Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7769-7772, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10075-2

Studies Toward the Synthesis of Popolohuanone E : Synthesis of Natural (+)-Arenarol Related to the Proposed Biogenetic Precursor of Popolohuanone E

Hideki Kawano,[1] Masanori Itoh,[1] Tadashi Katoh, Shiro Terashima*

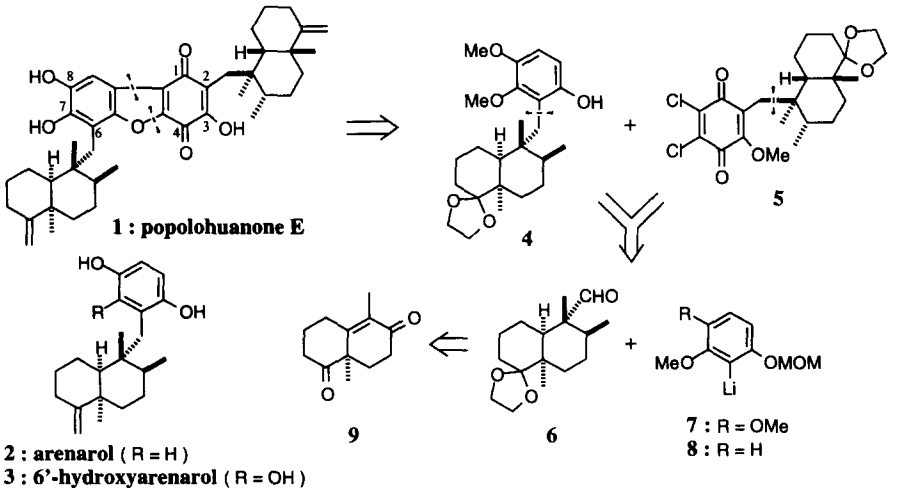
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Abstract: *The cis-fused decalin segment* **6** *required for the total synthesis of popolohuanone E (***1***) was efficiently synthesized starting from the enantiomerically pure (–)-Wieland-Miescher ketone derivative* **9***; the method features ortho ester Claisen rearrangement of* **15** *and Ir-catalyzed hydrogenation of* **17** *(**Scheme 2**). Furthermore, by employing* **6** *as the key decalin segment, the first total synthesis of natural (+)-arenarol (***2***) related to the proposed biogenetic precursor of* **1**, *was accomplished in an enantioselective manner (**Scheme 3**).* © 1997 Elsevier Science Ltd.

Popolohuanone E (**1**) isolated from the Pohnpei marine sponge *Dysidea* sp. along with the known arenarol (**2**) by Scheuer *et al.* in 1993, is a potent inhibitor of topoisomerase-II and exhibits highly selective cytotoxicity against human non-small cell lung cancer cells.[2] The structure of **1** was revealed by extensive spectroscopic studies to have a unique 3,7,8-trihydroxydibenzofuran-1,4-dione skeleton which possesses two identical *cis*-fused decalin moieties the same as in **2**.[2] It has been proposed that **1** may be produced biogenetically by oxidative dimerization of the as-yet-unreported 6'-hydroxyarenarol (**3**).[2,3] Its remarkable biological properties as well as its novel structural features make **1** an exceptionally intriguing and timely target for total synthesis.

In the course of our ongoing project directed toward the total synthesis of optically active **1**, we have already succeeded in developing the general and efficient synthetic pathway to the 2,6-disubstituted-3,7,8-trihydroxy-dibenzofuran-1,4-dione derivatives representing model compounds for the central tricyclic ring system of **1**.[4] Based on these preliminary studies, our retrosynthetic plan for **1** was devised as outlined in **Scheme 1**. The

Scheme 1. Retrosynthetic analysis for popolohuanone E (**1**) and structures of its related compounds

