

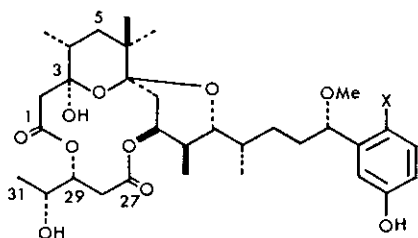
SYNTHETIC STUDIES ON APLYSIATOXIN. INTRAMOLECULAR ESTER
FORMATION FROM 3-ACETOXYFURAN DERIVATIVE VIA OXIDATIVE
RING OPENING REACTION

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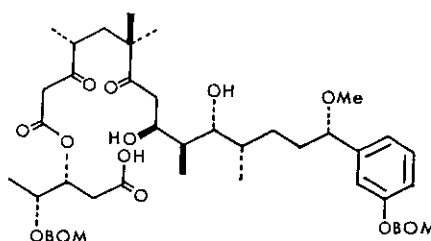
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Abstract-Two steps synthesis of 3-acetoxyfuran derivative (4)
from acetylene derivative (3) and the conversion of 4 to
(3R,4R)-3,4-dihydroxypentanoic acid derivative (5) are described.

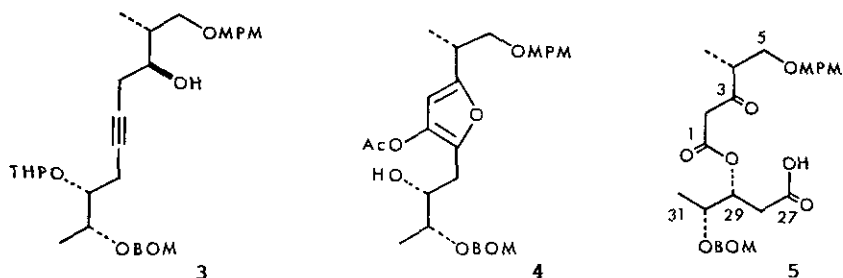
As part of research for the total synthesis of aplysiatoxin (1), a tumor
promotor ¹ isolated from the sea hare *Stylocheilus longicauda*,² and the
blue green alga *Lyngbya majuscula*,³ we have been interested in whether 2
is a promising intermediate leading to aplysiatoxin (1).⁴ In this regard,
the present investigation was undertaken to develop a new method for the
construction of acyclic precursor (2). After extensive evaluation, it
was found that disubstituted acetylene derivative (3) was a key
intermediate for the synthesis of 3-acetoxyfuran derivative (4), which was
converted to (3R,4R)-3,4-dihydroxypentanoic acid derivative (5)
corresponding to the C₂₇-C₃₁ moiety of aplysiatoxin connected to the C₁-C₅
moiety via ester linkage.



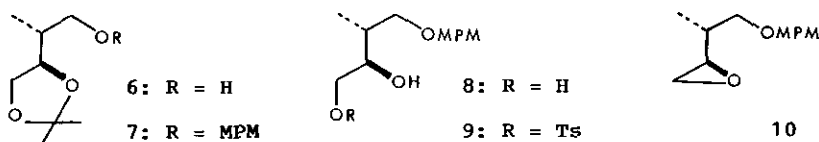
1: aplysiatoxin (X=Br)



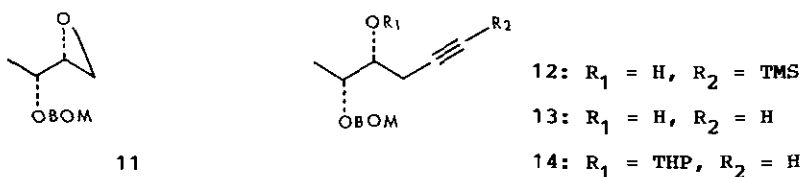
2



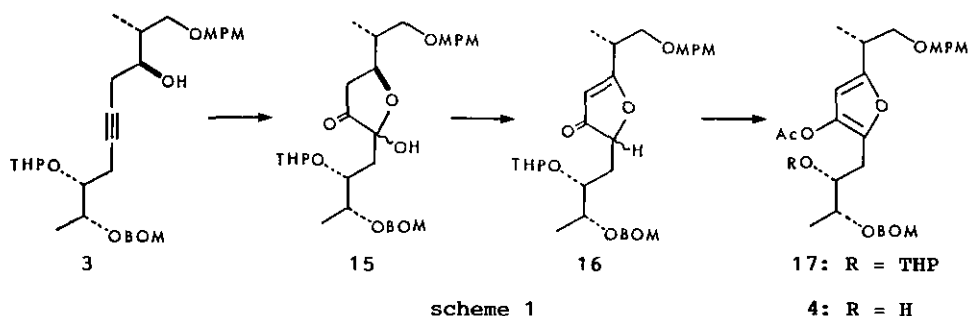
As a key intermediate of our synthesis, **3** was prepared by the coupling of **10** with **14**, both synthesized as follows. As the first step, *p*-methoxyphenylmethylation of a known synthon (**6**)⁵ [$[\alpha]_D^{25} -18^\circ$ (c 1.14, CHCl_3)] was followed by deprotection of the acetonide of the resulting product (**7**) to give diol (**8**) in 80% overall yield. Treatment of **8** with tosyl chloride (1.1 equiv.) in pyridine led to monotosylate (**9**) (80%), which, on basic treatment (0.1N KOH-MeOH), gave the desired epoxide (**10**)⁶ [$[\alpha]_D^{25} +4.56^\circ$ (c 1.12, CHCl_3)] in 85% yield.



