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STUDIES ON THE SYNTHESES OF THE APLYSIATOXINS: SYNTHESIS OF A SELECTIVELY-PROTECTED FORM OF THE C_{27} - C_{30} (DIHYDROXYBUTANOATE) MOIETY OF OSCILLATOXIN A‡

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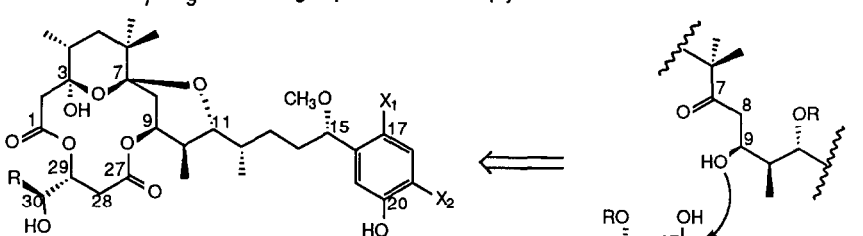
Abstract: A protected form of (R)-3,4-dihydroxybutanoic acid bearing a benzyl protecting group at the C_4 hydroxyl and a dimethylthexylsilyl protecting group at the C_3 hydroxyl was synthesized via a selective Ag(I)-mediated monobenzylation of (R)-methyl 3,4-dihydroxybutanoate. An alternative synthetic route from a chiral allylic ether was successful but problematic. The acid could be cleanly coupled to a model for the C_3 - C_{11} moiety of the aplysiatoxins.

The aplysiatoxins (**1** - **6**) are a class of natural products which have been found in three species of tropical marine bluegreen algae.[1] They are noted for their activities as tumor promotors, and aplysiatoxin (**1**) exhibits an activity very similar to that of the better-known phorbol ester tumor promotor TPA.[2] In fact, the aplysiatoxins **1** and **2** have been observed to compete with TPA for binding to a protein kinase C (PKC) - Ca^{+2} - phospholipid complex to activate PKC,[3] which is apparently an important step in tumorogenesis.[4] A concise and versatile synthetic route to the aplysiatoxins would aid in the study of the details of their binding interactions with PKC by providing a reliable source of these tumor promotors as well as structural analogues.[5] We have embarked upon a total synthesis of the simplest aplysiatoxin, oscillatoxin A (**4**), and report below our synthesis, by two routes, of a selectively-protected form (**7**) of the (R)-3,4-dihydroxybutanoate (C_{27} - C_{30}) moiety of oscillatoxin A, and its coupling to a model system (**16**) which mimics the sensitive β-hydroxyketone moiety representative of the C_7 - C_9 functional group domain of the aplysiatoxins.



1 : APLYSIATOXIN: R=CH_3, X_1=Br, X_2=H.
2 : DEBROMOAPLYSIATOXIN: R=CH_3, X_1=X_2=H.
3 : 19-BROMOAPLYSIATOXIN: R=CH_3, X_1=X_2=Br.
4 : OSCILLATOXIN A: R=X_1=X_2=H.
5 : 17-BROMOOSCILLATOXIN A: R=X_2=H, X_1=Br.
6 : 17,19-DIBROMOOSCILLATOXIN A: R=H, X_1=X_2=Br.

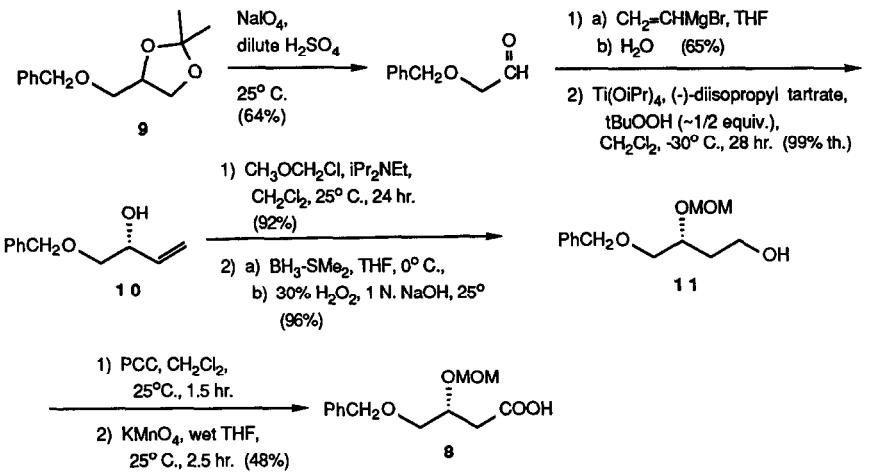
7 (R = alkoxyalkyl or trialkylsilyl)

‡*This paper is dedicated to the memory of our late friend and colleague Brian Earl Knudsen (1960 - 1986).*