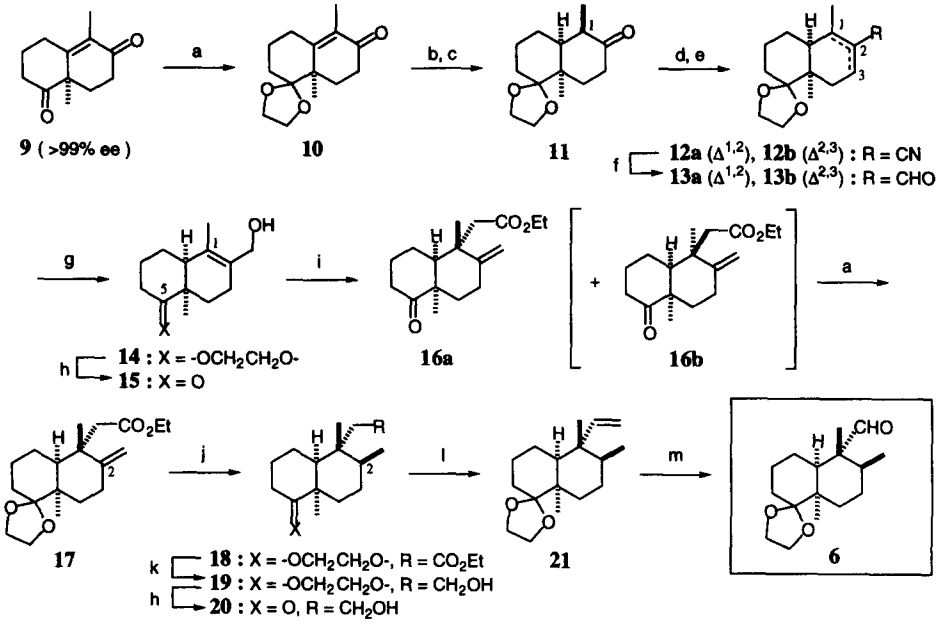


key feature in this plan consists of the regiocontrolled annulation of the phenolic segment **4** with the quinone segment **5** to construct the core structure for **1**. These segments **4** and **5** are anticipated to be elaborated through the coupling reaction of the *cis*-fused decalin segment **6** accessible from the enantiomerically pure (–)-Wieland-Miescher ketone derivative **9**, with the corresponding aromatic segments **7** and **8**, respectively. In this communication, we wish to report a facile synthesis of optically active **6**, which contains four contiguous asymmetric stereogenic centers and two quaternary carbons, starting from **9**. The sequence involves ortho ester Claisen rearrangement of the allylic alcohol **15** to construct stereoselectively the quaternary carbon at the C-1 position (**15**→**16**) and Ir-catalyzed hydrogenation of the exocyclic olefin **17** to control the stereochemistry at the C-2 position (**17**→**18**) as the key steps (**Scheme 2**). Furthermore, we demonstrate the utility of **6** in the first enantioselective total synthesis of natural (+)-arenarol (**2**) related to the proposed biogenetic precursor of **1**, 6'-hydroxyarenarol (**3**)[2] (**Scheme 3**). Arenarol was first isolated from the marine sponge *Dysidea arenaria* in 1984[5] and subsequently from a *Fenestraspngia* species.[6] This marine natural product is reported to show moderate cytotoxicity against the P388 murine leukemia cell.[5] The structure of **2**, including its relative stereochemistry, was revealed by X-ray diffraction analysis of the corresponding diacetate,[5] and the absolute configuration was subsequently established by extensive chemical correlation.[7] Only one total synthesis of racemic **2** was achieved by Wiemer *et al.* in 1995,[8] while the total synthesis of optically active **2** has not been reported to date.

