Total Synthesis of Aplyronine A, a Potent Antitumor Substance of Marine Origin

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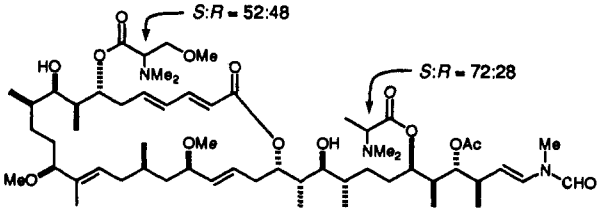
Recently, we elucidated the gross structure of aplyronine A (**1**) isolated as a minute constituent of the Japanese sea hare *Aplysia kurodai*.[1a] Further, the absolute stereochemistry of **1** has been fully determined.[1b-d] Although aplyronine A (**1**) exhibits



aplyronine A (1)

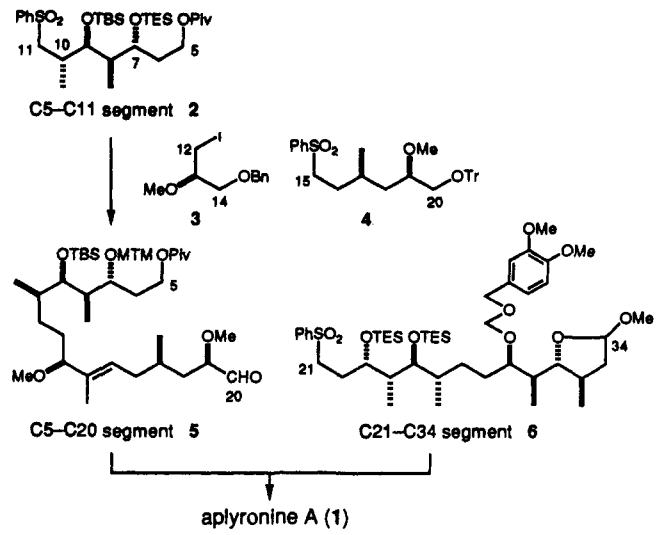
exceedingly potent antitumor activities,[1a] the scarcity of **1** from natural sources has prevented further evaluation of this compound as a potential therapeutic agent thus far. This fact and the novel polyfunctional 24-membered lactone structure prompted us to initiate the investigation toward the synthesis of **1**. Recently, the synthesis of the C21–C34 segment[2] of **1** has been reported.[3] We describe herein the total synthesis of **1**.

Scheme 1 outlines the synthesis of aplyronine A (**1**), which includes the following key operations: (1) the four contiguous asymmetric centers C7–C10 of the C5–C11 segment **2** were constructed by the Evans aldol reaction[4] and the Sharpless epoxidation;[5] (2) the C5–C20 segment **5** was synthesized by connecting the three segments **2**, **3**, and **4** in order; and (3) a Julia olefination reaction[6] between the C5–C20 segment **5** and the C21–C34 segment **6**.[3]

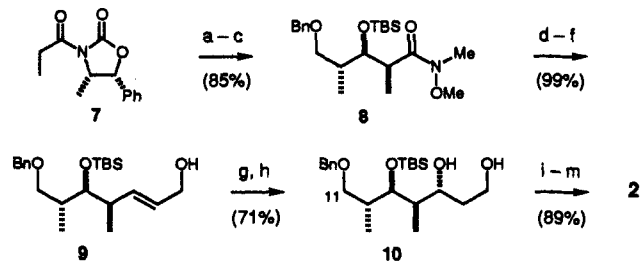
The synthesis of the C5–C11 segment **2** began with the Evans aldol reaction between imide **7**[4] and (*R*)-3-(benzyloxy)-2-methylpropanal[7] (Scheme 2), which led to amide **8**[8] by two steps. Conversion of **8** into allyl alcohol **9** was effected by a three-step sequence including the Horner–Emmons reaction. The Sharpless epoxidation[5] of **9** followed by regioselective reduction with Red-Al[9] provided diol **10**, which was transformed into **2** (53% overall yield from imide **7**) by a five-step sequence.

