bromines in place (e.g. as part of the aldehyde **11**) until the end the synthesis. Thus the nonbrominated intermediate **11** is truly general.

10) Nakajima, N., Horita, K., Abe, R. Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29* , 4139.

11) 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.

12) Evans, D.A. *Aldrichimica Acta* **1982**, *15* , 23 (and references therein). The diethylboron enolate **14** was formed by treating the N-propionyloxazolidinone with diethylboron triflate generated from triethylborane and triflic acid in situ. See Oppolzer, W., Blagg, J., Rodriguez, I., Walther, E. *J. Am. Chem. Soc.* **1990**, *112* , 2767.

13) Oikawa, Y., Yoshioka, T., Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23* , 889.

14) As an alternative to purifying the major aldol product **15**, we have found that the crude aldol product could be converted to the diol **17** and then purified by crystallization to yield the diastereomerically pure material.

15) Attempts to synthesize **18** from the aldol **15** by alternative routes met with various difficulties. For example, installation of the tert-butyldimethylsilyl ether *before* the elaboration of $C_{13}$ to the iodomethyl group resulted in the removal of the MPM group during the reaction of the 13-mesylate with NaI.

16) Whitesell, J.W., Whitesell, M.A. *Synthesis* **1983**, 517.

17) Corey, E.J., Bakshi, R.K., Shibata, S., Chen, C.-P., Singh, V.K. *J. Am. Chem. Soc.* **1987**, *109* , 7925.

18) Noyori, R., Tominu, I., Tanimoto, Y., Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106* , 6709.

19) Chandrasekharan, J., Ramachandran, P.V., Brown, H.C. *J. Org. Chem.* **1985**, *50* , 5446.

20) This research was made possible by funding from the Robert A. Welch Foundation 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 spectrometer employed was purchased using funds provided by the NSF (#CHE-851404). The assistance of Dr. Masakazu Hirasawa with the measurement of CD spectra is gratefully acknowledged.

(Received in USA 11 October 1990)