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Absolute Stereochemistry and Synthesis of Aplyronines B and C, the Congeners of Aplyronine A, a Potent Antitumor Substance of Marine Origin

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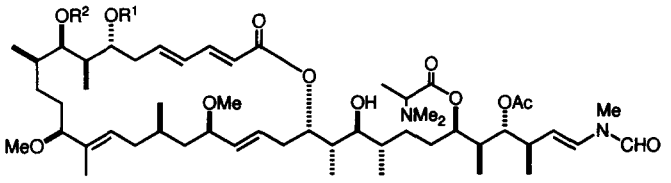
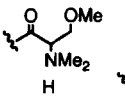
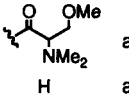
Abstract: Synthesis of aplyronines B and C, the congeners of aplyronine A, was achieved enantioselectively, which established their stereostructures.

We have elucidated the structure of aplyronine A (**1**), a potent antitumor substance isolated from the sea hare *Aplysia kurodai*[1] and have recently synthesized **1** to confirm the stereostructure.[2] Aplyronines B and C have also been isolated as minute constituents of *A. kurodai* along with **1**.[1a] The gross structures of aplyronines B and C were deduced by comparison of their spectral data (FABMS, ^{1}H and ^{13}C NMR) with those of aplyronine A (**1**) as depicted in formulas **2** and **3**, respectively.