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Synthetic Studies on Aplyronine A, a Potent Antitumor Substance of Marine Origin: Stereocontrolled Synthesis of the C21–C34 Segment

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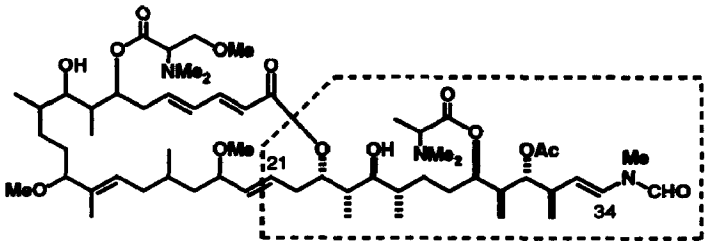
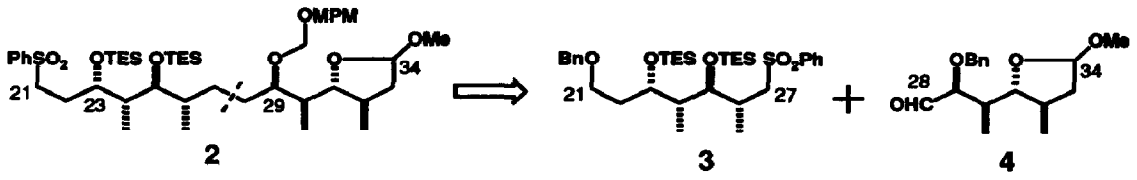
Abstract: The C21–C34 segment **2** of aplyronine A (**1**), a potent antitumor substance of marine origin, was synthesized enantioselectively in 25 steps (17% overall yield) from imide **11**.

Recently, we have isolated aplyronine A (**1**) as a minute constituent from the sea hare *Aplysia kurodai* and have elucidated the gross structure of **1** by means of the spectral analysis and the degradation experiments.[1] Further, we have determined the absolute stereochemistry of the eight chiral centers, C23–C26 and C29–C32, by the enantioselective synthetic method.[2,3] Aplyronine A (**1**) exhibits extraordinary *in vitro* and *in vivo* antitumor activity.[1] However, the scarcity of the sample of **1** from natural sources has prevented further evaluation of this compound as a potential therapeutic agent thus far. This fact and the novel polyfunctional 24-membered lactone structure prompted us to initiate the investigation toward efficient synthesis of aplyronine A (**1**). As a part of our synthetic studies toward aplyronine A (**1**), we describe herein the stereocontrolled synthesis of the C21–C34 segment **2**.



1 aplyronine A

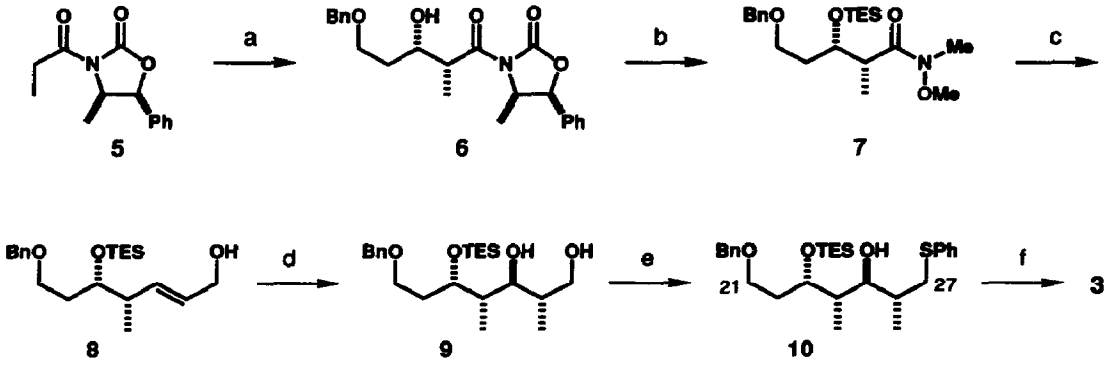


2 **3** **4**

The C21–C34 segment **2** of aplyronine A (**1**) has two sets of four contiguous chiral centers C23–C26 and C29–C32, and the stereochemistry of both sets is *syn-anti-anti*. Therefore, construction of the C21–C34 segment **2** has been carried out by the convergent synthetic methodology connecting the two segments, the C21–C27 and C28–C34 segments, **3** and **4**. Introduction of the chiral centers to **3** and **4** could be effected using the identical synthetic strategy.