At first, the synthesis of the *cis*-fused decalin segment **6** was investigated as shown in **Scheme 2**. The starting material **9**, $[\alpha]_D^{20}$ -140° (*c* 0.21, MeOH) [lit.,[9] $[\alpha]_D^{20}$ -140° (*c* 0.20, MeOH)] and mp 50-51°C [lit.,[9] mp 47-48°C], was readily prepared in an enantiomerically pure form (>99% *ee*)[10] according to the reported procedure.[9] Chemoselective protection[9] of **9** followed by stereocontrolled hydrogenation[11] of the resulting acetal **10** provided exclusively the desired *cis*-fused decalin derivative as a hardly separable mixture of the C-1 epimers (α:β=1:13), which smoothly converged to the thermodynamically more stable **11** (69% from **9**), $[\alpha]_D^{20}$ -72.0° (*c* 1.08, $CHCl_3$) and mp 84-85°C, by base-catalyzed epimerization. A single crystal X-ray analysis of **11** established its stereostructure unambiguously.[12] Treatment of **11** with potassium cyanide in the presence of acetic acid followed by dehydration with thionyl chloride in pyridine yielded the nitriles **12a** and **12b** as a hardly separable mixture of two possible regioisomers ($\Delta^{1,2}$:$\Delta^{2,3}$=20:1) (70%, 2 steps). This mixture was reduced with diisobutylaluminium hydride (DIBAL) to furnish the corresponding aldehydes **13a** and **13b** (20:1), which could be readily separated by recrystallization from hexane to afford the desired $\Delta^{1,2}$ aldehyde **13a** (70%), $[\alpha]_D^{20}$ -101° (*c* 1.02, $CHCl_3$) and mp 89-91°C. Further reduction of **13a** with sodium borohydride followed by removal of the acetal moiety in the resulting alcohol **14** provided **15**, $[\alpha]_D^{20}$ -129° (*c* 1.00, $CHCl_3$), in 98% yield for the two steps.

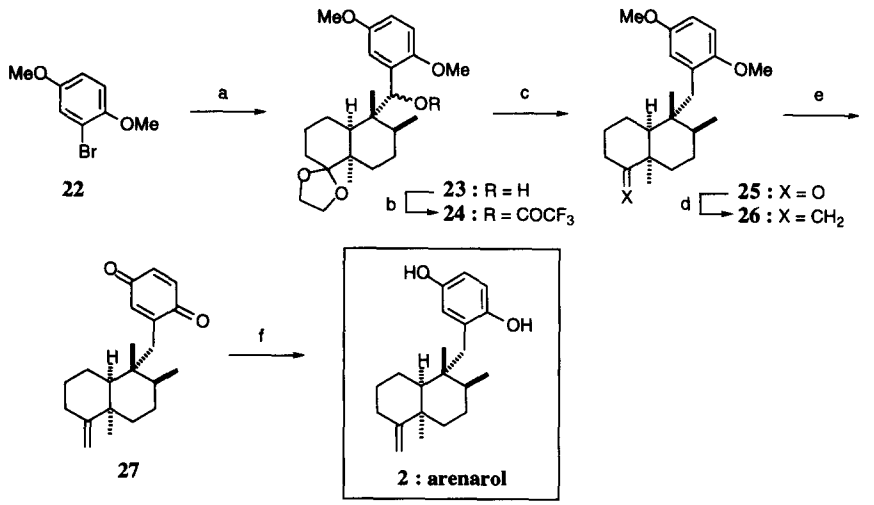
The crucial ortho ester Claisen rearrangement[13] of **15** was achieved by treating with triethyl orthoacetate in the presence of hydroquinone in *o*-dichlorobenzene at 180°C, giving rise to a mixture of the stereoisomers **16a** and **16b** in a ratio of 3:2 in 50% combined yield.[14,15] After separation of this mixture by column chromatography on silica gel, the carbonyl function in the desired **16a** was reprotected to give the acetal **17** (97%), $[\alpha]_D^{20}$ -15.0° (*c* 1.00, $CHCl_3$). The critical stereocontrolled hydrogenation of the exocyclic olefin moiety in **17** was best accomplished by employing [Ir(cod)(PCy_3)py]PF_6 catalyst,[8,16] affording the requisite **18**, $[\alpha]_D^{20}$ +9.8° (*c* 0.98, $CHCl_3$), as a single stereoisomer in 87% yield. When the hydrogenation was carried out by employing a conventional palladium-carbon catalyst, a 3:1 mixture of the stereoisomers was produced in 89% yield, favoring the undesired C-2 epimer of **18**. The stereostructure of **18** was rigorously confirmed by X-ray diffraction analysis of its derivative **20**.[12] After reduction of **18** with lithium aluminium hydride, the resulting alcohol **19**, $[\alpha]_D^{20}$ +7.4° (*c* 1.00, $CHCl_3$) and mp 70-72°C, was converted to the olefin **21** (74%, 2 steps), $[\alpha]_D^{20}$ -8.0° (*c* 1.10, $CHCl_3$), by reaction with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine followed by treatment with 30% hydrogen peroxide.[17] Finally, ozonolysis of the terminal olefin in **21** furnished the first target compound **6**[18] in 85% yield.