[1a] However, the scarcity of the samples of aplyronines B (**2**) and C (**3**) from natural sources has prevented us from determining their stereostructures by chemical means employed for aplyronine A (**1**). Comparison of cytotoxicities among aplyronines reveals that the *N,N,O*-trimethylserine group in **1** seems to play an important role to exhibit remarkable cytotoxicity.[1a] We describe herein the synthesis of aplyronines B and C that determines their stereostructures unambiguously.

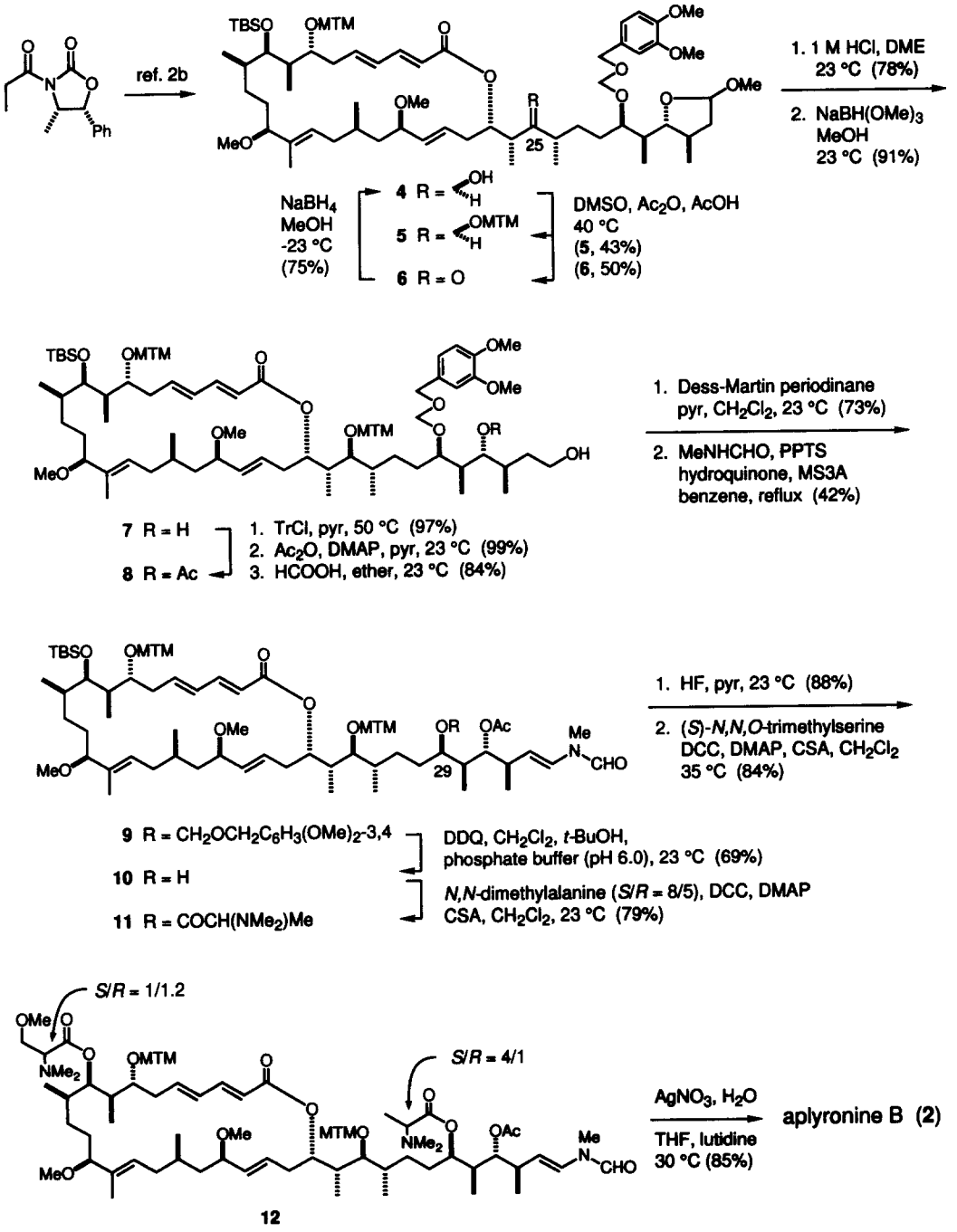
The assumption was made that the stereochemistry of the main chain in aplyronines B and C was identical with that of aplyronine A on the basis of the fact that these three compounds were isolated from the same animals. We planned to synthesize aplyronines B and C by using the intermediates for the synthesis of aplyronine A.