Synthesis of the C21–C27 segment 3. The synthesis of **3** began with the Evans aldol reaction between imide **5** and 3-benzyloxypropanal to give hydroxy imide **6** (Scheme 1). Removal of the chiral auxiliary and subsequent protection of the hydroxy group afforded amide **7**, which was converted into allyl alcohol **8** by a three-step sequence (1. DIBAL; 2. Horner-Emmons reaction; 3. DIBAL). The Sharpless epoxidation of **8** followed by reaction with Me_2CuLi provided diol **9**,[4] which had the *syn-anti-anti* stereochemistry concerning four contiguous chiral centers. The reaction of diol **9** with PhSSPh–*n*-Bu_3P gave sulfide **10**. After protection of the secondary hydroxy group in **10**, the sulfide group was oxidized to produce the C21–C27 segment **3**[5] (55% from imide **5**).

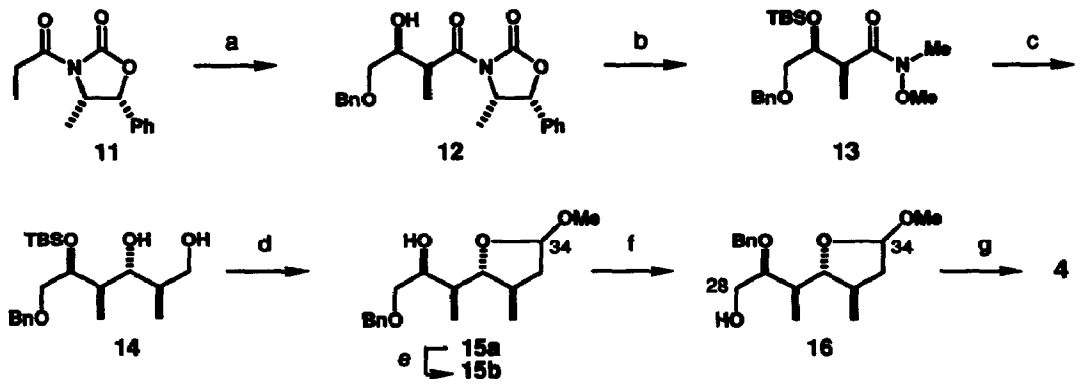
Scheme 1.



Reagents and Reaction Conditions
(a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C; $BnOCH_2CH_2CHO$, -78 → 0 °C (85%).
(b) 1. $Me_2AlN(Me)OMe$, THF, -10 → 0 °C; 2. TES-Cl, imidazole, DMF, 23 °C (99%).
(c) 1. DIBAL, THF, -78 °C; 2. $(i\text{-}PrO)_2P(O)CH_2COOEt$, *t*-BuOK, THF, -78 → 0 °C; 3. DIBAL, hexane, CH_2Cl_2, -78 °C (94%).
(d) 1. $Ti(OPr\text{-}i)_4$, (-)-diethyl tartrate, *t*-BuOOH, CH_2Cl_2, -23 °C; 2. Me_2CuLi, ether, -23 °C (71%).
(e) PhSSPh, *n*-Bu_3P, THF, 23 °C (98%)
(f) 1. TES-Cl, imidazole, DMF, 23 °C; 2. MCPBA, $NaHCO_3$, CH_2Cl_2, 23 °C (100%).

