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SYNTHETIC STUDY ON APLYSIATOXINS, HIGHLY INFLAMMATORY AGENTS AND TUMOR PROMOTERS
SYNTHESIS OF 3-DEOXYDEBROMOAPLYSIATOXIN

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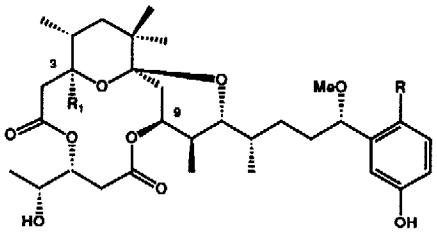
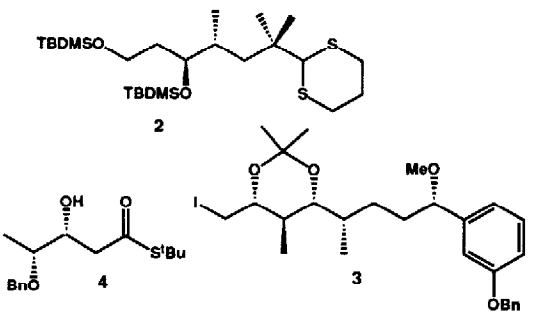
3-Deoxydebromoaplysiatoxin (**1**), possessing a competitive activity to debromoaplysiatoxin, has been synthesized from the corresponding synthetic intermediates.

Of marine toxins aplysiatoxin, debromoaplysiatoxin and related compounds, isolated from the sea hare Stylocheilus longicauda,[1] and the blue-green algae, Lyngbya majuscula, and others[2,3] are classified as tumor promoters comparable to phorbols and teleocigins.[4] Among them debromoaplysiatoxin shows antineoplastic activities.[5] In connection with the structure - activity relationship, their polyfunctional structures are attractive to synthetic chemists.[6] In the preceding paper, we have synthesized the three segments (**2**, **3** and **4**),[7] which might be the useful synthetic intermediates not only for debromoaplysiatoxin, but also for other aplysiatoxins. In our synthetic project toward aplysiatoxins, such a spiroketal compound as **7** is regarded as an important intermediate, which has a possibility that the C_3-OH group may be introduced using the neighboring ester CO group to afford debromoaplysiatoxin. Hence, our investigation was focussed on construction of the spiroketal compound carrying the same stereostructure as that of the natural products. We describe herein the synthesis of 3-deoxydebromoaplysiatoxin (**1**), which has been known to exhibit the comparable activities to that of debromoaplysiatoxin.[8]

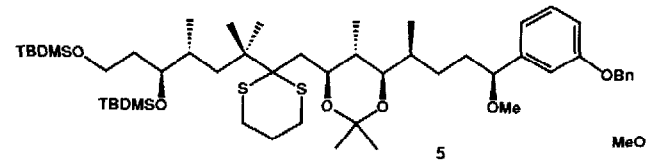


Aplysiatoxin R = Br, R_1 = OH
Debromoaplysiatoxin R = H, R_1 = OH
3-Deoxydebromoaplysiatoxin (1) R = H, R_1 = H



The 1,3-dithian derivative (**2**) was successfully coupled with **3** to afford **5**[9] in 90% yield (^tBuLi in THF - HMPA, -78 °C, 5 min and -30 → -25 °C, 30 min, then **3**, -78 °C, 30 min). This compound (**5**) was then oxidized to the corresponding methyl ester (**6**)[9] in five steps [1) $HgCl_2$-HgO, room temp., 30 min (97%); 2) PPTS in EtOH, room temp., 30 h (96%); 3) Swern oxid.; 4) Jones oxid. (87% in two steps); 5) CH_2N_2 (100%)]. Among several methods attempted, we