	R^1	R^2	
		H	aplyronine A (**1**)
H			aplyronine B (**2**)
H	H		aplyronine C (**3**)

Synthesis of aplyronine B (**2**) started with an intermediate **4**[2b] for the synthesis of aplyronine A (**1**) (Scheme 1). The hydroxyl group at C25 in **4** was protected to give methylthiomethyl (MTM) ether **5**[3,4] along with ketone **6**.[5] The acidic hydrolysis of **5** afforded a hemiacetal, which was reduced to afford diol **7**. Diol **7** was converted into alcohol **8** as follows: (1) tritylation of the primary hydroxyl group of **7**; (2) acetylation of the secondary hydroxyl group; (3) removal of the trityl group. Oxidation of **8** and subsequent condensation with *N*-methylformamide provided enamide **9**. Deprotection of 3,4-dimethoxybenzyloxy-

Scheme 1.

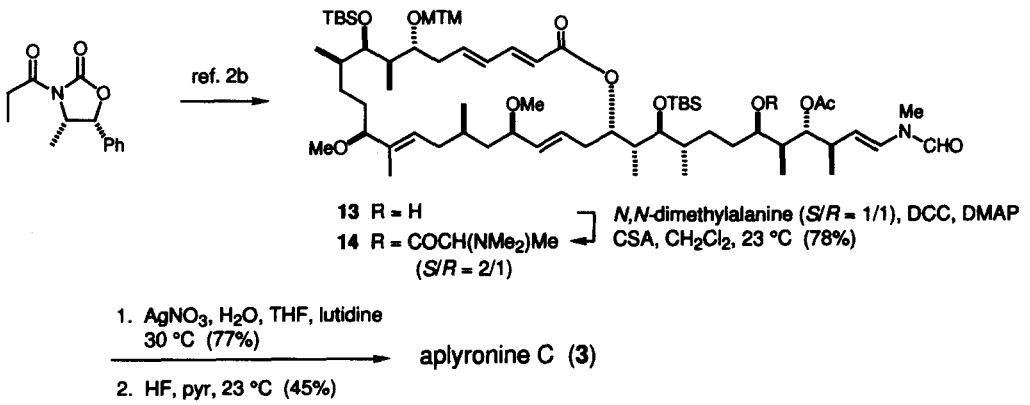

ref. 2b
1. 1 M HCl, DME
23 °C (78%)
2. NaBH(OMe)3
MeOH
23 °C (91%)
NaBH4
MeOH
-23 °C
(75%)
4 R = OH, H
5 R = OMTM, H
6 R = O
DMSO, Ac2O, AcOH
40 °C
(5, 43%)
(6, 50%)
1. Dess-Martin periodinane
pyr, CH2Cl2, 23 °C (73%)
2. MeNHCHO, PPTS
hydroquinone, MS3A
benzene, reflux (42%)
7 R = H
8 R = Ac
1. TrCl, pyr, 50 °C (97%)
2. Ac2O, DMAP, pyr, 23 °C (99%)
3. HCOOH, ether, 23 °C (84%)
1. HF, pyr, 23 °C (88%)
2. (S)-N,N,O-trimethylserine
DCC, DMAP, CSA, CH2Cl2
35 °C (84%)
9 R = CH2OCH2C6H3(OMe)2-3,4
10 R = H
11 R = COCH(NMe2)Me
DDQ, CH2Cl2, t-BuOH,
phosphate buffer (pH 6.0), 23 °C (69%)
N,N-dimethylalanine (S/R = 8/5), DCC, DMAP
CSA, CH2Cl2, 23 °C (79%)
S/R = 1/1.2
S/R = 4/1
AgNO3, H2O
THF, lutidine
30 °C (85%)
aplyronine B (2)
12

methyl group at C29 of **9** gave alcohol **10**, which was esterified with *N,N*-dimethylalanine (*S*/*R* = 8/5) under the Keck conditions to afford *N,N*-dimethylalanine ester **11** (*S*/*R* = 4/1).[6,7] Desilylation of **11** followed by esterification with (*S*)-*N,N,O*-trimethylserine gave *N,N,O*-trimethylserine ester **12** (*S*/*R* = 1/1.2).[7] Finally, hydrolysis of the MTM groups in **12** furnished aplyronine B (**2**). Synthetic aplyronine B was found to correspond uniquely to natural aplyronine B by comparison of the spectroscopic[8] (UV, IR, ^{1}H NMR, FABMS, and CD) and chromatographic properties.

Aplyronine C (**3**) was easily prepared from an intermediate **13**[2b] for the synthesis of aplyronine A (**1**) (Scheme 2). The secondary hydroxyl group of **13** was esterified with *N,N*-dimethylalanine (*S*/*R* = 1/1) under the Keck conditions to afford *N,N*-dimethylalanine ester **14** (*S*/*R* = 2/1).[6,9] The MTM and the silyl groups in **14** were removed in two steps to give aplyronine C (**3**). The spectral data including the CD spectrum of synthetic aplyronine C were identical with those of natural **3**.[10]

Thus, we have elucidated the stereostructures of aplyronines B and C as depicted in formulas **2** and **3**, respectively.

Scheme 2.



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2. (a) Kigoshi, H.; Ojika, M.; Suenaga, K.; Mutou, T.; Hirano, J.; Sakakura, A.; Ogawa, T.; Nisiwaki, M.; Yamada, K. *Tetrahedron Lett.* **1994**, *35*, 1247–1250. (b) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443–7444.
3. Satisfactory spectral (IR, ^{1}H NMR, and mass spectra) and high-resolution mass spectral data were obtained for all new compounds.

