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# SYNTHETIC STUDY ON APLYSIATOXINS, HIGHLY INFLAMMATORY AGENTS AND TUMOR PROMOTERS SYNTHESIS OF THE THREE OPTICALLY ACTIVE SEGMENTS

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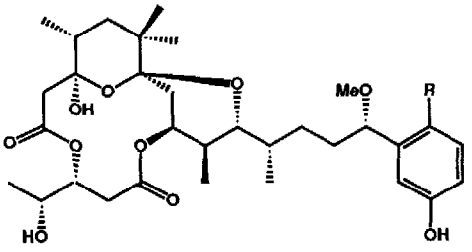
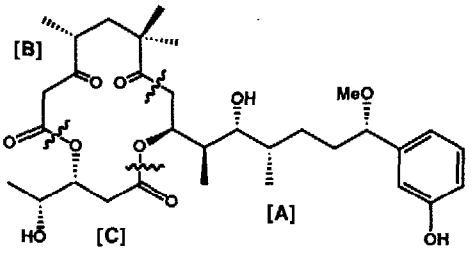
The main segments in debromoaplysiatoxin and related aplysiatoxins have been efficiently synthesized from D-glucose and L- and D-tartaric acids.

Both aplysiatoxin and debromoaplysiatoxin, highly inflammatory agents, were first isolated from the digestive gland of the sea hare Stylocheilus longicauda.[1] Since then, a number of related toxins have been isolated from blue-green algae, Lyngbya majuscula, Schizothrix calcicola, Oscillatoria nigroviridis and others,[2,3] and their stereostructures including the absolute configuration have also been elucidated on the basis of optical and $^1H$ NMR spectral data together with an X-ray crystallographic analysis of dibromoaplysiatoxin.[3] The challenging structures of these natural products have prompted many synthetic chemists to investigate the total synthesis.[4] From structural and physiological points of view, we are interested in debromoaplysiatoxin (1),[5] which shows some antineoplastic activity[6] and has also been found to be one of the powerful tumor promoters.[7]




**Aplysiatoxin R = Br**
**Debromoaplysiatoxin (1) R = H**



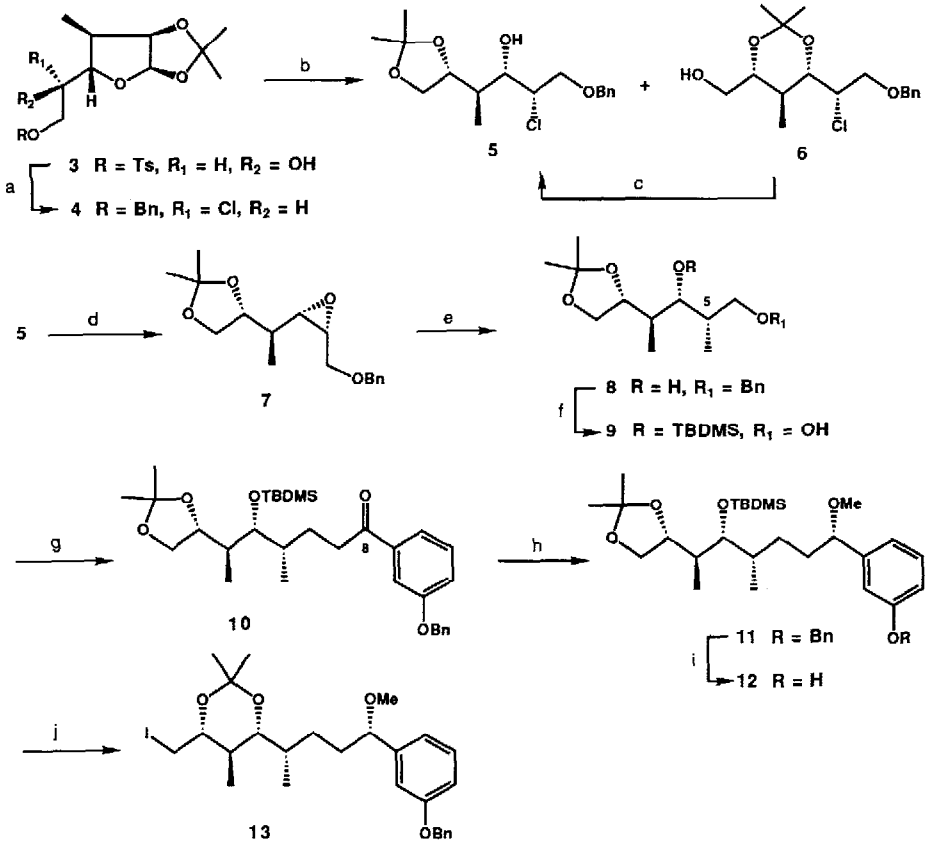

**2**

In retrosynthetic analysis, **1** seems to be derived from the corresponding diketone (**2**), the structure of which is mainly divided into three segments [**A**, **B** and **C**], as seen in **2**. In the present paper, we describe synthetic results of these segments starting from D-glucose, L-tartaric acids and D-tartaric acid. These synthesized segments might also be applicable for the syntheses of other aplysiatoxins.