could not obtain better results than this stepwise manipulation. On treatment with 2N HCl in THF (room temp., overnight, and 50 °C, 4 h, then CH_2N_2),[10] the ester (**6**) was transformed into a mixture of **7**, **8**, and **9**[9] in 24, 17, and 46% yields, respectively. The desired spiro derivative (**7**) could be distinguished from its isomer (**8**) by the comparison of the ^1H NMR spectra of their acetates (**7a** and **8a**), both of which revealed the characteristic signals due to the H-9 proton attached to the carbon atom (C_9) carrying acetoxyl group [**7a**: δ 5.02 (m, half-width = 14.3 Hz); **8a**: δ 4.73 (dt, J= 4,4, 10.7 Hz)]. The H-9 protons, equatorial in **7a** and axial in **8a**, indicated their conformations as depicted in figures. On treatment with TsOH in $CHCl_3$ (room temp., 30 min), **8** gave ca. 1 : 1 mixture of **7** and **8**, therefore, on repeated equilibrium reaction **8** could be converted to **7** in nearly quantitative yield. The spiro ester was then subjected to alkaline hydrolysis (0.5 N NaOH in THF, room temp., overnight) to yield a carboxylic acid (**10**)[9] in 94% yield. At this stage, the upper segment could be assembled,



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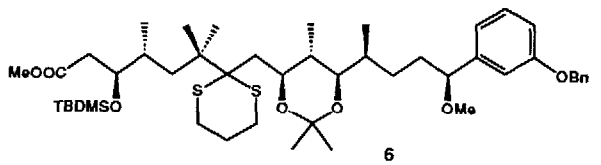

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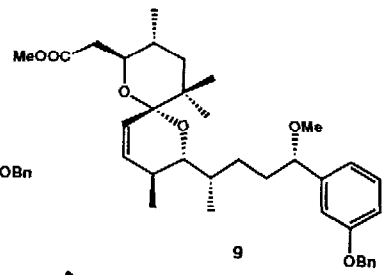

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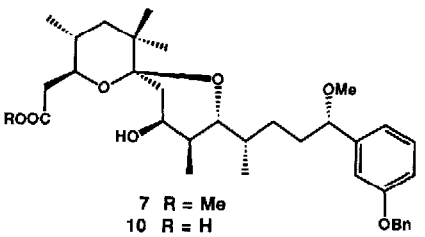
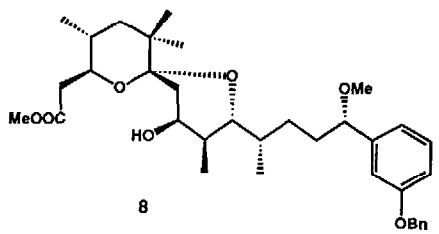


7 R = Me
10 R = H



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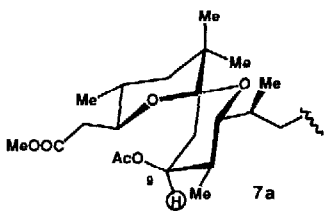
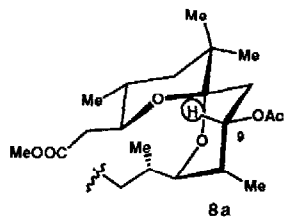
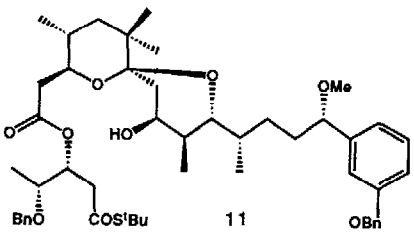


7a



8a



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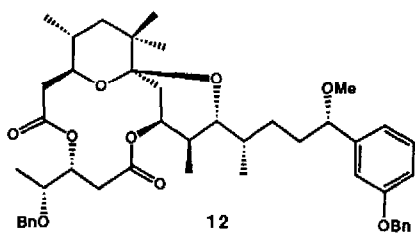

12

and was submitted to the next esterification without any protection of the hydroxyl group at C_9 position, because the carboxylic acid in **10** might preferencially react with the hydroxyl group in **4** rather than the structurally hindered one at C_9. As expected, coupling reaction of **10** with **4** could be accomplished with DCC in the presence of catalytic DMAP in Et_2O (room temp., 5 h) to afford an ester (**11**)[9] in 65% yield, and any by-product reacted at C_9 position could not be detected. The thiol ester (**11**) so far obtained was subjected to the lactonization with AgOTf and Na_2HPO_4 in benzene (room temp., 27 h)[11] to yield a desired lactone (**12**)[9] in 23% yield.[12] The final catalytic hydrogenation of **12** (Pd-C, EtOH) afforded 3-deoxydebromoaplysiatoxin[13] in quantitative yield, whose spectral data were in good agreement with those of Kishi's sample.[8] Based on these results, further synthetic studies on aplysiatoxins are still going on.