4. The 2,2,2-trichloroethoxycarbonyl group was first chosen as a protecting group of the C25 hydroxyl, which was found to be labile under the conditions of $NaBH_4$ or $NaBH(OMe)_3$ reduction.
5. Ketone **6** could be converted into alcohol **4** (75%) by reduction with $NaBH_4$ in MeOH together with the 25-epimer (9%).
6. The ratio (*S*/*R*) of the *N*,*N*-dimethylalanine moiety in **11** or **14** differs from that (*S*/*R*) of *N*,*N*-dimethylalanine employed for esterification, because there is the interconversion between *R* and *S* enantiomers of *N*,*N*-dimethylalanine through their activated forms and further the rate of esterification of alcohol **10** or **13** with (*S*)-*N*,*N*-dimethylalanine is different from that with (*R*)-*N*,*N*-dimethylalanine (cf. ref 2b)
7. The diastereomeric ratios of the amino acid moieties in aplyronine B varied with the animal samples employed. The diastereomeric ratios of the *N*,*N*-dimethylalanine moiety and of the *N*,*N*,*O*-trimethylserine moiety in natural aplyronine B employed for comparison purpose were *S*/*R* = 4/1 and *S*/*R* = 1/1, respectively.
8. A colorless amorphous powder. $[\alpha]^{24}_D$ –5.1 (*c* 0.051, MeOH); UV (MeOH) 258 nm (ε 29000); IR ($CHCl_3$) 3470 (br), 1725, 1695, 1655, 1240, 1090, 975 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.37[a] [8.11] (s, 1 H), 7.27 (dd, *J* = 15.4, 10.3 Hz, 1 H), 6.85[a] [7.16] (d, *J* = 14.3 Hz, 1 H), 6.51–6.43 (m, 2 H), 5.94 (d, *J* = 15.4 Hz, 1 H), 5.62 (ddd, *J* = 15.0, 10.6, 4.0 Hz, 1 H), 5.49 (br d, *J* = 11.0 Hz, 1 H), 5.25 (m, 1 H), 5.05[a] [5.10] (dd, *J* = 14.3, 9.5 Hz, 1 H), 5.03 (m, 1 H), 4.98 (dd, *J* = 15.0, 9.9 Hz, 1 H), 4.93 (dd, *J* = 9.2, 1.8 Hz, 1 H), 4.80[a] [4.80] (dd, *J* = 10.3, 2.6 Hz, 1 H), 3.79 (dd, *J* = 8.4, 4.8 Hz, 1 H), 3.68 (dd, *J* = 9.2, 7.3 Hz, 1 H), 3.67 (br s, 1 H), 3.62–3.57 (m, 2 H), 3.53–3.46 (m, 2 H), 3.41[c] [3.40] (dd, *J* = 6.6, 6.6 Hz, 1 H), 3.29[c] [3.28] (s, 3 H), 3.18 (m, 1 H), 3.12 (s, 3 H), 3.11 (s, 3 H), 3.06 (m, 1 H), 2.97[a] [3.09] (s, 3 H), 2.65 (m, 1 H), 2.45 (m, 1 H), 2.36[c] [2.37] (s, 6 H), 2.35–2.23 (m, 2 H), 2.33[b] [2.31] (s, 6 H), 2.15 (m, 1 H), 2.09–1.91 (m, 3 H), 1.87–1.78 (m, 2 H), 1.73 (m, 1 H), 1.67–1.48 (m, 6 H), 1.45–1.08 (m, 6 H), 1.44 (s, 3 H), 1.26[b] [1.20] (d, *J* = 7.3 Hz, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.90[c] [0.91] (d, *J* = 7.0 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.88[c] [0.94] (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H). Three protons were overlapped with the solvent signals. The minor counterparts of doubled signals in the ratios of 2:1 (superscript a), 4:1 (superscript b), and 1.2:1 (superscript c), respectively, are in brackets; HRFABMS *m*/*z* calcd for $C_{59}H_{102}N_3O_{14}$ $(M + H)^+$ 1076.7362, found 1076.7370.