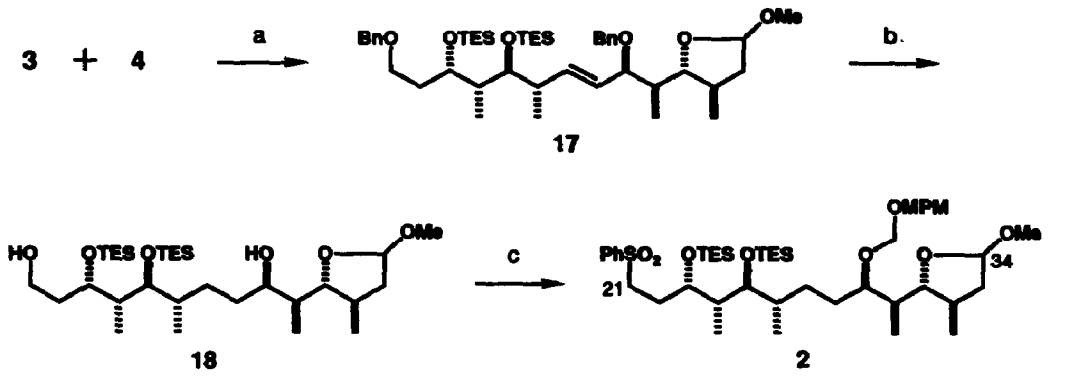
Synthesis of the C28–C34 segment 4. The synthesis of **4** was effected using the same synthetic strategy as that of **3**. The Evans aldol reaction of imide **11** with benzyloxyacetaldehyde gave hydroxy imide **12**, which was converted into amide **13** (Scheme 2). The amide **13** was transformed into diol **14**[4] by the same sequence of reactions as described for the preparation of diol **9** from amide **7**. The primary hydroxyl group in **14** was transformed into the cyano group and the reduction of the cyano group gave the cyclic hemiacetal compound, acid treatment of which in MeOH afforded a separable 4:5 mixture of diastereomeric acetals **15a** and **15b**.[6] The minor acetal **15a** was subjected to equilibration (camphorsulfonic acid, MeOH, 23 °C) to afford a 4:5 mixture of **15a** and **15b**, from which the major acetal **15b** was obtained. By repeating this procedure, **15a** could be transformed into **15b**. Manipulation of the benzyl protecting group in **15b** afforded alcohol **16**, the Swern oxidation of which provided the C28–C34 segment **4**[7] (25% from imide **11**).

Scheme 2.



Reagents and Reaction Conditions
(a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C; $BnOCH_2CHO$, -78 → 0°C (79%).
(b) 1. $Me_2AlN(Me)OMe$, THF, 0 °C; 2.TBS-Cl, imidazole, DMF, 23 °C (99%).
(c) 1. DIBAL, THF, -78 °C; 2. $(i\text{-}PrO)_2P(O)CH_2COOEt$, *t*-BuOK, THF, -78 → 0 °C; 3. DIBAL, hexane, CH_2Cl_2, -78 °C; 4. $Ti(OPr\text{-}i)_4$, (+)-diethyl tartrate, *t*-BuOOH, CH_2Cl_2, -23 °C; 5.Me_2CuLi, ether, 0 °C (73%).
(d) 1. TsCl, pyr, 0 °C; 2. NaCN, DMSO, 50 °C; 3. DIBAL, CH_2Cl_2, -78 °C; 4. camphorsulfonic acid, MeOH, reflux.
(e) camphorsulfonic acid, MeOH, 23 °C (63% from 14).
(f) 1. Na, liq. NH_3, THF, -78 °C; 2. TBDPS-Cl, imidazole, DMF, 0 °C; 3. BnBr, NaH, DMF, 23 °C; 4. *n*-Bu_4NF, THF, 23 °C (71%).
(g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 → 0 °C (97%).

Scheme 3.

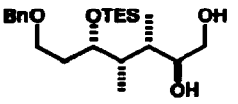


Reagents and Reaction Conditions
(a) 1. *n*-BuLi, THF, -78 °C; 2. 6% Na/Hg, Na_2HPO_4, MeOH, 0 °C (84%).
(b) 1. Ca, liq. NH_3, THF, *i*-PrOH, -78 °C; 2. H_2, 5% Rh/Al_2O_3, EtOH, 23 °C (87%).
(c) 1. PhSSPh, *n*-Bu_3P, DMF, 23 °C; 2.MCPBA, $NaHCO_3$, CH_2Cl_2, 23 °C; 3. *p*-$MeOC_6H_4CH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 23 °C (91%).

Synthesis of the C21–C34 segment 2. The Julia coupling reaction of the carbanion of the C21–C27 segment **3** with the C28–C34 segment **4** was achieved[8] to give a hydroxy sulfone, which was converted into olefin **17** by reduction (Scheme 3). Two benzyl protecting groups in **17** were reductively removed and subsequent hydrogenation provided diol **18**.[9] The primary hydroxyl group of diol **18** was converted into a

phenylsulfonyl group by two steps, and the secondary hydroxyl group was protected as a *p*-methoxybenzyloxymethyl ether group[10] to afford the C21–C34 segment **2**.[11]

We have efficiently synthesized the C21–C34 segment **2** of aplyronine A (**1**), and further investigation toward the total synthesis of aplyronine A (**1**) is in progress.