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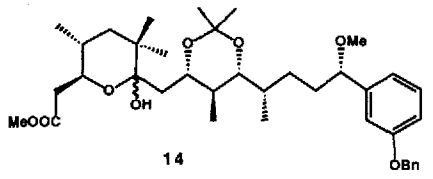
REFERENCES

1. Y. Kato and P. J. Scheuer, J. Am. Chem. Soc., **96**, 2245 (1974); Pure. Appl. Chem., **41**, 1 (1975); ibid., **48**, 29 (1976).
2. J. S. Mynderse and R. E. Moore, J. Org. Chem., **43**, 2301 (1978).
3. R. E. Moore, A. J. Blackman, C. E. Cheuk, J. S. Mynderse, G. K. Matsumoto, J. Clardy, R. W. Woodard, and J. C. Craig, J. Org. Chem., **49**, 2484 (1984).
4. H. Fujiki, M. Suganuma, M. Nakayasu, H. Hoshino, R. E. Moore, and T. Sugimura, Gann, **73**, 495 (1982); M. Suganuma, H. Fujiki, T. Tahira, C. Cheuk, R. E. Moore, and T. Sugimura, Carcinogenesis, (N.Y.), **5**, 315 and many references cited therein.
5. J. S. Mynderse, R. E. Moore, M. Kashiwagi, and T. R. Science, **196**, 538 (1977).
6. Total synthesis of aplysiatoxin: P. Park, C. A. Broka, B. F. Johnson, and Y. Kishi, J. Am. Chem. Soc., **109**, 6205 (1987); 3-deoxy-20-O-methylaplysiatoxin: R. E. Ireland, S. Thaisrivongs, and P. H. Dussault, ibid., **110**, 5768 (1988).
7. H. Toshima, S. Yoshida, T. Suzuki, S. Nishiyama, and S. Yamamura, submitted to Tetahedron Lett.
8. H. Nakamura, P. Park, and Y. Kishi, 58th Annual Meeting of the Chem. Soc. Jpn., April 1989 (Kyoto), Abstract Papers II, p 1189. We are indebted to them for provision of their spectral data.
9. *The spectral data for the new compounds were in accord with the structures assigned, and* only selected data are cited: **5**: $[\alpha]_D^{24}$ -14.1° (c 1.70, $CHCl_3$); IR (film) 1595 and 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.05 (6H, s), 0.81 (3H, J= 7.3 Hz), 0.82 (3H, d, J= 6.8 Hz), 0.88 (9H, s), 0.89 (9H, s), 0.93 (3H, d, J= 6.8 Hz), 1.12 (3H, s), 1.19 (3H, s), 1.28 (3H, s), 1.35 (3H, s), 2.18 (1H, dd, J= 7.1, 16.3 Hz), 2.37 (1H, d, J= 16.3 Hz), 2.69 (2H, m), 2.85 (1H, m), 3.00 (1H, m), 3.20 (3H, s), 3.42 (1H, dd, J= 1.7, 10.0 Hz), 3.62 (2H, m), 3.70 (1H, m), 3.88 (1H, dd, J= 6.8, 9.8 Hz), 4.01 (1H, t, J= 6.6 Hz), and 5.07 (2H, s). **6**: $[\alpha]_D^{26}$ -36.4° (c 0.99, $CHCl_3$); IR (film) 1740, 1705, 1605, 1595, and 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (3H, s), 0.04 (3H, s), 0.68 (3H, d, J= 6.8 Hz), 0.81 (3H, d, J= 6.8 Hz), 0.84 (3H, d, J= 6.4 Hz), 0.84 (9H, s), 1.108 (3H, s), 1.13 (3H, s), 1.21 (3H, s), 1.32 (3H, s), 1.78 (1H, m), 2.76 (1H, dd, J= 8.5, 16.4 Hz), 3.19 (3H, s), 3.41 (1H, dd, J= 2.0, 10.3 Hz), 3.66 (3H, s), and 5.07 (2H, s). **7**: $C_{34}H_{45}O_5$ [m/z 533.3258 (M^+-MeO-H_2O)]; $[\alpha]_D^{26}$ -3.89° (c 0.32, $CHCl_3$); IR (film) 3550, 1740, 1605, 1600, and 1585 cm^{-1}; ^1H NMR δ 0.77 (3H, d, J= 6.4 Hz), 0.81 (3H, d, J= 6.8 Hz), 0.82 (3H, s), 0.85 (3H, d, J= 6.8 Hz), 0.86 (3H, s), 2.58 (1H, dd, J= 2.7, 15.9 Hz), 3.21 (3H, s), 3.55 (3H, s), 4.00 (1H, dd, J= 5.9, 7.3 Hz), 5.066 (1H, d, J= 12.2 Hz), and 5.073 (1H, d, J= 12.2 Hz). **8**: $[\alpha]_D^{27}$ -25.4° (c 0.35, $CHCl_3$); IR (film) 3450, 1735, 1605, 1595 and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (3H, d, J= 6.8 Hz), 0.81 (3H, d, J= 6.4 Hz), 0.83 (3H, s), 0.84 (3H, d, J= 5.9 Hz), 0.87 (3H, s), 2.27 (1H, dd, J= 10.3, 14.2 Hz), 2.39 (1H, dd, J= 4.4, 12.7 Hz), 2.51 (1H, dd, J= 2.9, 14.2 Hz), 3.22 (3H, s), 3.53 (3H, s), 4.01 (1H, dd, J= 5.6, 7.6 Hz), 5.066 (1H, d, J= 12.2 Hz), and 5.073 (1H, d, J= 12.2 Hz). **9**: $C_{34}H_{45}O_5$ [m/z 533.3261 (M^+-MeO)]; IR (film) 1740, 1605, 1595, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (3H, s), 0.75 (3H, d, J= 6.4 Hz), 0.82 (3H, d, J= 6.8 Hz), 0.83 (3H, d, J=