The alkylation reaction[10] of **2** with iodide **3**[11] and subsequent reductive removal of the sulfonyl group afforded benzyl ether **11**,

Scheme 1



Scheme 2[a]



[a] (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then (*R*)-3-(benzyloxy)-2-methylpropanal, −78 → 0 °C. (b) $Me_2AlN(Me)OMe$, THF, toluene, −10 → 0 °C. (c) *t*-$BuMe_2SiOTf$ (TBSOTf), 2,6-lutidine, CH_2Cl_2, 0 °C. (d) DIBAL, THF, hexane, -78 °C. (e) $(i\text{-}PrO)_2P(O)CH_2COOEt$, *t*-BuOK, THF, −78 → 0 °C. (f) DIBAL, hexane, CH_2Cl_2, −78 °C. (g) $Ti(OPr\text{-}i)_4$, (+)-diethyl tartrate, *t*-BuOOH, molecular sieves 4 Å, CH_2Cl_2, −23 °C. (h) Red-Al, DME, 0 °C. (i) Pivaloyl chloride (PivCl), pyridine, 0 °C. (j) H_2, 10% Pd–C, EtOH. (k) $(PhS)_2$, Bu_3P, DMF. (l) Et_3SiCl (TESCl), imidazole, DMF. (m) *m*-CPBA, $NaHCO_3$, CH_2Cl_2.

which was converted into methyl ketone **12** in four steps (Scheme 3). The Julia coupling[6] between **12** and the C15–C20 segment **4**[13] provided *trans*-olefin **13**,[15] which was transformed into the C5–C20 segment **5** (17% overall yield from **2**) in four steps.

The Julia coupling between the C5–C20 segment **5** and the C21–C34 segment **6**[16] gave an olefin[18] (Scheme 4), which was converted into *seco*-acid **14**[19] by a five-step sequence involving the Horner–Emmons reaction.[20] The macrolactonization of **14**

(1) (a) Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020–11021. (b) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8501–8504. (c) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Mizuta, K.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8505–8508. (d) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Tsukada, I.; Tsuboi, T.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) The numbering used in this paper corresponds to that of **1**.

(3) Kigoshi, H.; Ojika, M.; Suenaga, K.; Mutou, T.; Hirano, J.; Sakakura, A.; Ogawa, T.; Nisiwaki, M.; Yamada, K. *Tetrahedron Lett.* **1994**, *35*, 1247–1250.

(4) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(5) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(6) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836.

(7) Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015–5024.

(8) Satisfactory spectroscopic data (IR, ^1H NMR, MS, and HRMS) were obtained for all new compounds.

(9) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719–2722. Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292–1293.

(10) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1007–1010.

(11) The iodide **3** was prepared in 81% overall yield from commercially available (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol in seven steps [(1) BnBr, NaH; (2) HCl, aqueous acetone; (3) TBSCl, DMAP, Et_3N; (4) MeI, NaH; (5) Bu_4NF; (6) TsCl, pyridine; (7) NaI].

(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(13) The C15–C20 segment **4** was prepared in 31% overall yield from commercially available (*R*)-(−)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone [(1) TrCl, pyridine; (2) MeI, LDA;[14] (3) $LiAlH_4$; (4) TBDPSCl, imidazole; (5) MeI, NaH; (6) Bu_4NF; (7) TsCl, pyridine; (8) $PhSO_2Me$, BuLi].

(14) Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094–4098.

(15) The *cis*-olefin (20%) and the C14-tertiary alcohol (23%) were obtained along with *trans*-olefin **13** (44%).

(16) The C21–C34 segment **6** was synthesized by protection of the C29 hydroxyl group of the corresponding alcohol[3] as its (3,4-dimethoxyphenyl)-methoxymethyl ether ((3,4-dimethoxyphenyl)methoxymethyl chloride,[17] *i*-Pr_2-NEt, CH_2Cl_2, 98%).

(17) Gündel, W.-H.; Kramer, W. *Chem. Ber.* **1978**, *111*, 2594–2604. Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125–5128.

(18) The *trans*/*cis* ratio of the olefin was ca. 10:1. The minor isomer could be separated by HPLC after macrolactonization.

(19) The *trans*/*cis* ratio at the C4 double bond was ca. 20:1. The minor isomer could be separated by HPLC after macrolactonization.

