Tetrahedron Letters, Vol. 34, No. 52, pp. 8505-8508, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Studies on the Stereochemistry of Aplyronine A: Determination of the Stereochemistry of the C21–C34 Fragment

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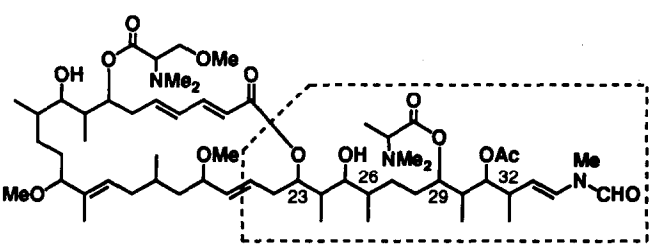
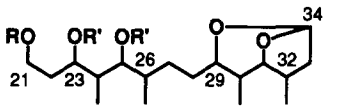
Abstract: The absolute stereochemistry of the C21–C34 fragment **2** of aplyronine A (**1**), a potent antitumor substance of marine origin, was determined by the enantioselective synthesis.

Aplyronine A (**1**) is a potent antitumor substance isolated from the sea hare *Aplysia kurodai*. We have elucidated the gross structure[1] of **1** by means of the spectral analysis and the degradation experiments. Further, we have deduced the relative stereochemistry of three contiguous chiral centers C23–C25 and established that of four contiguous chiral centers C29–C32 in **1** to be **I** and **II** respectively, based on the ^{1}H NMR data of the degradation products, **2** and **3**, of **1**.[2] In this communication, we report the elucidation of the relative stereochemistry of four contiguous chiral centers C23–C26 by comparison of the spectral data of the synthetic model compounds **7a–7h** with those of natural C21–C34 fragment **3** and also describe the determination of the absolute stereochemistry of the C21–C34 fragment **2** by the enantioselective synthesis.

We have deduced the stereochemistry of the C23–C25 part to be *syn-anti* as shown in **I** on the basis of the coupling constants in the ^{1}H NMR spectrum of acetonide **3**[2]: the coupling constant values[3] concerned in **3** were not typical for *syn* and *anti* configurations, presumably because the acetonide ring in **3** adopted a distorted chair conformation, and this configurational assignment was not so definitive. In order to elucidate the stereochemistry of the C23–C26 part unambiguously, we have synthesized eight diastereoisomers of