Synthesis of segment **A**.

The readily available tosylate (**3**)[8] was converted to a chloro benzyl ether (**4**)[9] in three steps. Acid hydrolysis of **4** followed by $NaBH_4$ reduction afforded an open-chain sugar, which was again protected with 2,2-dimethoxypropane to give **5** and **6**[9] in 50 and 46% yields, respec-

tively. Acidic isomerization of **6** afforded further desired ketal (**5**) in 91% yield, which was treated with NaOMe to give the corresponding epoxide (**7**)[9] in quantitative yield. On methylation of **7** with $Me_2CuLi$, an alcohol (**8**)[9] was produced as a main product (regioselectivity: ca. 11:1) in 81% yield. The alcohol (**8**) was further derivatized in two steps to another alcohol (**9**).[9] Chain elongation of **9** was performed with Swern oxidation followed by Wittig reaction using the corresponding phosphorane and then catalytic hydrogenation to give a ketone (**10**)[9] in moderate yield, which did not accompany such by-products as an epimer at the $C_5$ carbon. After evaluation of asymmetric reductions of the carbonyl group at $C_8$ in **10**, Brown reduction using diisopinocampheylchloroborane[10] followed by methylation with MeI-NaH promised a successful result, in which only one desired methyl ether (**11**)[9] was obtained in ca. 100% ee[11] and 74% overall yield. This ether (**11**) was readily converted to the corresponding phenol (**12**) in quantitative yield, the CD curve ($[\theta]_{260}$ +404° (EtOH)) of which was quite similar to that of debromoaplysiatoxin (**1**).[3] The compound (**11**) was then subjected to a four step

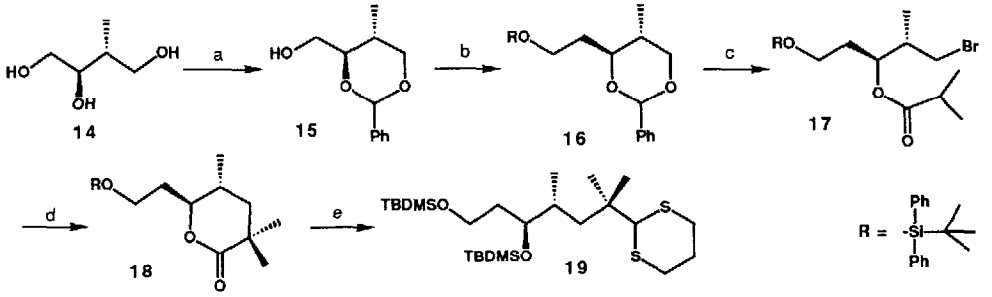



a. i) NaOMe/BnOH-THF, room temp, overnight (95%); ii) MsCl, pyr. (100%); iii) $^nBu_4NCl$/ PhH, reflux temp, overnight (94%). b. i) IR-120 ($H^+$)/ dioxane-$H_2O$, reflux temp, 15 h (100%); ii) $NaBH_4$/ aq. MeOH (88%); iii) 2,2-dimethoxypropane, TsOH/acetone (**5**: 50%, **6**: 46%). c. TsOH (cat.)/ acetone, room temp, overnight (**5**: 53%, **6**: 42%). d. NaOMe/MeOH, 0 → 40°C, 2 h (100%). e. $Me_2CuLi/Et_2O$, -30 → 0°C, 3 h (81%). f. i) TBDMSOTf, $Et_3N/CH_2Cl_2$, -10 → 0°C, 30 min (100%); ii) $H_2$, Pd-C/MeOH, overnight (100%). g. i) Swern oxi.; ii) $Ph_3P{=}CHCOC_6H_4OBn$/PhMe, reflux temp, 7.5 h (71% in two steps); iii) $H_2$, Pd-C/EtOAc, room temp, 20 min (85%). h. i) $Ipc_2BCl$/THF, -25°C, overnight; MeI, NaH/THF (74% in two steps). i. $H_2$, Pd-C/MeOH (quantitative yield). j. i)$nBu_4NF$ (100%); ii) TsOH/acetone (100%); iii) MsCl, pyr. (100%); iv) NaI/acetone, reflux temp, overnight (99%).

conversion to an iodo derivative (**13**)[9] in quantitative yield, which possessed the same stereostructure as that of **1** and the required functional group for the coupling reaction with other segments.