Scheme 2. Synthesis of the optically active *cis*-fused decalin segment **6**



a) ethylene glycol, *p*- TsOH, benzene, reflux, 89% for **10**, 97% for **17** b) H_2 (10 atm), 10% Pd-C, piperidine, rt c) MeONa, MeOH, reflux, 77% (2 steps) d) KCN, AcOH, EtOH, 15°C e) $SOCl_2$, pyridine, CH_2Cl_2, 0°C, 70% (2 steps, **12a**:**12b**=20:1) f) DIBAL, toluene, -78°C, 70% g) $NaBH_4$,THF-H_2O, 0°C, 99% h) 4M HCl, MeOH, rt, 99% for **15**, 97% for **20** i) $CH_3C(OEt)_3$, hydroquinone,*o*-dichlorobenzene,180°C, 30% for **16a**, 20% for **16b** j) H_2 (1 atm), [Ir(cod)(PCy$_3$)py]PF_3, CH_2Cl_2, rt, 87% k) $LiAlH_4$, THF, 0°C, 98% l) *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt ; 30% H_2O_2, 0°C, 75% m) O_3, CH_2Cl_2 , -78°C ; PPh_3, -78→0°C, 85%

Scheme 3. Synthesis of natural (+)-arenarol (**2**)



a) *n*-BuLi, Et_2O, -78°C; **6** in Et_2O, -78°C, 68% b) $(CF_3CO)_2O$, pyridine, 0°C, 88% c) H_2 (5 atm), 10%Pd-C, MeOH, rt, 85% d) CH_2Br_2, Zn, $TiCl_4$, THF, rt, 83% e) $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, rt, 33% f) $Na_2S_2O_4$, THF-H_2O, rt, 75%

Having obtained the key *cis*-fused decalin segment **6**, our next efforts were directed toward the synthesis of (+)-arenarol (**2**). As shown in **Scheme 3**, the coupling reaction of **6** with the aryllithium generated *in situ* from commercially available 1-bromo-2,3-dimethoxybenzene (**22**) proceeded smoothly, affording the desired coupling product **23** as a diastereomeric mixture in 68% yield. Conversion of **23** to the ketone **25**, $[\alpha]_D^{20}$ +37.8° (*c* 1.01, $CHCl_3$) and mp 127-129°C, was conducted by initial formation of the trifluoroacetate **24** and subsequent treatment under the conditions for hydrogenolysis (72%, 2 steps). Methylenation of the carbonyl group in **25** was achieved by employing a combination of dibromomethane, zinc powder, and titanium tetrachloride developed by Ohsima *et al.*,[19,20] giving rise to the olefin **26** (83%), $[\alpha]_D^{20}$ +47.0° (*c* 1.04, $CHCl_3$) and mp 62-64°C. Since the racemic version of **26** is an intermediate in Wiemer's synthesis of (±)-**2**,[8] the final two-step sequence was carried out according to his protocol. Thus, treatment of **26** with ceric ammonium nitrate (CAN) followed by reduction of the resulting arenarone (**27**)[21] with sodium hydrosulfite furnished the target (+)-arenarol (**2**) (25%, 2 steps), $[\alpha]_D^{20}$ +18.1° (*c* 0.13, $CHCl_3$) [lit.,[5] $[\alpha]_D$ +19° (*c* 0.1, $CHCl_3$)] and mp 129-132°C [lit.,[5] mp 128-130°C]. The IR, ^{1}H-NMR, and MS spectra of **2** were identical with those reported[5] for natural arenarol.

In summary, we have succeeded in developing a facile synthetic pathway to the optically active *cis*-fused decalin segment **6** starting from the (–)-Wieland-Miescher ketone derivative **9** (>99% *ee*). Additionally, the first enantioselective total synthesis of natural (+)-arenarol (**2**) was accomplished by utilizing **6** as the key decalin segment, demonstrating the feasibility of our designed synthetic strategy for optically active popolohuanone E (**1**) (see, **Scheme 1**). Work on the total synthesis of **1** is in progress and will be reported shortly.