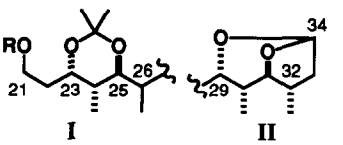


1 aplyronine A



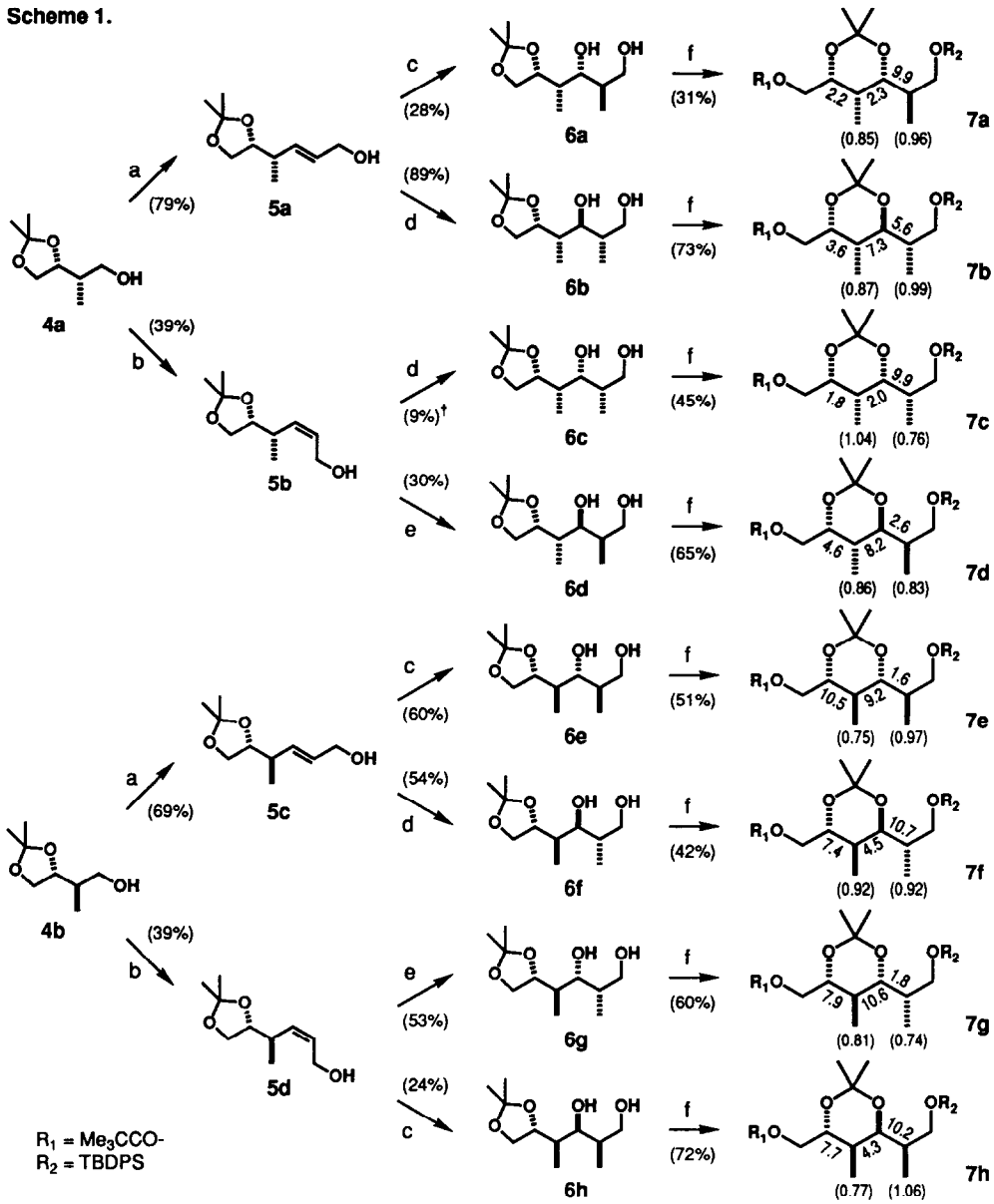
2 R = $CONHC_6H_4$-*p*-Br
R' = Ac

3 R = $CONHC_6H_4$-*p*-Br
R' = acetonide



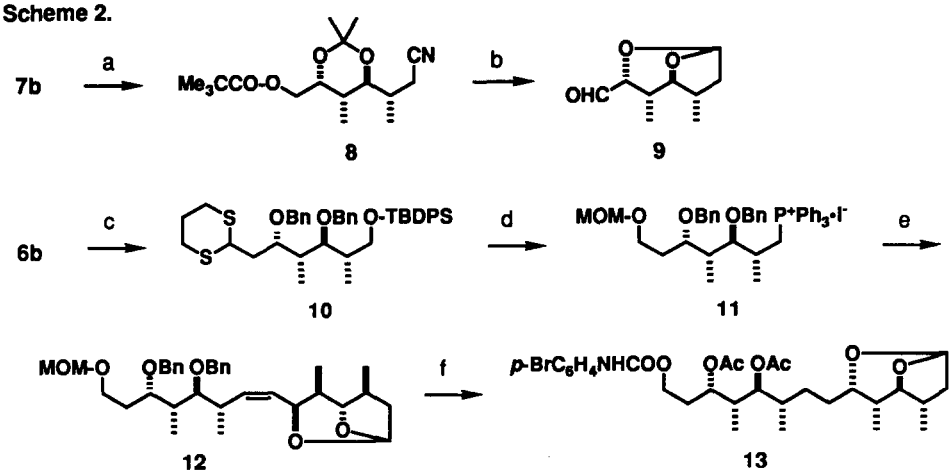
I **II**

Scheme 1.



Reagents and Reaction Conditions.
(a) 1. Swern oxidation; 2. $(i\text{-PrO})_2P(O)CH_2COOEt$, *t*-BuOK, *t*-BuOH, -78 °C; 3. DIBAL, CH_2Cl_2, hexane, -78 °C.
(b) 1. Swern oxidation; 2. CBr_4, PPh_3, CH_2Cl_2, 0 °C; 3. *n*-BuLi, ClCOOMe, THF, -78 → 23 °C; 4. H_2, Lindlar cat., quinoline, hexane, 23 °C; 5. DIBAL, CH_2Cl_2, -78 °C.
(c) 1. Ti(O-Pr-*i*)$_4$, (+)-diethyl tartrate, *t*-BuOOH, CH_2Cl_2, -23 °C; 2. Me_2CuLi, ether, -40 → -23 °C.
(d) 1. Ti(O-Pr-*i*)$_4$, (-)-diethyl tartrate, *t*-BuOOH, CH_2Cl_2, -23 °C; 2. Me_2CuLi, ether, -40 → -23 °C.
(e) 1. MCPBA, CH_2Cl_2, -10 → 0 °C; 2. Me_2CuLi, ether, -40 → 0 °C.
(f) 1. TBDPS-Cl, imidazole, DMF, 0 °C; 2. AcOH, H_2O, 23 °C; 3. Me_3CCOCl, pyr, 0 °C; 4. $Me_2C(OMe)_2$, CSA, acetone, 23 °C.
Yields are not optimized. *J* values are in Hz and chemical shifts ($CDCl_3$) in parentheses.
† The starting compound **5b** was recovered (50%).