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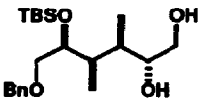

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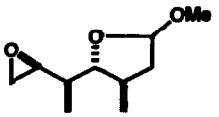

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1. Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* in press.
2. Ojika, M.; Kigoshi, H.; Ishigaki, T.; Yamada, K. *Tetrahedron Lett.*, in press.
3. Ojika, M.; Kigoshi, H.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Mizuta, K.; Yamada, K. *Tetrahedron Lett.*, in press.
4. In the reactions of the epoxy alcohols with Me_2CuLi, 1,2-diols were also obtained: **19**, 24%; **20**, 7%.
5. **3**: oil; $[\alpha]^{21}_D$ +4.56° (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 1580, 1300, 1140 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2 H), 7.67–7.50 (m, 3 H), 7.40–7.23 (m, 5 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.43 (d, *J* = 12.2 Hz, 1 H), 3.91 (dt, *J* = 3.6, 6.6 Hz, 1 H), 3.55 (dd, *J* = 6.9, 1.6 Hz, 1 H), 3.40 (t, *J* = 6.6 Hz, 2 H), 3.27 (dd, *J* = 14.5, 1.3 Hz, 1 H), 2.85 (dd, *J* = 14.5, 10.2 Hz, 1 H), 2.23 (m, 1 H), 1.79 (dt, *J* = 6.6, 6.6 Hz, 2 H), 1.42 (ddq, *J* = 6.9, 3.6, 6.9 Hz, 1 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 0.92 (t, *J* = 7.6 Hz, 9 H), 0.90 (t, *J* = 7.6 Hz, 9 H), 0.60 (q, *J* = 7.6 Hz, 6 H), 0.57 (d, *J* = 6.9 Hz, 3 H), 0.57 (q, *J* = 7.6 Hz, 6 H); EIMS *m/z* 634 (M^+), 605, 257, 185, 91.
6. The stereochemistry at C34 of acetals **15a** and **15b** was not determined. The diastereomeric acetals **15a** and **15b** were easily separated by silica gel column chromatography (hexane-ether).
7. **4**: oil; $[\alpha]^{19}_D$ +26.3° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 2700, 1725, 1455, 1095, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.0 Hz, 1 H), 7.42–7.26 (m, 5 H), 4.92 (d, *J* = 4.9 Hz, 1 H), 4.73 (d, *J* = 11.2 Hz, 1 H), 4.61 (d, *J* = 11.2 Hz, 1 H), 4.23 (dd, *J* = 2.9, 1.0 Hz, 1 H), 3.60 (dd, *J* = 9.8, 6.3 Hz, 1 H), 3.31 (s, 3 H), 2.28 (dddq, *J* = 9.8, 9.8, 7.3, 6.3 Hz, 1 H), 2.12 (dd, *J* = 12.7, 7.3 Hz, 1 H), 2.10 (ddq, *J* = 6.3, 2.9, 7.3 Hz, 1 H), 1.66 (ddd, *J* = 12.7, 9.8, 4.9 Hz, 1 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 0.92 (d, *J* = 7.3 Hz, 3 H); CIMS (CH_4) *m/z* 261 $(M - OMe)^+$, 243, 153, 91.
8. The Julia coupling reaction employing sulfone **3** and epoxide **21** did not occur virtually.
9. Although attempts were made to convert olefin **17** into diol **18** in one step by catalytic hydrogenation (H_2, Pd/C), the yield of **18** was poor because of low reactivity of the benzyl groups in **17** toward hydrogenolysis.
10. Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125–5128.
11. **2**: oil; $[\alpha]^{24}_D$ +16.1° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 1610, 1515, 1310, 1150, 1030 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.92–7.86 (m, 2 H), 7.69–7.52 (m, 3 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.89 (d, *J* = 4.6 Hz, 1 H), 4.82 (d, *J* = 6.9 Hz, 1 H), 4.79 (d, *J* = 6.9 Hz, 1 H), 4.57 (s, 2 H), 4.01 (ddd, *J* = 6.6, 6.6, 1.6 Hz, 1 H), 3.80 (s, 3 H), 3.79 (m, 1 H), 3.57 (dd, *J* = 9.9, 6.6 Hz, 1 H), 3.41 (dd, *J* = 6.9, 2.6 Hz, 1 H), 3.25 (s, 3 H), 3.16–2.94 (m, 2 H), 2.23 (m, 1 H), 2.08 (dd, *J* = 12.5, 7.6 Hz, 1 H), 1.94–1.77 (m, 2 H), 1.70–1.24 (m, 8 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 0.95–0.84 (m, 24 H), 0.75 (d, *J* = 6.9 Hz, 3 H), 0.60–0.46 (m, 12 H); FABMS *m/z* 887 $(M + Na)^+$.

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