ORGANIC LETTERS

2001
Vol. 3, No. 26
4291−4294

Syntheses and Absolute Stereochemistries of UPA0043 and UPA0044, Cytotoxic Antibiotics Having a *p*-Quinone-methide Structure

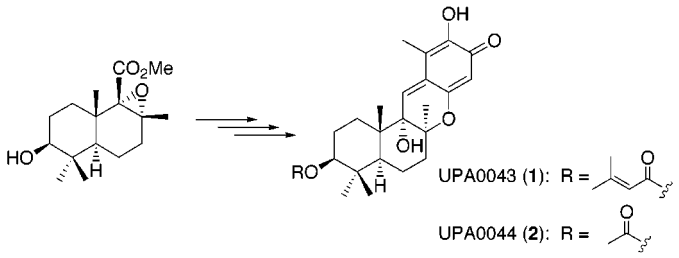
Ken-ichi Takao,[†] Tomoko Sasaki,[†] Tomohito Kozaki,[†] Yumiko Yanagisawa,[†] Kin-ichi Tadano,*[,†] Akira Kawashima,[‡] and Hideki Shinonaga[‡]

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan, and Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403, Yoshino-cho, Saitama 330-8530, Japan

tadano@applc.keio.ac.jp

Received October 26, 2001

ABSTRACT



The first syntheses of new antibiotics UPA0043 and UPA0044 were accomplished starting from commercially available 18*β*-glycyrrhetinic acid and vanillin. The present syntheses involve the coupling of a sesquiterpenoid aldehyde and an aryllithium, the stereoselective formation of a *p*-quinone-methide system, and regioselective intramolecular cyclization via an epoxy ring opening.

UPA0043 (**1**) and UPA0044 (**2**) (Figure 1), which exhibit significant cytotoxic and antifungal activities, were isolated from the culture broth of a fungus by the Taisho research group.[1] Their gross structures and relative stereochemistries were determined by spectroscopic means; the absolute configurations were not determined. Structurally related natural products, such as puupehenone (**3**)[2] and its analogues,[3] were also discovered from marine sponges. Most of this family exhibits a variety of biological activities.[2,3] These compounds **1**−**3** have a common *p*-quinone-methide system that is thought to be responsible for their biological activities.[4] As a result of their unique structures and biological properties, this class of compounds has attracted considerable attention among several research groups studying synthetics.[5,6] We report herein the enantiospecific syntheses of UPA0043 (**1**) and UPA0044 (**2**), thereby establishing their absolute stereochemistries.

[†] Keio University.
[‡] Taisho Pharmaceutical Co., Ltd.

(1) Shinonaga, H.; Obuchi, T.; Kawashima, A. Unpublished results.
(2) (a) Ravi, B. N.; Perzanowski, H. P.; Ross, R. A.; Erdman, T. R.; Scheuer, P. J.; Finer, J.; Clardy, J. *Pure Appl. Chem.* **1979**, *51*, 1893−1900. (b) Urban, S.; Capon, R. J. *J. Nat. Prod.* **1996**, *59*, 900−901.
(3) (a) Amade, P.; Chevelot, L.; Perzanowski, H. P.; Scheuer, P. J. *Helv. Chim. Acta* **1983**, *66*, 1672−1675. (b) Hamann, M. T.; Scheuer, P. J. *Tetrahedron Lett.* **1991**, *32*, 5671−5672. (c) Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1993**, *58*, 6565−6569. (d) Nasu, S. S.; Yeung, B. K. S.; Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M.; Goins, K. *J. Org. Chem.* **1995**, *60*, 7290−7292. (e) Bourguet-Kondracki, M.-L.; Debitus, C.; Guyot, M. *Tetrahedron Lett.* **1996**, *37*, 3861−3864. (f) Bourguet-Kondracki, M.-L.; Lacombe, F.; Guyot, M. *J. Nat. Prod.* **1999**, *62*, 1304−1305. (g) El Sayed, K. A.; Bartyzel, P.; Shen, X.; Perry, T. L.; Zjawiony, J. K.; Hamann, M. T. *Tetrahedron* **2000**, *56*, 949−953.
(4) Zjawiony, J. K.; Bartyzel, P.; Hamann, M. T. *J. Nat. Prod.* **1998**, *61*, 1502−1508 and references therein.
(5) (a) The total synthesis of **3** in racemic form: Trammell, G. L. *Tetrahedron Lett.* **1978**, 1525−1528. (b) The total synthesis of **3** in optically active form: Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **1997**, *38*, 2325−2328.