We envisioned that a key step in our synthesis of oscillatoxin A would be the esterification of (R)-3,4-dihydroxybutanoic acid, in a form which bears a very stable protecting group on the C_{30} hydroxyl group, a more compliant protecting group on the C_{29} hydroxyl group, and a free carboxylic acid group, to the C_7 - C_9 β-hydroxyketone moiety under conditions which would avoid β-eliminations of the C_9 and/or the C_{29} substituents. We felt that the acid **7**, bearing a benzyl ether at C_{30} and a trialkylsilyl or alkoxyalkyl ether at C_{29}, would meet our criteria for the C_{27} - C_{30} synthon for oscillatoxin A, so we approached its synthesis by two routes designed to yield **7** in high optical purity. We note recent syntheses of similar systems by routes which are not easily adaptable to a facile synthesis of **7** due to nonoptimal enantioselectivity[6] or excessive length.[7]

We first synthesized the methoxymethyl (MOM) ether form of **7**, namely **8**, as indicated in Scheme 1,

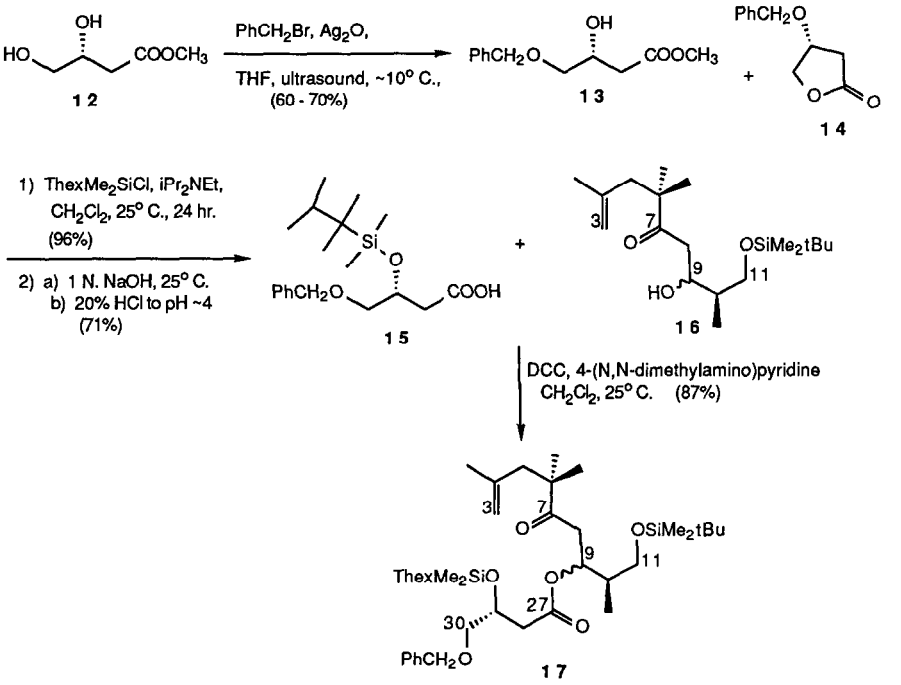
SCHEME 1



starting with the benzyl ether derivative of solketal (**9**). An in situ hydrolysis-periodate cleavage reaction of **11** cleanly provided α-benzyloxyacetaldehyde,[8] which was subjected to vinylmagnesium bromide addition to yield, upon workup, the allylic alcohol. Kinetic resolution using the Sharpless epoxidation reaction[9] yielded the (R)-allylic alcohol **10**[10] in greater than 98% enantiomeric excess, based upon the ^{19}F-NMR analysis of its Mosher ester derivative.[11] Protection of the hydroxyl group followed by hydroboration yielded the alcohol **11**,[10] which proved to be unstable to storage, as it underwent intramolecular transacetalization of the MOM group to yield a 1,3-dioxane product. PCC oxidation[12] of **11** yielded an unstable aldehyde[13] which was oxidized using potassium permanganate to give the acid **8**[10] in yields which varied widely from one run to another.[14] This acid rapidly decomposed to intractable material during storage, and we attribute this instability to a fundamental incompatibility between the proximal MOM ether and carboxylic acid functional groups. A repetition of the synthesis in which a tert-butyldimethylsilyl (TBDMS) group was used instead of the MOM group yielded the TBDMS-protected form of **7**, but this acid was also unstable. The acid **8** and its TBDMS analogue were shown to undergo dicyclohexylcarbodiimide (DCC)-mediated coupling reactions with β-hydroxyketones, indicating that they are viable synthons for a synthesis of oscillatoxin A. However, the length of the synthesis of **8**, the loss of material associated with the kinetic resolution step, and our problems with the reproducibility of the final oxidation steps which formed **8** prompted us to consider alternative synthetic routes to **7**.