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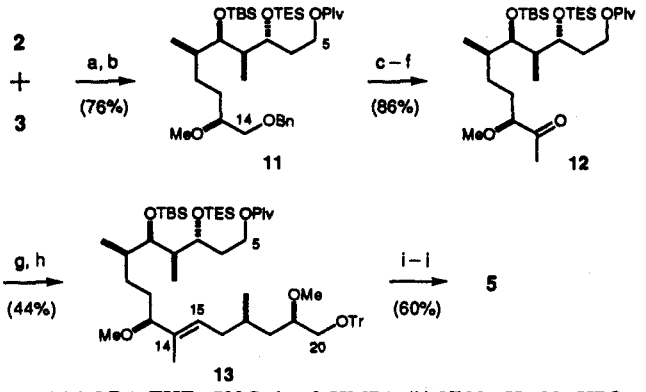
Scheme 3[a]



[a] (a) **2**, LDA, THF, –78 °C, then **3**, HMPA. (b) 5% Na–Hg, Na_2HPO_4, MeOH, 0 °C. (c) H_2, 10% Pd–C, $NaHCO_3$, EtOH. (d) Dess–Martin reagent,[12] pyridine, CH_2Cl_2. (e) Me_2CuLi, ether, –78 °C. (f) Dess–Martin reagent,[12] pyridine, CH_2Cl_2. (g) **4**, BuLi, THF, –78 °C. (h) 6% Na–Hg, Na_2HPO_4, MeOH, 0 °C. (i) AcOH, H_2O, THF. (j) DMSO, Ac_2O, AcOH, 23 → 40 °C. (k) HCOOH, ether. (l) Dess–Martin reagent,[12] pyridine, CH_2Cl_2.

was accomplished by the Yamaguchi method[21] to yield the 24-membered lactone **15** (42%) and a 26-membered lactone (28%).[22] After silylation of the hydroxyl group of **15**, the methyl acetal moiety was hydrolyzed to afford a hemiacetal, which was reduced to give diol **16**. Diol **16** was converted into aldehyde **17** by a four-step sequence. The terminal *N*-methyl-*N*-vinylformamide structure was constructed by reaction of **17** with *N*-methylformamide to afford enamide **18**. Removal of the protecting group at C29 in **18** was accomplished by DDQ,[23] and the resulting hydroxyl group was acylated with *N,N*-dimethylalanine (*S*:*R* = 3:2[24]) under Keck conditions[25] to give a diastereomeric mixture of dimethylalanine esters (*S*:*R* = 4:1).[26] Further, hydrolysis of the (methylthio)methyl (MTM) group at C7 with $AgNO_3$[27] and acylation of the hydroxyl group with *N,N,O*-trimethylserine (*S*:*R* = 5:2[28]) gave a diastereomeric mixture of trimethylserine esters (*S*:*R* = 4:3),[26] the two silyl groups of which were removed to provide aplyronine A (**1**). Synthetic aplyronine A (**1**) was found to correspond uniquely to natural **1** by comparison of the spectroscopic (UV, IR, ^{1}H NMR, MS, α_D) and chromatographic properties and cytotoxicity.[29]

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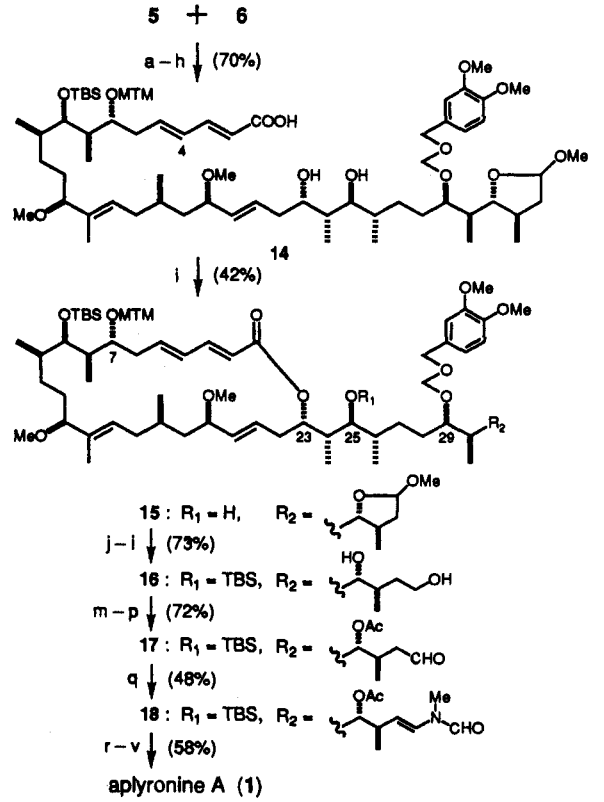
Scheme 4[a]