10.1021/ol016960n CCC: $20.00
Published on Web 12/01/2001

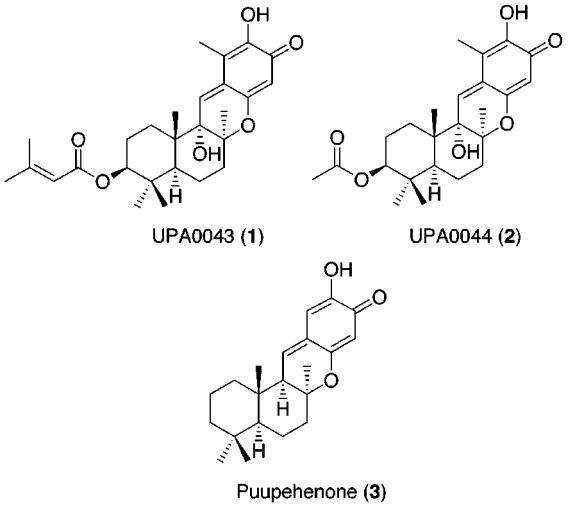
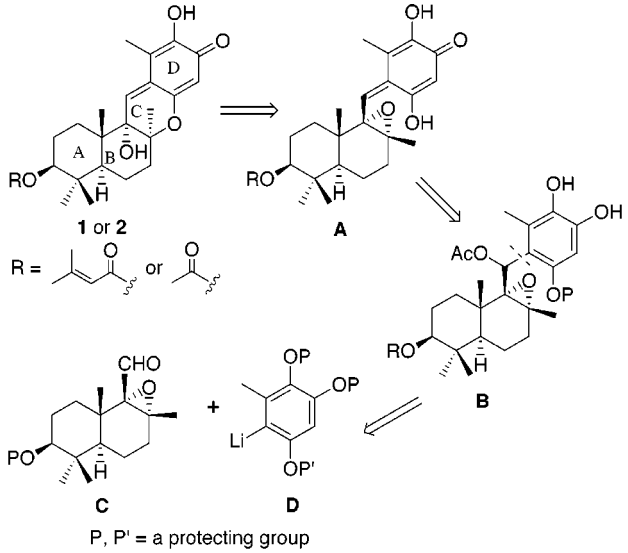


Figure 1. Structures of UPA0043, UPA0044, and puupehenone.

Unlike **3**, the target compounds **1** and **2** possess an angular hydroxy group at the B/C ring juncture. Thus, previously reported synthetic approaches to **3**[5] could not be applied to the synthesis of **1** or **2**. Our retrosynthetic analysis for **1** and **2** is shown in Scheme 1. We anticipated that the cyclization

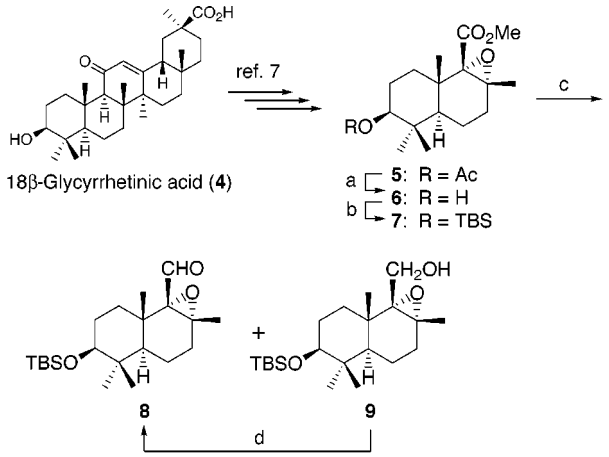
Scheme 1



of epoxy alcohol **A** would proceed regioselectively to construct the tetracyclic skeleton, installing a hydroxy group at the angular carbon of the B/C ring.[6c] The advanced synthetic intermediate **A** would be obtained by the elimination of an acetoxy group in **B**, forming the *p*-quinone-methide system. We envisioned the intermediate **B** to be divided into two segments, a drimane-type sesquiterpenoid **C** and an aromatic derivative **D**.

