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

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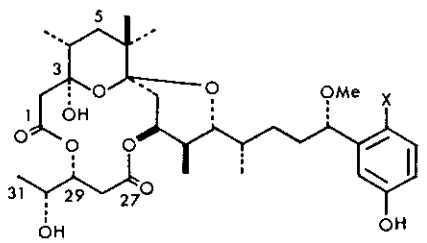
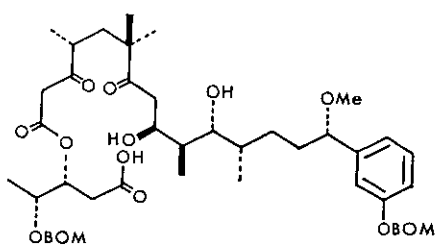
Abstract-Two steps synthesis of 3-acetoxyfuran derivative (4) from acetylene derivative (3) and the conversion of 4 to (3R,4R)-3,4-dihydroxypentanoic acid derivative (5) are described.

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 C_{27}-C_{31} moiety of aplysiatoxin connected to the C_1-C_5 moiety via ester linkage.



1: aplysiatoxin (X=Br)



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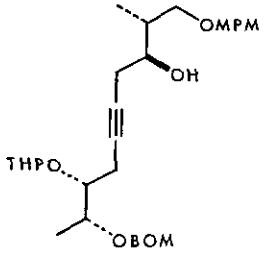

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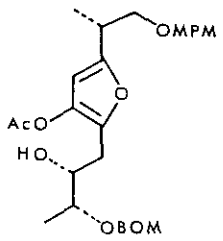

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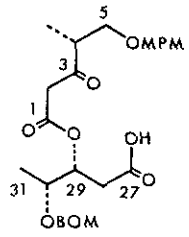
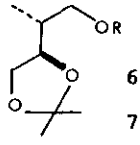


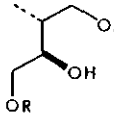
5

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° (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° (c 1.12, $CHCl_3$)] in 85% yield.



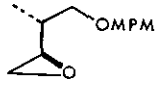
6: R = H

7: R = MPM



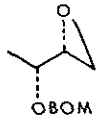
8: R = H

9: R = Ts



10

The preparation of another building block (**14**) started from the readily available epoxide (**11**)[7] [$[\alpha]_D^{25}$ +29.37°(c 0.80 $CHCl_3$)]. Treatment of **11** with lithium trimethylsilylethynyltrifluoroborate[8] in THF at -78°C gave **12** (94%), which was converted to **13**[9] [98%, $[\alpha]_D^{25}$ -35.30°(c 1.01, $CHCl_3$)] by successive treatment with K_2CO_3 in MeOH. Protection of the resulting secondary alcohol of **13** with dihydropyrane gave the desired THP-ether (**14**) (95%) as a diastereoisomeric mixture.



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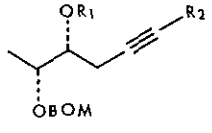
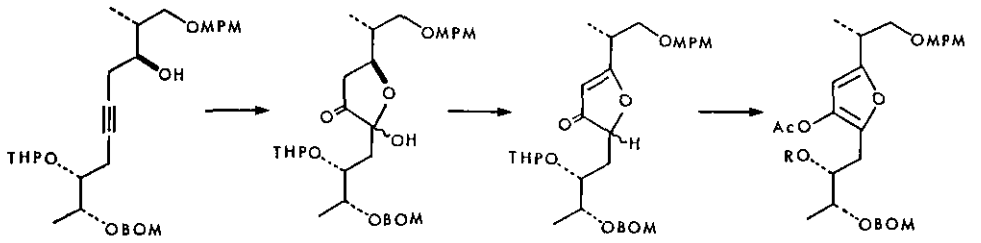


12: R_1 = H, R_2 = TMS

13: R_1 = H, R_2 = H

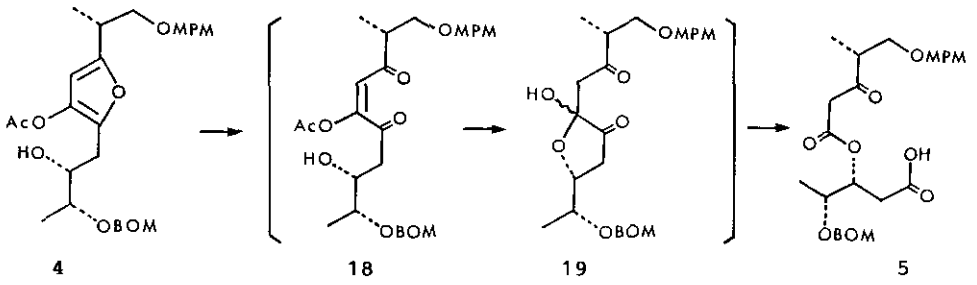
14: R_1 = THP, R_2 = H

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 tetraoxide 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}H-nmr($CDCl_3$) 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-acetoxyfuran 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}H-nmr($CDCl_3$) δ: 2.20 (3H, s, acetyl), 6.01 (1H, s, vinyl proton)], which, under acidic conditions (AcOH-THF-H_2O=4:2:1, 50°C, 1 h), was further converted to **4** [$[\alpha]_D^{25}$ +9.31°(c 0.35, $CHCl_3$)] by the selective deprotection of THP. The ^{1}H-nmr spectrum of **4**[10] showed sharp and clearly splited signals, all reasonably attributable to the protons in **4**.



scheme 1

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**)



4 **18** **19** **5**

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, -CHCOOH), 2.73 (1H, dd, J=16.0, 5.1 Hz, -CHCOOH), 3.56 (2H, s, -$COCH_2COO$-), 5.40 (1H, m, -COOCH-)]. This transformation process may take place in the following steps: 1) the oxidative ring cleavage of the 3-acetoxyfuran 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-acetoxyfuran 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

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6. ^{1}H 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) $NaNO_2/H_2SO_4$, 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. ^{1}H 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. ^{1}H 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. ^{1}H 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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