Scheme 2.

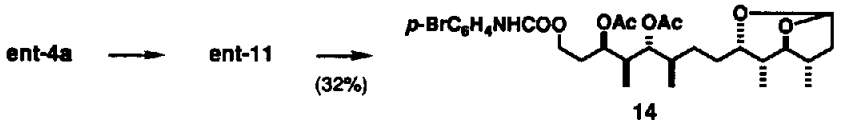


Reagents and Reaction Conditions
(a) 1. *n*-Bu_4NF, THF, 23 °C; 2. *p*-TsCl, pyr, 0 °C; 3. NaCN, DMSO, 80 °C (88%).
(b) 1. DIBAL, CH_2Cl_2, -78 °C; 2. AcOH, H_2O, THF, 23 °C; 3. Swern oxidation (49%).
(c) 1. TBDMS-Cl, imidazole, DMF, 0 °C; 2. BnBr, NaH, DMF, THF, 23 °C; 3. AcOH, EtOH, H_2O, 23 °C; 4. *p*-TsCl, pyr, 0 °C; 5. K_2CO_3, MeOH, 0 °C; 5. 1,3-dithiane, *n*-BuLi, THF, 23 °C; 6. BnBr, NaH, DMF, THF, 23 °C (68%).
(d) 1. $CuCl_2$, CuO, acetone, H_2O, reflux; 2. $NaBH_4$, EtOH, -30 °C; 3. MOM-Cl, *i*-Pr_2NEt, CH_2Cl_2, 23 °C; 4. *n*-Bu_4NF, THF, 23 °C; 5. I_2, PPh_3, imidazole, benzene, 10 °C; 6. PPh_3, acetonitrile, 90 °C (58%).
(e) **9**, $NaN(TMS)_2$, toluene, -78 → 23 °C (44% from **9**).
(f) 1. H_2, Pd/C, EtOH, 23 °C; 2. HCl, MeOH, H_2O, 23 °C; 3. TrCl, pyr, 80 °C, then Ac_2O, 23 °C; 4. AcOH, H_2O, 80 °C; 5. *p*-BrC_6H_4NCO, pyr, 23 °C (37%).

acetonides **7a–7h** by applying Kishi's methods for polypropionates synthesis[4] (Scheme 1). The alcohol **4a**,[5] obtained from *cis*-2-buten-1,4-diol, was converted into *trans*- and *cis*-allyl alcohols **5a**[6] and **5b** using Kishi's protocol.[4] Epoxidation of allyl alcohols **5a** and **5b** by using Sharpless or MCPBA oxidation followed by treatment with Me_2CuLi afforded four diastereomeric diols **6a–6d**. Using the same sequence of reactions, four diastereomeric diols **6e–6h** were prepared from alcohol **4b**.[7] The diastereomeric diols **6a–6h** were transformed into acetonides **7a–7h**, respectively (Scheme 1). The selected ^1H NMR spectral data of eight diastereomeric acetonides **7a–7h** are summarized in Scheme 1. The ^1H NMR spectral data[3] of the natural C21–C34 fragment **3** were nearly identical with those of acetonide **7b** with respect to the coupling constants of protons on an acetonide moiety and the chemical shifts of secondary methyl groups. Thus, the stereochemistry of the C23–C26 part has been determined to be *syn-anti-anti*.

In order to establish the relative stereochemistry between the C23–C26 and the C29–C32 parts in the natural C21–C34 fragment **2** and to determine the absolute stereochemistry of **2**, we have synthesized two diastereomeric urethanes **13** and **14** enantioselectively (Scheme 2, 3). The acetonide **7b** was converted into aldehyde **9** via cyanide **8** by a six-step sequence: 1) Bu_4NF, THF; 2) *p*-TsCl, pyridine; 3) NaCN, DMSO; 4) DIBAL, CH_2Cl_2; 5) AcOH, H_2O, THF; 6) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2. Protection of two hydroxyl groups of diol **6b** (TBDPSCl and BnBr) followed by manipulation of the 1,2-diol moiety gave an epoxide, which was transformed into dithiane **10**. The dithiane **10** was converted into phosphonium salt **11** as follows: 1) hydrolysis of a dithiane moiety; 2) $NaBH_4$ reduction; 3) protection of the primary hydroxyl group; 4) desilylation; 5) conversion into the iodide; and 6) treatment with PPh_3. The Wittig reaction of