The synthesis of the sesquiterpenoid segment **8** (P = TBS in **C**) began with commercially available 18β-glycyrrhetinic acid (**4**), the aglycone of glycyrrhizic acid occurring in licorice root (Scheme 2). According to Falck's report, the

Scheme 2[a]



[a] Reagents and conditions: (a) NaOMe, MeOH, 25% for 10 steps from **4**; (b) TBSOTf, pyridine, 0 °C, 86%; (c) Dibal-H, toluene, −78 °C, 70% for **8** and 22% for **9**; (d) Dess−Martin periodinane, DMSO, 88%.

triterpene **4** was degraded to a mixture of the known A/B ring-derived compound **5** and D/E ring-derived products.[7] Without separation, the mixture was treated with sodium methoxide to provide **6**,[8] which was isolated in its pure form by chromatography on silica gel. After silylation of **6**, the resulting *tert*-butyldimethylsilyl (TBS) ether **7** was reduced with diisobutylaluminum hydride (Dibal-H) in toluene to give aldehyde **8** (70%) and alcohol **9** (22%).[9] Dess−Martin oxidation[10] of **9** afforded additional **8**.

The aromatic segment **14** (P = Bn, P′ = TBS in **D**) was synthesized using a well-established reaction sequence (Scheme 3). A trisubstituted benzaldehyde **11**, efficiently prepared from vanillin (**10**) by a known procedure,[11] underwent Baeyer−Villiger oxidation with *m*-chloroper-

(6) Syntheses of analogues of **3**: (a) Arjona, O.; Garranzo, M.; Mahugo, J.; Maroto, E.; Plumet, J.; Sáez, B. *Tetrahedron Lett.* **1997**, *38*, 7249−7252. (b) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Valdivia, M. V.; Chahboun, R. *Tetrahedron Lett.* **1998**, *39*, 2425−2428. (c) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181−15208. (d) Maiti, S.; Sengupta, S.; Giri, C.; Achari, B.; Banerjee, A. K. *Tetrahedron Lett.* **2001**, *42*, 2389−2391.

(7) Manna, S.; Yadagiri, P.; Falck, J. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1324−1325.

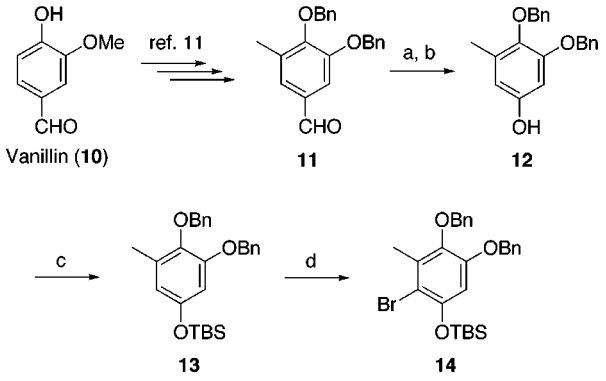
(8) All new compounds were fully characterized by spectroscopic means [^{1}H (270 or 300 MHz in $CDCl_3$) and ^{13}C (68 or 75 MHz in $CDCl_3$) NMR, IR] and gave satisfactory HRMS. Yields refer to homogeneous samples purified by chromatography on silica gel.

(9) When **7** was reduced with Dibal-H in CH_2Cl_2 instead of toluene, the epoxy ring opening was observed in some extent.

(10) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(11) (a) Sinhababu, A. K.; Borchardt, R. T. *Synth. Commun.* **1983**, *13*, 677−683. (b) Sinhababu, A. K.; Ghosh, A. K.; Borchardt, R. T. *J. Med. Chem.* **1985**, *28*, 1273−1279.

Scheme 3[a]

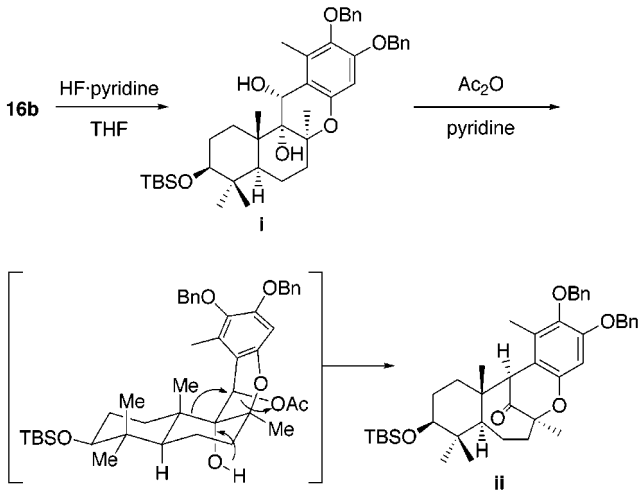


[a] Reagents and conditions: (a) mCPBA, CH_2Cl_2; (b) Et_3N, MeOH, 93% for 2 steps; (c) TBSCl, imidazole, DMF, 93%; (d) NBS, SiO_2, CH_2Cl_2, 85%.

