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Studies toward the Total Synthesis of Popolohuanone E: Enantioselective Synthesis of 8-*O*-Methylpopolohuanone E

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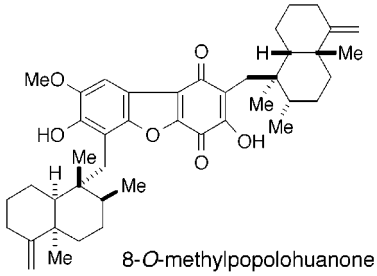
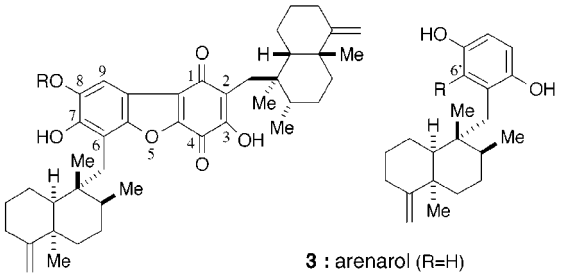
ABSTRACT



8-*O*-methylpopolohuanone E (**2**)

8-*O*-Methylpopolohuanone E (2) was synthesized in a highly convergent manner starting from the *cis*-fused decalin derivative accessible from the (−)-Wieland−Miescher ketone analogue. The synthetic method features a biogenetic-type annulation of the phenolic and quinone segments to regioselectively construct the central tricyclic ring system as the key step.

Popolohuanone E (**1**, Figure 1), isolated from the Pohnpei marine sponge *Dysidea* sp. along with the known arenarol (**3**) by Scheuer et al. in 1993, is a potent inhibitor of topoisomerase II and shows highly selective cytotoxicity against the A549 human non-small cell lung cancer cells.[1−3] The gross structure of **1** was revealed by means of extensive spectroscopic studies to have a unique 3,7,8-trihydroxy-dibenzofuran-1,4-dione nucleus which possesses two identical *cis*-fused decalin moieties, the same as in **3**.[1] Scheuer et



3 : arenarol (R=H)
4 : 6'-hydroxyarenarol (R=OH)
1 : popolohuanone E (R=H)
2 : 8-*O*-methylpopolohuanone E (R=Me)

Figure 1. Structures of popolohuanone E (**1**), 8-*O*-methylpopolohuanone E (**2**), arenarol (**3**), and 6′-hydroxyarenarol (**4**).

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(1) Carney, J. R.; Scheuer, P. J. *Tetrahedron Lett.* **1993**, *34*, 3727.

(2) The IC_{50} values of the inhibitory activity of topoisomerase II and cytotoxicity against the A549 human non-small cell lung cancer cells are 0.4 μM and 2.5 μg/mL, respectively, which are comparable to those of the epipodophyllotoxins and other anticancer agents currently in clinical use for lung cancer.

(3) Arenarol (**3**) was first isolated from the marine sponge *Dysidea arenaria* in 1984, subsequently from a *Fenestraspongia* species, see: (a) Schmitz, F. J.; Lakshmi, V.; Powell, D. R.; van der Helm, D. *J. Org. Chem.* **1984**, *49*, 241. (b) Carte, B.; Rose, C. B.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 2785.

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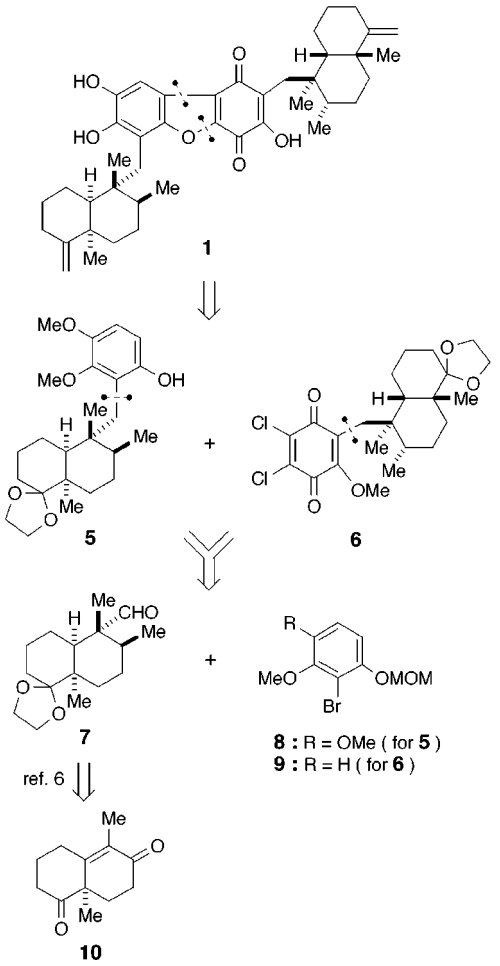
al. proposed that **1** might be produced biogenetically by oxidative dimerization of the putative 6′-hydroxyarenarol (**4**) which has not been isolated so far.[1] Its remarkable biological properties, unique structural features, and plausible biogenetic pathway make **1** an exceptionally intriguing and timely target for total synthesis. To the best of our knowledge, the total synthesis of **1** has not been achieved to date, while a synthetic study toward **1** was reported by Anderson et al. in 1998.[4]