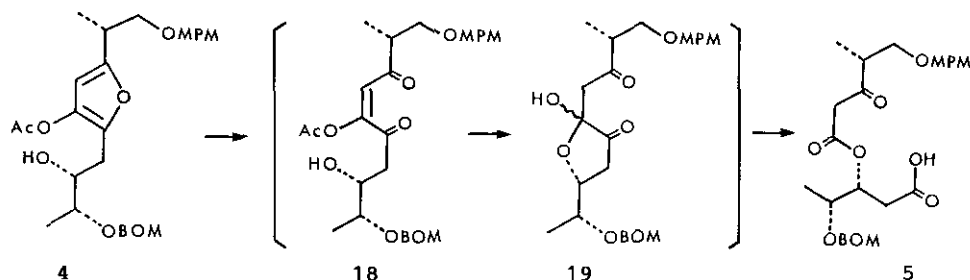
The preparation of another building block (**14**) started from the readily available epoxide (**11**)⁷ [$[\alpha]_D^{25} +29.37^\circ$ (c 0.80 CHCl_3)]. Treatment of **11** with lithium trimethylsilylethynyltrifluoroborate⁸ in THF at -78°C gave **12** (94%), which was converted to **13**⁹ [98%, $[\alpha]_D^{25} -35.30^\circ$ (c 1.01, CHCl_3)] by successive treatment with K_2CO_3 in MeOH. Protection of the resulting secondary alcohol of **13** with dihydropyran gave the desired THP-ether (**14**) (95%) as a diastereoisomeric mixture.



The coupling of segments (10) with (14) was accomplished as follows. The reaction of lithium alkynyltrifluoroborate,⁸ generated from the lithium salt of 14 and boron trifluoride etherate at -78°C , with the epoxide (10) in THF at -78°C furnished a clean reaction mixture which was separated on a silica gel column (hexane-acetone=3:1) to give acetylene alcohol (3) in 84% isolated yield. With the key intermediate (3) in hand, the most crucial two steps in the present synthesis were studied. (Scheme 1) First, the oxidation of the acetylene group in 3 with osmium tetroxide in pyridine at room temperature was followed by the reductive decomposition of osmate (10% aq. NaHSO_3 -pyridine=1:2, room temperature) to give hemiacetal (15) [ir (film) 3500-3200, 1755 cm^{-1}] as an inseparable diastereoisomeric mixture in 90% yield. After several trials at the dehydration of 15, as the next step, the following conditions were found to give the best results. That is, when 15 was treated with freshly distilled thionyl chloride (1.5 equiv.) in the mixture of pyridine and THF (1:10,v/v) at 0°C for 2.5 h and then 5°C overnight, a diastereoisomeric mixture of 3(2H)-furanone (16) was obtained in 73% yield. The characteristic spectral data [ir (film): 1690, 1582 cm^{-1} ; $^1\text{H-nmr}(\text{CDCl}_3)$ δ : 5.45 (0.5H, s) and 5.47 (0.5H, s)] suggested the structure of the product to be 16. This was confirmed by the successive conversion of 16 into the 3-acetoxymethylfuran derivative (4); i.e., treatment of 16 with Ac_2O -DMAP in CH_2Cl_2 (40°C , 1 h) yielded the acetate (17) [90%, $^1\text{H-nmr}(\text{CDCl}_3)$ δ : 2.20 (3H, s, acetyl), 6.01 (1H, s, vinyl proton)], which, under acidic conditions ($\text{AcOH-THF-H}_2\text{O}=4:2:1$, 50°C , 1 h), was further converted to 4 [[α]_D²⁵ +9.31°(c 0.35, CHCl_3)] by the selective deprotection of THP. The $^1\text{H-nmr}$ spectrum of 4¹⁰ showed sharp and clearly split signals, all reasonably attributable to the protons in 4.