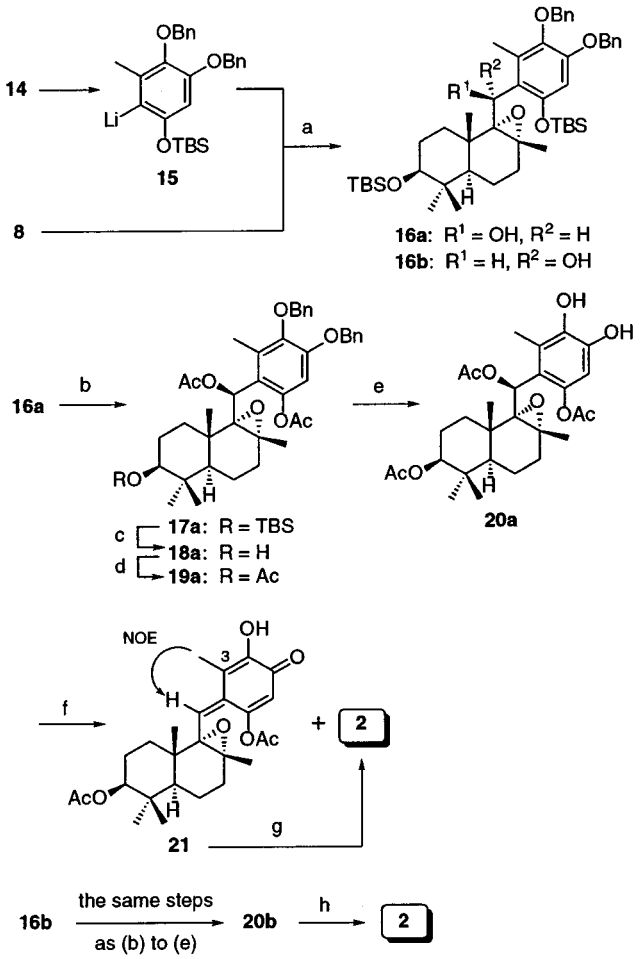
benzoic acid (mCPBA), and methanolysis of the resulting formate gave a trisubstituted phenol **12**. The phenolic hydroxy group in **12** was protected as a silyl ether to provide **13**, which was subjected to regioselective bromination with *N*-bromosuccinimide (NBS) affording **14**. The brominated position in **14** was secured on the basis of NOE experiment.

With the upper and lower segments in hand, the coupling of **8** and **14** was examined (Scheme 4). Thus, the bromide **14** was treated with *tert*-butyllithium in Et_2O at −78 °C, and the resulting aryllithium **15** was reacted with the aldehyde **8**. The reaction proceeded smoothly at −78 °C, and separable coupling products **16a** (48%) and **16b** (15%) were obtained.[12] Acetylation of the major product **16a** in the presence of 4-(dimethylamino)pyridine (DMAP) gave diacetate **17a** as a result of concomitant conversion of the phenolic silyl ether into an acetyl ester. Desilylation of **17a** followed by introduction of an acetyl group in the A ring of **18a** afforded triacetate **19a**. The benzyl protecting groups in **19a** were

(12) Deprotection of the phenolic silyl ether of **16b** afforded the 6-*endo* cyclization product **i** via an epoxy ring opening, which underwent a concerted pinacol rearrangement under acetylation conditions. The structure of the resulting rearrangement product **ii** determined the stereochemistry of the benzylic hydroxy group in **16b**.



Scheme 4[a]