[a] (a) **6**, BuLi, THF, –78 °C, then **5**. (b) Ac_2O, DMAP, pyridine. (c) 5% Na–Hg, Na_2HPO_4, MeOH, 0 °C. (d) DIBAL, hexane, CH_2Cl_2, –78 °C. (e) Dess–Martin reagent,[12] pyridine, CH_2Cl_2. (f) $(EtO)_2P(O)CH_2$-CH=CHCOOEt, LDA, THF, –40 → 0 °C. (g) HF·pyridine, pyridine, THF. (h) LiOH, MeOH, H_2O. (i) $C_6H_2Cl_3COCl$, DMAP, Et_3N, $CHCl_3$. (j) *t*-$BuMe_2SiCl$ (TBSCl), imidazole, DMF, 60 °C. (k) HCl, H_2O, DME. (l) $NaBH(OMe)_3$, MeOH. (m) TrCl, pyridine, 50 °C. (n) Ac_2O, DMAP, pyridine. (o) HCOOH, ether. (p) Dess–Martin reagent,[12] pyridine, CH_2Cl_2. (q) MeNHCHO, PPTS, hydroquinone, benzene, reflux. (r) DDQ, phosphate buffer (pH 6), *t*-BuOH, CH_2Cl_2. (s) *N,N*-Dimethylalanine (*S*:*R* = 3:2), DCC, DMAP, CSA, CH_2Cl_2. (t) $AgNO_3$, 2,6-lutidine, H_2O, THF. (u) *N,N,O*-trimethylserine (*S*:*R* = 5:2), DCC, DMAP, CSA, CH_2Cl_2, 35 °C. (v) HF·pyridine, pyridine.

Supplementary Material Available: Spectral data of intermediates and synthetic **1**; ^{1}H NMR spectra of the pentaacetate[1b] obtained from both natural and synthetic **1**; ^{1}H and ^{13}C NMR spectra and HPLC traces of natural and synthetic **1** (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) Sato, K.; Mizuno, S.; Hirayama, M. *J. Org. Chem.* **1967**, *32*, 177–180.

(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993. Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367–6370.

(22) The 26-membered lactone could be isomerized to the 24-membered lactone **15** under the equilibrium conditions (**15**/26-membered lactone = ca. 2.5:1) in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ (**15**, 60–65% isolation yield).

(23) Under a variety of conditions for the deprotection of the corresponding (*p*-methoxyphenyl)methoxymethyl ether protecting group at C29 with DDQ, the conjugated lactone group was oxidatively decomposed.

(24) Esterification of the C29 hydroxyl group with (*S*)-*N,N*-dimethylalanine gave a >9:1 mixture of the (2″*S*)- and (2″*R*)-dimethylalanine esters, whereas that with (*R*)-*N,N*-dimethylalanine afforded a 1:1 mixture of the esters.

(25) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.

(26) Natural aplyronine A (**1**) was obtained as a diastereomeric mixture with respect to two amino acids.[1a] The ratios varied with the animal samples employed, although the compounds with *S* configuration were always predominant (2–1.1:1 and 6–3:1 ratios for *N,N,O*-trimethylserine and *N,N*-dimethylalanine moieties, respectively).

(27) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269–3270.

(28) Esterification of the C7 hydroxyl group with (*S*)-*N,N,O*-trimethylserine gave a 3:2 mixture of (2′*S*)- and (2′*R*)-trimethylserine esters, whereas that with (*R*)-*N,N,O*-trimethylserine afforded a 1:3 mixture of the esters.

(29) The very small differences in the signal intensity of the ^{1}H and ^{13}C NMR spectra which were observed between natural and synthetic aplyronine A (**1**) are due to the different diastereomeric ratios of two amino acids. Synthetic **1** was subjected to the same sequence of degradations that was previously employed with natural **1** for removal of the two amino acids[1b] to give the pentaacetate ($[\alpha]^{21}_D$ –14° (*c* 0.06, $CHCl_3$)), corresponding to the carbon backbone of **1**. The pentaacetate thus obtained was identical with that from natural **1** ($[\alpha]^{24}_D$ –15° (*c* 0.16, $CHCl_3$))[1b] in all respects.