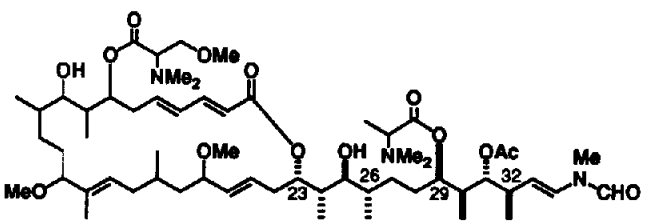
Scheme 3.



aldehyde **9** with phosphonium salt **11** afforded olefin **12** (44%). Catalytic reduction of olefin **12** and the subsequent transformation of the functional groups provided urethane **13**.[8]

Starting from alcohol **ent-4a**,[5] phosphonium salt **ent-11** was prepared by the same sequence of reactions as described above (Scheme 3). The Wittig reaction of aldehyde **9** with phosphonium salt **ent-11** followed by the sequence of reactions described for the synthesis of urethane **13** furnished urethane **14**.[9]

The natural C21–C34 fragment **2** derived from **1** was identical with synthetic urethane **14** except for the sign of optical rotation [synthetic **14**, $[\alpha]^{16}_{D}$ +31° (*c* 0.48, $CHCl_3$); natural **2**, $[\alpha]^{15}_{D}$ −31° (*c* 0.40, $CHCl_3$)], thus establishing the absolute stereostructure of the C21–C34 fragment **2** to be the enantiomer of **14**. On the basis of these results, the absolute stereochemistry of eight chiral centers in aplyronine A (**1**) was determined to be 23*S*,24*S*,25*S*,26*S*,29*R*,30*R*,31*R*,32*R* as shown below.



Acknowledgment. This work was supported in part by Grants-in-Aid for Scientific Research (Nos. 04403009 and 03640472) from the Ministry of Education, Science, and Culture, Japan, the Fujisawa Foundation, the Shorai Foundation for Science and Technology, the Naito Foundation, the Ciba-Geigy Foundation (Japan) for the Promation of Science, and the Asahi Glass Foundation.

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2. Ojika, M.; Kigoshi, H.; Ishigaki, T.; Yamada, K. *Tetrahedron Lett.*, preceding paper in this issue.
3. The selected ^{1}H NMR data ($CDCl_3$, 500 MHz) for **3**: $J_{23,24}$ = 4.2 Hz, $J_{24,25}$ = 7.3 Hz $J_{25,26}$ = 4.9 Hz; $\delta_{24\text{-Me}}$= 0.85, $\delta_{26\text{-Me}}$ = 0.96.
4. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888 and references cited therein.
5. **ent-4a**: Mori, K.; Seu, Y.-B. *Tetrahedron*, **1988**, *44*, 1035–1038.
6. All new compounds described here afforded satisfactory spectroscopic data including HRMS.
7. The alcohol **4b** was prepared from *trans*-4-benzyloxy-2-buten-1-ol. cf. Roush, W. R.; Adam, M. A.; Peseckis S. M. *Tetrahedron Lett.* **1983**, 24, 1377–1380.
8. $[\alpha]^{20}_{D}$ −14° (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) 3430, 1730, 1595, 1520, 1375, 1075, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.84–0.95 (m, 1 H), 0.88 (d, *J* = 7 Hz, 3 H), 0.97 (d, *J* = 7 Hz, 3 H), 1.05–2.08 (m, 8 H), 1.09 (d, *J* = 7 Hz, 3 H), 1.09 (d, *J* = 6 Hz, 3 H), 2.02 (s, 3 H), 2.02 (s, 3 H,), 2.14–2.34 (m, 3 H), 3.76–3.82 (m, 1 H), 3.79 (d, *J* = 2 Hz, 1 H), 4.05–4.26 (m, 2 H), 4.81 (dd, *J* = 10, 3 Hz, 1 H), 5.10 (ddd, *J* = 8, 6, 2 Hz, 1 H), 5.42 (d, *J* = 4 Hz, 1 H), 6.78 (br s, 1 H), 7.27–7.43 (m, 4 H); HRFABMS *m/z* 612.2175 (M + H)$^+$, calcd for $C_{29}H_{43}{}^{79}BrNO_8$ 612.2172.
9. $[\alpha]^{16}_{D}$ +31° (*c* 0.48, $CHCl_3$); HRFABMS m/z 612.2199 (M + H)$^+$, calcd for $C_{29}H_{43}{}^{79}BrNO_8$ 612.2172.

(Received in Japan 13 September 1993)