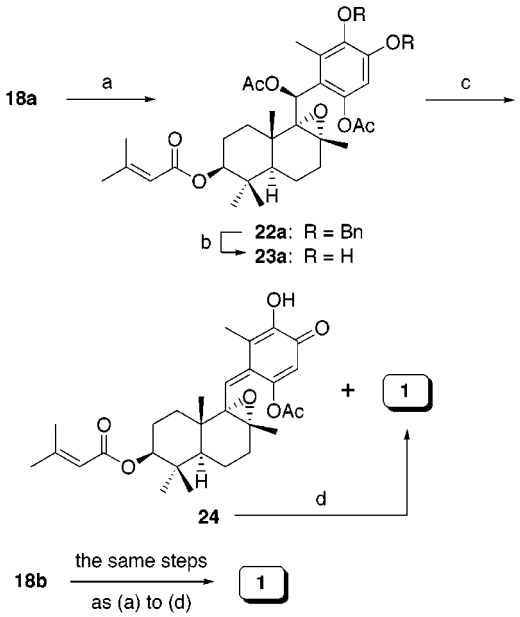


[a] Reagents and conditions: (a) **14**, *t*-BuLi, Et_2O, −78 °C, then **8**, Et_2O, −78 °C, 48% for **16a** and 15% for **16b**; (b) Ac_2O, DMAP, pyridine, 95%; (c) aq HF, MeCN, 84%; (d) Ac_2O, pyridine, 92%; (e) H_2, Pd on C, MeOH, quant; (f) $NaHCO_3$, MeOH, 1 h, 51% for **21** and 14% for **2**; (g) same as (f), 33%; (h) $NaHCO_3$, MeOH, 4 h, 46%.

removed by hydrogenolysis to give a catechol derivative **20a**. Brief exposure of **20a** to sodium bicarbonate in methanol underwent elimination of the benzylic acetoxy group. As a result, the *p*-quinone-methide system was constructed to provide the desired **21**. The *Z*-geometrical structure of **21** was established on the basis of the NOE experiment.[13] Under these conditions, the target compound UPA0044 (**2**) was also produced as a minor product. Accordingly, **21** was separately treated under the same conditions. Additional **2** was produced as a result of deacetylation of the aromatic acetate and subsequent regioselective (6-*endo*) cyclization. The minor coupling product **16b** was transformed into **20b** in an overall yield of 68% by the same reaction sequence used for the conversion of **16a** to **20a**. Prolonged treatment of **20b** with sodium bicarbonate gave **2** directly. The spectroscopic data

(13) As shown in Scheme 4, significant signal enhancement (17%) of the methide proton was observed when the methyl group at C-3 was irradiated.

Scheme 5[a]



[a] Reagents and conditions: (a) 3-methylcrotonyl chloride, Na_2CO_3, $BnN^+Et_3Cl^-$ (cat.), CCl_4, reflux, 89%; (b) Pd on C, cyclohexene/EtOH (1:2), reflux, 98%; (c) $NaHCO_3$, EtOH, 4 h, 54% for **24** and 14% for **1**; (d) Et_3N, MeOH, 24 h, 30% for **1** and 23% for recovered **24**.

(IR, ^1H and ^{13}C NMR, MS) of synthetic **2** were well matched with those of natural **2**. The optical rotation of synthetic **2** {$[\alpha]^{26}_D$ +235 (*c* 0.18, MeOH); for natural $[\alpha]_D$ +234 (*c* 1.0, MeOH)} established the absolute stereochemistry of natural **2** as depicted.

Next, we conducted the synthesis of UPA0043 (**1**) (Scheme 5). The esterification of **18a** with 3-methylcrotonyl chloride under phase-transfer catalyzed conditions[14] proceeded smoothly, giving **22a**.[15] Deprotection of the benzyl groups in **22a** by hydrogen-transfer conditions provided **23a** with the α,β-unsaturated ester moiety intact. The treatment of **23a** with sodium bicarbonate in ethanol produced a *p*-quinone-methide **24** and UPA0043 (**1**). Additional **1** was obtained from **24** under basic conditions, although the yield was less efficient. The minor coupling-product-derived **18b** was also transformed into **1** in a similar fashion in an overall yield of 11%. Synthetic **1** was identical to an authentic sample of natural **1** in all respects, including the optical rotation {$[\alpha]^{27}_D$ +232 (*c* 0.21, MeOH) for synthetic, $[\alpha]_D$ +241 (*c* 1.0, MeOH) for natural}.

In conclusion, we have achieved the syntheses of UPA0043 (**1**) and UPA0044 (**2**) in natural enantiomeric form starting from 18β-glycyrrhetinic acid (**4**) and vanillin (**10**). These syntheses established the absolute stereochemistries of **1** and **2**.

Supporting Information Available: Experimental procedures and spectroscopic characterization (^1H and ^{13}C NMR, IR, and HRMS) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016960N

(14) Szeja, W. *Synthesis* **1980**, 402−403.

(15) Under the standard esterification conditions (3-methylcrotonic acid, WSC·HCl, DMAP, Et_3N, CH_2Cl_2; 3-methylcrotonyl chloride, pyridine), the double-bond isomerization of the 3-methylcrotonyl moiety occurred and the β,γ-unsaturated ester was introduced: Ozeki, T.; Kusaka, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2686−2688.