Synthesis of segment **B**.

Treatment of the known triol (**14**) with dimethoxytoluene afforded a benzylidene derivative (**15**)[9,12] in 86% yield, which was converted to a silyl ether (**16**)[9] in four steps involving the hydroboration using 9-BBN. This compound (**16**) was submitted to Hanessian's bromination to open the acetal ring, and then the resulted benzoyl ester was transformed into an isobutyryl ester (**17**).[9] Cyclization of **17** with LDA resulted in the desired δ-lactone (**18**)[9] in high yield. After partial reduction of **18** with DIBAL, the lactol so far obtained was reacted with 1,3-propanedithiol followed by protection of the OH groups to give an acyclic derivative (**19**)[9] in good overall yield. This compound would be coupled with the aforementioned **13** and the two silylated OH groups will be converted to the corresponding ester and ketonic CO groups, as seen in segment [**B**]. In particular, **19** may be used as a versatile intermediate for other aplysiatoxins.

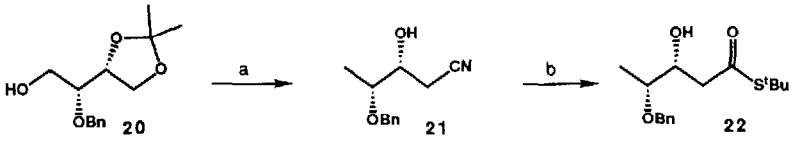



14 15 16 17 18 19

a. $PhCH(OMe)_2$, $TsOH/CH_2Cl_2$ (86%). b. i) Swern oxi. (91%); ii) $Ph_3P{=}CH_2$/THF, 0 °C→ room temp. (81%); iii) 9-BBN/THF, 0 °C→ room temp., overnight, then $NaOH$-$H_2O_2$ (93%); iv) TBDPSCl, Imd./DMF (100%). c. i) NBS, $BaCO_3/CCl_4$, reflux temp, 1 h (89%); ii) DIBAL-H/PhMe, -78°C, 20 min (88%); iii) $^{i}$PrCOCl, pyr. (99%). d. LDA/THF, -78 → 0°C, 4 h (86%). e. i) DIBAL-H/PhMe, -78°C, 30 min (95%); ii) 1,3-propanedithiol, $BF_3OEt_2$ (73%); iii) TBDMSCl, Imd./DMF (96%).

Synthesis of segment **C**.

According to the known procedure,[13] a thiol ester (*22*)[9] could be synthesized from *D*-tartaric acid via an alcohol (**20**) and a cyano derivative (**21**).




20 21 22

a. i) TsCl, pyr. ; ii) LiAlH4/THF; iii) aq. HCl-MeOH; iv) TsCl, pyr.; v) KCN/DMSO. b. i) HCl/MeOH; ii) aq. NaOH-THF; iii) tBuSH, DCC, DMAP/DMF