6.8 Hz), 0.95 (3H, s), 1.87 (1H, m), 2.16 (1H, m), 2.30 (1H, dd, J= 9.3, 14.2 Hz), 2.47 (1H, dd, J= 3.4, 14.2 Hz), 3.22 (3H, s,), 3.48 (1H, m), 3.49 (3H, s), 3.56 (1H, dt, J= 3.4, 9.8 Hz), 4.03 (1H, t, J= 6.6 Hz), 5.065 (1H, d, J= 12.2 Hz), 5.073 (1H, d, J= 12.2 Hz), 5.73 (1H, dd, J= 2.0, 10.3 Hz), and 6.10 (1H, dd, J= 2.5, 10.3 Hz). **10**: $[\alpha]_D^{26}$ +19.3° (c 0.50, $CHCl_3$); IR (film) 3500, 3400 - 2500(br.), 1715, 1605, 1600, and 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (3H, d, J= 6.8 Hz), 0.81 (3H, s), 0.81 (3H, d, J= 6.4 Hz), 0.84 (3H, d, J= 6.8 Hz), 0.86 (3H, s), 2.34 (1H, dd, J= 2.9, 14.7 Hz), 2.41 (1H, dd, J= 7.3, 15.1 Hz), 2.64 (1H, dd, J= 3.9, 15.1 Hz), 3.21 (3H, s), 3.69 (1H, m), 4.05 (1H, t, J= 6.8 Hz), 5.07 (1H, d, J= 11.2 Hz), and 5.10 (1H, d, J= 11.2 Hz). **11**: $[\alpha]_D^{24}$ -18.9° (c 0.44, $CHCl_3$); IR (film) 3530, 1735, 1680, 1605, 1595, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (3H, d, J= 6.4 Hz), 0.81 (3H, d, J= 6.8 Hz), 0.82 (3H, s), 0.83 (3H, d, J= 7.3 Hz), 0.88 (3H, s), 1.01 (3H, d, J= 6.4 Hz), 1.42 (9H, s), 2.33 (1H, dd, J= 2.5,14.7 Hz), 2.37 (1H, dd, J= 9.3, 17.1 Hz), 2.57 (1H, dd, J= 2.0, 17.1 Hz), 2.74 (1H, dd, J= 8.1, 15.5 Hz), 2.83 (1H, dd, J= 4.9, 15.5 Hz), 3.19 (3H, s), 3.65 (1H, dd, J= 2.2, 11.0 Hz), 3.99 (1H, dd, J= 5.9, 7.3 Hz), 4.49 (1H, d, J= 11.7 Hz), 4.58 (1H, d, J= 11.7 Hz), 5.04 (1H, d, J= 11.5 Hz), 5.05 (1H, d, J= 11.5 Hz), and 5.41 (1H, m). **12**: $C_{45}H_{56}O_8$ [m/z 724.3955 (M^+-MeOH)]; $[\alpha]_D^{26}$ +6.53° (c 0.10, $CHCl_3$); IR (film) 1735(br.), 1600, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (3H, d, J= 6.8 Hz), 0.73 (3H, d, J= 6.3 Hz), 0.78 (3H, d, J= 6.8 Hz), 0.79 (3H, s), 0.85 (3H, s), 1.13 (3H, d, J= 6.4 Hz), 1.89 (1H, m), 2.14 (1H, dd, J= 11.2, 12.2 Hz), 2.37 (1H, dd, J= 2.0, 15.6 Hz), 2.57 (1H, dd, J= 2.4, 12.2 Hz), 2.69 (1H, dd, J= 3.2, 17.3 Hz), 2.82 (1H, dd, J= 12.0, 17.3 Hz), 3.24 (3H, s), 3.32 (1H, dt, J= 2.5, 10.8 Hz), 3.84 (1H, dq, J= 3.9, 6.4 Hz), 3.90 (1H, dd, J= 2.0, 10.7 Hz), 4.07 (1H, t, J= 6.3 Hz), 4.50 (1H, d, J= 11.7 Hz), 4.62 (1H, d, J= 11.7 Hz), 5.03 (1H, m), 5.05 (1H, d, J= 11.7 Hz), 5.07 (1H, d, J= 11.7 Hz), 5.22 (1H, dt, J= 12.0, 3.7 Hz), 6.86 (1H, dd, J= 2.5, 7.8 Hz), 6.96 (1H, d, J= 7.3 Hz), and 7.05 (1H, br.s).