   Because of the difference in the diastereomeric ratio concerning trimethylserine moiety between natural and synthetic aplyronine B, there were slight differences in the intensity of signals as to the *N*,*N*,*O*-trimethylserine moiety in the ^1H NMR spectra, and the specific rotation of synthetic aplyronine B ($[\alpha]^{24}_D$ –5.1) is different from that of natural one ($[\alpha]^{24}_D$ +3.7). We have elucidated that the absolute configuration of the main chain of natural aplyronine B was identical with that of synthetic one as depicted in **2** by comparison of their CD spectra: both natural and synthetic aplyronine B showed negative Cotton effect at 265 nm, respectively; natural **2** λ_{ext} (MeOH) 265 nm (Δε –3.3); synthetic **2** λ_{ext} (MeOH) 265 nm (Δε –3.7).
9. The diastereomeric ratio of the dimethylalanine moiety in natural aplyronine C employed for comparison purpose was *S*/*R* = 2/1.
10. A colorless amorphous powder. $[\alpha]^{27}_D$ +19 (*c* 0.042, MeOH); UV (MeOH) 259 nm (ε 33000); IR ($CHCl_3$) 3620, 3480 (br), 1730, 1690, 1655, 1240, 1090, 1080, 970 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.37 [8.10] (s, 1 H), 7.26 (dd, *J* = 15.4, 10.3 Hz, 1 H), 6.85 [7.15] (d, *J* = 13.9 Hz, 1 H), 6.42 (ddd, *J* = 15.4, 9.2, 5.1 Hz, 1 H), 6.37 (dd, *J* = 15.4, 10.3 Hz, 1 H), 5.93 (d, *J* = 15.4 Hz, 1 H), 5.62 (ddd, *J* = 15.0, 10.6, 4.4 Hz, 1 H), 5.47 (br d, *J* = 11.4 Hz, 1 H), 5.22 (br dd, *J* = 10.6, 4.8 Hz, 1 H), 5.05 [5.10] (dd, *J* = 14.3, 9.5 Hz, 1 H), 5.03–4.97 (m, 2 H), 4.80 (br d, *J* = 9.9 Hz, 1 H), 3.80 (br d, *J* = 4.0 Hz, 1 H), 3.66 (m, 1 H), 3.60 (br d, *J* = 5.1 Hz, 1 H), 3.50–3.46 (m, 2 H), 3.40 (m, 1 H), 3.37 (br d, *J* = 5.1 Hz, 1 H), 3.18 (m, 1 H), 3.12 (s, 3 H), 3.11 (s, 3 H), 3.05 (m, 1 H), 2.97 [3.09] (s, 3 H), 2.70–2.63 (m, 1 H), 2.44 (m, 1 H), 2.33 [2.31] (s, 6 H), 2.33–2.24 (m, 2 H), 2.14 (m, 1 H), 2.09–1.91 (m, 2 H), 2.03 [2.02] (s, 3 H), 1.79 (m, 1 H), 1.73–1.70 (m, 2 H), 1.67–1.63 (m, 3 H), 1.60–1.56 (m, 2 H), 1.54–1.52 (m, 2 H), 1.43 (s, 3 H), 1.37 (m, 1 H), 1.31–1.13 (m, 5 H), 1.25 [1.20] (d, *J* = 7.0 Hz, 3 H), 1.01–0.97 (m, 15 H), 0.89 (m, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H). The minor counterparts of doubled signals in the ratio of 2:1 are in brackets; HRFABMS *m*/*z* calcd for $C_{53}H_{91}N_2O_{12}$ $(M + H)^+$ 947.6572, found 947.6600.
    CD (MeOH) natural **3** λ_{ext} 273 nm (Δε –1.0); synthetic **3** λ_{ext} 277 nm (Δε –0.90).

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