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9. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: **4**: $C_{17}H_{23}O_4{}^{35}Cl$ [m/z 326.1268($M^+$)]; $[\alpha]_D{}^{25}$ +17.6° (c 1.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.01 (3H, d, J= 7 Hz), 1.30 (3H, s), 1.47 (3H, s), 2.27 (1H, m), 3.7 - 4.2 (4H, complex), 4.52 (1H, t, J= 4 Hz), 4.56 (2H, s), 5.76 (1H, d, J= 3 Hz), and 7.32 (5H, br.s). **5**: $C_{17}H_{25}O_4{}^{35}Cl$ [m/z 328.1435($M^+$)]; $[\alpha]_D{}^{25}$ -6.2° (c 1.7, $CHCl_3$); IR (film) 3480 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.78 (3H, d, J= 7 Hz), 1.34 (3H, s), 1.39 (3H, s), 1.98 (1H, m), 3.5 - 4.3 (7H, complex), 4.56 (2H, s), and 7.32 (5H, br.s). **7**: $C_{16}H_{21}O_4$ [m/z 277.1427 ($M^+$-Me)]; $[\alpha]_D{}^{26}$ -27.4° (c 1.25, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.97 (3H, d, J= 7.5 Hz), 2.90 (1H, dd, J= 4.8, 9 Hz), and 3.14 (1H, dt, J= 4.8, 9 Hz). **8**: $C_{17}H_{25}O_4$ [m/z 293.1751($M^+$-Me)]; $[\alpha]_D{}^{25}$ -0.72° (c 1.12, $CHCl_3$); IR (film) 3520 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.75 (3H, d, J= 6.8 Hz), 0.91 (3H, d, J= 7.0 Hz), 1.37 (3H,s), 1.42 (3H, s), 1.77 (1H, m), 1.96(1H, m) , 3.43 (1H, dd, J= 6, 9 Hz), 3.59 (1H, dd, J= 7, 9 Hz), 3.66 (1H, t, J= 7 Hz), 3.73 (1H, br.d, J= 9 Hz), 3.82 (1H, s), 4.10 (2H, m), 4.51 (1H, d, J= 12 Hz), 4.56 (1H, d, J= 12 Hz), and 7.34 (5H, complex). **9**: $C_{17}H_{35}O_3Si$ [m/z 315.2352($M^+$-OH)]; $[\alpha]_D{}^{25}$ -0.84° (c 1.03, $CHCl_3$); IR (film) 3450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.8 - 0.9 (15H, complex), and 3.4 - 4.2 (6H, complex). **10**: $C_{31}H_{45}O_5Si$ [m/z 525.3042 ($M^+$-Me)]; $[\alpha]_D{}^{24}$ -10.0° (c 0.18, $CHCl_3$); IR (film) 1680 and 1580 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.87 (3H, d, J= 7.3 Hz), 0.94 (3H, d, J= 6.3 Hz), 1.62 (1H, m), 1.70 - 1.88 (2H, complex), 1.94 (1H, m), 2.98 (2H, m), 3.59 (1H, t, J= 7.6 Hz), and 3.76 (1H, dd, J= 3.2, 4.2 Hz). **11**: $C_{32}H_{49}O_4Si$ [m/z 525.3394 ($M^+$-MeO)]; $[\alpha]_D{}^{31}$ -24.0° (c 0.58, $CHCl_3$); IR (film) 1580 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.30 (3H, s), 1.37 (3H, s), 3.20 (3H, s), and 3.92 (1H, dd, J= 6.1, 8.1 Hz). **13**: $C_{27}H_{37}O_4I$ [m/z 552.1711 ($M^+$); $[\alpha]_D{}^{29}$ -23.9° (c 1.02, $CHCl_3$); IR (film) 1595 and 1580 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.69 (3H, d, J= 6.5 Hz), 0.82 (3H, d, J= 6.3 Hz), 1.33 (6H, s), and 3.18 (3H, s). **15**: mp 53 - 54°C (benzene-hexane); $C_{12}H_{16}O_3$ [m/z 208.1077 ($M^+$)]; $^1H$ NMR ($CDCl_3$) δ 0.77 (3H, d, J= 7 Hz), 2.02 (1H, m), 2.29 (1H, broad signal), and 3.49 (1H, t, J= 11 Hz). **16**: $C_{25}H_{27}O_3Si$ [m/z 403.1713 ($M^+$-$C_4H_9$)]; $[\alpha]_D{}^{27}$ -39.1° (c 0.98, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.76 (3H, d, J= 7 Hz), 1.03 (9H, s), 3.46 (1H, t, J= 11 Hz), and 5.38 (1H, s). **17**: $C_{22}H_{28}O_3Si^{79}Br$ [m/z 447.1017 ($M^+$-$C_4H_9$)]; $[\alpha]_D{}^{25}$ -3.18° (c 1.87, $CHCl_3$); IR (film) 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.13 (1H, m), 3.20 (1H, dd, J= 7, 10 Hz), 3.40 (1H, dd, J= 5,10 Hz), 3.63 (2H, t, J= 6 Hz), and 5.02 (1H, dt, J= 5.4, 6 Hz). **18**: $C_{22}H_{27}O_3Si$ [m/z 367.1709 ($M^+$-$C_4H_9$)]; $[\alpha]_D{}^{28}$ -35.3° (c 0.99, $CHCl_3$); IR (film) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.93 (3H, d, J= 7 Hz), 1.03 (9H, s), and 1.26 (6H, s). **19**: $C_{21}H_{45}O_2S_2Si_2$ [m/z 449.2393 ($M^+$-$C_4H_9$); $[\alpha]_D{}^{26}$ -18.6° (c 1.02, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 0.88 (18H, s), 0.92 (3H, d, J= 7 Hz), 1.07 (6H, s), 2.85 (4H, dd, J= 3, 7 Hz), and 3.99 (1H, s). **22**: $C_{16}H_{25}O_3S$ [m/z 297.1520 ($M^+$+H)]; $[\alpha]_D{}^{25}$ -4.79° (c 0.59, $CHCl_3$); IR (film) 3500 and 1680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.21 (3H, d, J= 6.2 Hz), 1.46 (9H, s), 2.67 (2H, d, J= 6.2 Hz), 3.51 (1H, m), 4.00 (1H, m), 4.46 (1H, d, J= 11.7 Hz), 4.64 (1H, d, J= 11.7 Hz), and 7.33 (5H, s).
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