Now, the transformation of **4** into **5**, a model of aplysiatoxin seco-acid (**2**),⁴ was subsequently achieved via two steps oxidative ring opening reaction. (Scheme 2)



Scheme 2

The oxidation of **4** with mCPBA (1.05 equiv., CH_2Cl_2 , room temperature, 1 h) was followed by extractive workup and successive treatment of the resulting mixture with a solution of HIO_4 (10 equiv., in H_2O -dioxane (1:3 v/v)) for 16 h at room temperature gave a colorless oil, which was subsequently separated on a silica gel column (CH_2Cl_2 -MeOH=100:7). The structure of the major product (45%) thus obtained was assigned to **5**¹¹ [$[\alpha]_D^{25}$ -11.63° (c 0.32, CHCl_3)] based on the following spectral data: [ir (film) 3100-2800 (br), 1742, 1728 (sh), 1710 cm^{-1} ; ^1H nmr (270 MHz, CDCl_3) δ 2.68 (1H, dd, $J=16.0, 8.0$ Hz, $-\text{CHCOOH}$), 2.73 (1H, dd, $J=16.0, 5.1$ Hz, $-\text{CHCOOH}$), 3.56 (2H, s, $-\text{COCH}_2\text{COO}-$), 5.40 (1H, m, $-\text{COOCH}-$)]. This transformation process may take place in the following steps: 1) the oxidative ring cleavage of the 3-acetoxymethoxyfuran affords an acyclic diketone (**18**),¹² 2) deacetylation and cyclization of **18** to produce 2-hydroxytetrahydrofuran-3-one (**19**), and 3) C-C bond cleavage of the hydroxyketone moiety in **19** to give the desired ester (**5**). It is thus evident that the synthesis of the desired product (**5**) from 3-acetoxymethoxyfuran derivative (**4**) was successfully achieved. The application of this method to the synthesis of aplysiatoxin seco-acid (**2**) is promising and is now being conducted.

ACKNOWLEDGEMENT

The financial support by the Ministry of Education, Japanese Government (Grant-in Aid No. 01571170) is acknowledged.

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6. ^1H nmr(270 MHz, CDCl_3) δ 0.99(3H, d, $J=6.7$ Hz), 1.70(1H, m), 2.54(1H, dd, $J=5.0$, 2.7 Hz), 2.74(1H, t, $J=5.0$ Hz), 2.89(1H, m), 3.43(1H, dd, $J=9.1$, 6.0 Hz), 3.49(1H, dd, $J=9.1$, 5.7 Hz), 3.81(3H, s), 4.46(2H, s), 6.88(2H, d, $J=8.4$ Hz), 7.27(2H, d, $J=8.4$ Hz).
7. Synthesized from (-)-threonine by the following steps: 1) $\text{NaNO}_2/\text{H}_2\text{SO}_4$, 2) EtOH/CSA, 3) 2,2-dimethoxypropane/CSA, 4) LAH, 5) TsCl/Py, 6) 5% HCl/MeOH, 7) NaH/DMF, BOMCl. Unpublished results.
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9. ^1H nmr(270 MHz, CDCl_3) δ 1.26(3H, d, $J=6.4$ Hz), 2.03(1H, t, $J=2.7$ Hz), 2.43(1H, ddd, $J=16.8$, 6.2, 2.7 Hz), 2.53(1H, ddd, $J=16.8$, 5.7, 2.7 Hz), 2.72(1H, br s, -OH), 3.65(1H, m), 3.89(1H, m), 4.62(1H, d, $J=11.8$ Hz), 4.68(1H, d, $J=11.8$ Hz), 4.84(1H, d, $J=7.1$ Hz), 4.88(1H, d, $J=7.1$ Hz), 7.34(5H, m).

10. ^1H Nmr (270 MHz, CDCl_3) δ 1.24(3H, d, $J=7.1$ Hz), 1.25(3H, d, $J=6.4$ Hz), 2.22(3H, s), 2.59(1H, br d, $J=4.0$ Hz), 2.73(1H, dd, $J=15.1, 7.1$ Hz), 2.80(1H, dd, $J=15.1, 5.0$ Hz), 3.03(1H, m), 3.41(1H, dd, $J=9.1, 8.7$ Hz), 3.61(1H, dd, $J=9.1, 5.7$ Hz), 3.70(1H, m), 3.77(1H, m), 3.79(3H, s), 4.42(2H, s), 4.64(2H, s), 4.82(1H, d, $J=7.1$ Hz), 4.86(1H, d, $J=7.1$ Hz), 6.04(1H, s), 6.86(2H, d, $J=8.7$ Hz), 7.22(2H, d, $J=8.7$ Hz), 7.33(5H, m).
11. ^1H Nmr (270 MHz, CDCl_3) δ 1.09(3H, d, $J=7.1$ Hz), 1.20(3H, d, $J=6.4$ Hz), 2.68(1H, dd, $J=16.0, 8.0$ Hz), 2.73(1H, dd, $J=16.0, 5.0$ Hz), 2.96(1H, m), 3.43(1H, d, $J=5.0$ Hz), 3.47(1H, d, $J=5.0$ Hz), 3.56(2H, s), 3.80(3H, s), 4.00(1H, m), 4.39(1H, d, $J=11.8$ Hz), 4.44(1H, d, $J=11.8$ Hz), 4.61(2H, s), 4.77(1H, d, $J=11.4$ Hz), 4.82(1H, d, $J=11.4$ Hz), 5.40(1H, m), 6.87(2H, d, $J=8.7$ Hz), 7.22(2H, d, $J=8.7$ Hz), 7.33(5H, br s).
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Received, 25th December, 1990