References and Notes:

1. Visiting scientist from Research Laboratories, Research and Development Division, Sumitomo Pharmaceuticals Co. Ltd.
2. Carney, J. R., Scheuer, P. J., *Tetrahedron Lett.*, **1993**, *34*, 3727-3730.
3. 6'-Hydroxyarenarol (**3**) has not been isolated to date because this putative compound seems to be unusually unstable and/or prone to oxidation.[2]
4. Ueki, Y., Itoh, M., Katoh, T., Terashima, S., *Tetrahedron Lett.*, **1996**, *37*, 5719-5722.
5. Schmitz, F. J., Lakshmi, V., Powell, D. R., van der Helm, D., *J. Org. Chem.*, **1984**, *49*, 241-244.
6. Carte, B., Rose, C. B., Faulkner, D. J., *J. Org. Chem.*, **1985**, *50*, 2785-2787.
7. Urban, S., Capon, R. J., *Aust. J. Chem.*, **1994**, *47*, 1023-1029.
8. Watson, A. T., Park, K., Wiemer, D. F., *J. Org. Chem.*, **1995**, *60*, 5102-5106.
9. Hagiwara, H., Uda, H., *J. Org, Chem.*, **1988**, *53*, 2308-2311.
10. The *ee* was determined by HPLC analysis using chiralcel OD-H column (Daicel Chemical Industries, LTD.).
11. The stereocontrolled hydrogenation of **10** was carried out according to the reported procedure with several improvements in the reaction conditions. See, Park, K., Scott, W. J., Wiemer, D. F., *J. Org. Chem.*, **1994**, *59*, 6313-6317.
12. Details of X-ray crystallographic study will be reported in a separate paper.
13. For recent reviews on the Claisen rearrangement, see, a) Wipf, P., in *Comprehensive Organic Synthesis*, Trost, B. M., Ed., Pergamon Press, Oxford, 1991, Vol. 5, pp 827-873. b) Ziegler, F. E., *Chem. Rev.*, **1988**, *88*, 1423-1452.
14. When the acetal **14** was employed as the substrate for the ortho ester Claisen rearrangement, the reverse stereoselectivity was observed. This difference presumably results from conformational change attendant upon changing from the sp^2 hybridization of the C-5 ketone to the sp^3 hybridization at the C-5 dioxolane. Detailed discussion on this issue will be presented in a full account.
15. A related Claisen rearrangement has been reported for the total synthesis of (±)-annonene, a *trans*-clerodane diterpene. See, Takahashi, S., Kusumi, T., Kakisawa, H., *Chem. Lett.*, **1979**, 515-518.
16. This catalyst is known to participate in hydrogenations directed by oxygen-containing functional groups (*e.g.*, OH, CO_2R, C=O, $CONH_2$, *etc.*). See, Crabtree, R. H., Davis, M. W., *J. Org. Chem.*, **1986**, *51*, 2655-2661.
17. Grieco, P. A., Gilman, S., Nishizawa, M., *J. Org. Chem.*, **1976**, *41*, 1485-1486.
18. After purification by column chromatography on silica gel, this compound was immediately used for the next coupling reaction due to its instability.
19. Takai, K., Hotta, Y., Ohsima, K., Nozaki, H., *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 1698-1702.
20. Tokoroyama, T., Kanazawa, R., Yamamoto, S., Kamikawa, T., Suenaga, H., Miyabe, M., *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 1720-1728.
21. The specific rotation of synthesized (+)-arenarone (**27**), $[\alpha]_D^{20}$ +31.8° (*c* 0.21, $CDCl_3$), was inconsistent with the reported value for natural (+)-arenarone, lit.,[5] $[\alpha]_D$ +8.3° (*c* 0.18, $CDCl_3$). This is probably due to its instability in a choroform-*d* solution.

(*Received in Japan* 4 *August* 1997; *accepted* 4 *September* 1997)