The ready availability of (R)-methyl 3,4-dihydroxybutanoate (**12**) from (R)-dimethyl malate[15] led us to consider the challenge of selectively protecting each of the two hydroxyl groups by a route which minimized steps and satisfied our criteria for the protecting group arrangement on **7**. Recognizing that our initial attempts to alkylate **12** using basic conditions (e.g. NaH, benzyl bromide) led, not surprisingly, to γ-lactonization, we sought a "non-anionic" method for benzylating the primary hydroxyl group of **12** to form **13**. As indicated in Scheme 2,

SCHEME 2



treatment of **12** with benzyl bromide and silver(I) oxide led to the selective formation of **13**.[16] No dibenzylated product could be detected in the reaction mixture. However, the yields of **13** varied widely from one run to another. Reasoning that this problem was probably due to a coating of the silver oxide reagent by silver bromide formed during the course of the reaction, we performed the reaction under sonication. This protocol led to the reproducible production of **13**[10] in 60 - 70% yields, with the lactone **14** being formed as a side product in 5 - 10% yield.[17] To our knowledge, this is the first demonstration of a selective monobenzylation of a 1,2-diol at the primary alcohol site.

Silylation of **13** using chlorodimethylthexylsilane[18] followed by saponification and acidification yielded the β-silyloxyacid **15**.[10] We note the extraordinary stability of **15**, relative to the MOM- and TBDMS-protected analogues discussed above, accorded by the dimethylthexylsilyl protecting group;[18] the acid **15** can be stored indefinitely.

When the acid **15** was allowed to couple to the β-hydroxyketone **16** (a model for the C_3 - C_{11} portion of the aplysiatoxins)[19] in the presence of DCC, the ester **17**[10] was cleanly produced (Scheme 2); no products due to β-elimination were observed. This result indicates that the acid **15** can cleanly couple to a

β-hydroxyketone to introduce the C_{27} - C_{30} moiety of oscillatoxin A onto a multifunctional substrate. With this precedent in hand, further studies on the synthesis of oscillatoxin A and the other aplysiatoxins are currently underway in our laboratory.[20]

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10. All new compounds exhibited spectroscopic and analytical properties commensurate with their identities and purities. In the cases of intermediates **11** and **8**, precise analytical data could not be secured due to instability problems. Complete data is available upon request. Data for the key products: **15**: $[\alpha]_D = +5.3^o$ ($CHCl_3$, 0.037 g/ml). ^{1}H-NMR ($CDCl_3$, TMS): δ = 7.31 (s, 5H); 4.53 (s, 2H); 4.29 (br m, 1H); 3.45 (d of d, J=10, 8 cps, 2H); 2.61 (d of d, J=12, 7 cps, 1H); 2.42 (d of d, J=12, 7 cps, 1H); 1.61 (septet, J=6 cps, 1H); 0.88(d, J=6 cps, 6H); 0.81 (s, 6H); 0.106 (s, 6H). IR (film): 1760 cm^{-1}. **17**: $[\alpha]_D = -3.06^o$ ($CHCl_3$, 0.0075 g/ml). ^{1}H-NMR ($CDCl_3$, TMS): δ = 7.30 (s, 5H); 5.35 (m, 1H); 4.79 (br s, 1H); 4.60 (br s, 1H); 4.51 (s, 1H); 4.25 (pentet, J=6 cps, 1H); 3.47 (d, J=6 cps, 2H); 3.41 (d of d, J=8, 3 cps, 2H); 2.81 (d of d, J=17.5, 7.1 cps, 1H); 2.69 (d of d, J=17.5, 7.1 cps, 1H); 2.53 (d of d, J=16.8, 6.2 cps, 1H); 2.37 (d of d, J=16.8, 6.2 cps, 1H); 2.23 (s, 3H); 1.63 (s, 2H); 1.60 (m, 1H); 1.09 (s, 6H); 0.87 (s, 9H); 0.84 (d, J=6 cps, 6H); 0.78 (s, 6H); 0.10 (s, 6H); 0.02 (s, 6H). IR (film): 1750; 1720.
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17. Experimental procedure: A mixture of 0.077 g (0.58 mmol) of the diol **12**, 0.2 ml (~1.7 mmol) benzyl bromide, and 0.274 g (1.2 mmol) of Ag_2O in 5 ml dry THF was sonicated in a Branson sonicator bath filled with ice water for 30 minutes. Concentration and flash chromatography (Si gel, 9:1 (v/v) hexane : ethyl acetate eluant) yielded 0.092 g of the ester **13** contaminated with ~5% (molar) of the lactone **14** (according to NMR analysis). This mixture was carried on to the next step, as the lactone could be easily separated from the silylated derivative of **13**.
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19. The preparation of the model system **16** and other model substrates will be reported elsewhere. The alcohol **16** used here was a 60:40 mixture of inseparable diastereomers epimeric at the C_9 (aplysiatoxin numbering system) carbon.

20. This research was made possible by a grant from the Robert A. Welch Foundation (grant #D-998). The NMR spectrometers employed during the research were purchased using funds provided by the National Science Foundation (grant # CHE-8514104).

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