10. On using $^nBu_4NF$, **6** was converted to a hemiketal (**14**), and acid hydrolysis of which yielded also a mixture of **7**, **8**, and **9**. On the other hand, PDC oxidation of **14** gave a rather unstable β-keto ester (**15**) in 30% yield.



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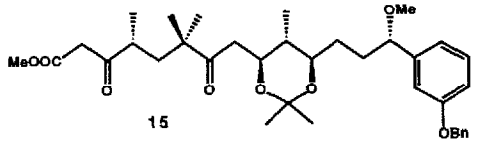

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11. When a carboxylic acid derivative instead of **11**, was treated with DCC - DMAP, β-elimination was observed, and any lactone was not detected.
12. The reaction condition has not been optimized.
13. **1**: $C_{32}H_{48}O_9$ [m/z 576.3319 (M^+)]; $[\alpha]_D^{25}$ +9.27° (c 0.10, $CHCl_3$); IR (film) 1720 and 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (3H, d, J= 6.8 Hz), 0.73 (3H, d, J= 6.8 Hz), 0.80 (3H, d, J= 6.4 Hz), 0.81 (3H, s), 0.90 (3H, s), 1.20 (3H, d, J= 6.4 Hz), 1.85 (1H, m), 2.29 (1H, dd, J= 11.2, 12.7 Hz), 2.42 (1H, dd, J= 2.4, 15.6 Hz), 3.24 (3H, s), 3.39 (1H, dt, J= 2.9, 10.7 Hz), 3.75 (1H, dd, J= 2.0, 11.2 Hz), 4.04 (1H, m), 4.06 (1H, t, J= 6.8 Hz), 4.99 (1H, m), 5.07 (1H, dt, J= 10.3, 4.4 Hz), 6.75 (1H, dd, J= 2.2, 7.8 Hz), 6.90 (1H, d, J= 7.8 Hz), 6.95 (1H, br.s), and 7.20 (1H, t, J= 7.8 Hz).

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