In the course of our ongoing project directed toward the total synthesis of optically active **1**, we have already succeeded in developing a general and efficient synthetic pathway to the 2,6-disubstituted-3,7,8-trihydroxydibenzofuran-1,4-dione derivatives representing model compounds for the central tricyclic ring system of **1**.[5] Furthermore, we have achieved the first total synthesis of natural (+)-arenarol [(+)-**3**] in an enantiomerically pure form which is closely related to the proposed biogenetic precursor **4**.[6,7] On the basis of these preliminary studies, our efforts were devoted to the total synthesis of **1**. As will be illustrated later (see Scheme 4), complete deprotection of the 3,7,8-tri-*O*-methyl groups in popolohuanone E trimethyl ether (**24**) to produce the targeted compound **1** at the final stage turned out to be fruitless, while we succeeded in synthesizing 8-*O*-methylpopolohuanone E (**2**) possessing the full carbon framework with the requisite substituents and asymmetric carbons involved in **1**. In this Letter, we report our preliminary results concerning the enantioselective total synthesis of **2**.

The retrosynthetic plan for **1** was designed as outlined in Scheme 1. The key feature in this plan is a biogenetic-type annulation of the phenolic segment **5** with the quinone segment **6** to regioselectively construct the tricyclic ring system of **1** as the pivotal step. The key segments **5** and **6** would be elaborated by the coupling reaction of the *cis*-fused decalin **7** with the corresponding aromatic segments **8** and **9**, respectively. The enantiomerically pure *cis*-decalin **7**, which contains four contiguous asymmetric centers and two quaternary carbons, has been already prepared starting from the known (−)-Wieland−Miescher ketone analogue **10**[8] in our previous work.[6,9]

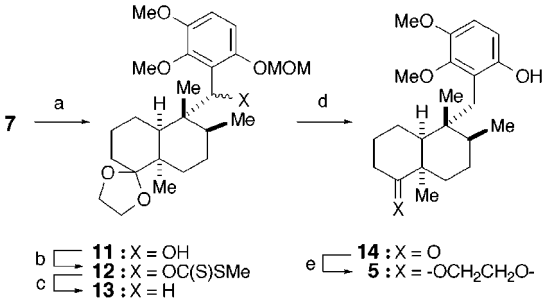
As shown in Scheme 2, we initially pursued the synthesis of the phenolic segment **5** through the coupling reaction of the *cis*-decalin **7**[6,9] with 1-bromo-2,3-dimethoxy-6-(methoxymethoxy)benzene (**8**).[10] Thus, the aryllithium generated in situ by treatment of **8** with *n*-butyllithium in THF at −40 °C was allowed to react with **7** at −40 → −20 °C, providing an excellent yield (97%) of the coupling product **11** as a

Scheme 1. Retrosynthetic Plan for Popolohuanone E (**1**)



mixture of epimeric alcohols (ca. 3:1 by 500 MHz ^{1}H NMR) that were very difficult to separate. Removal of the sterically hindered hydroxy group in **11** was best achieved by applying the Barton procedure[11] with some improvements of the reaction conditions. Thus, reaction of **11** with sodium bis-

Scheme 2. Synthesis of the Phenolic Segment **5**[a]



[a] Reagents and conditions: (a) 1-bromo-2,3-dimethoxy-6-(methoxymethoxy)benzene (**8**), *n*-BuLi, THF, −40 °C; **7**, −40 → −20 °C, 97%; (b) $NaN(TMS)_2$, THF, −78 °C; CS_2, −78 → −55 °C; MeI, −78 → −55 °C, 94%; (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 77%; (d) 12 M HCl, MeOH, 40 °C, 98%; (e) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux, 94%.

(4) Anderson, J. C.; Pearson, D. J.*J. Chem. Soc., Perkin Trans. 1* **1998**, 2023.

(5) Ueki, Y.; Itoh, M.; Katoh, T.; Terashima, S.*Tetrahedron Lett.* **1996**, *37*, 5719.

(6) Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S.*Tetrahedron Lett.* **1997**, *38*, 7769.

(7) The total synthesis of racemic arenarol [(±)-**3**] has been reported by Wiemer et al., see: Watson, A. T.; Park, K.; Wiemer, D. F. *J. Org. Chem.* **1995**, *60*, 5102.

(8) Hagiwara, H.; Uda, H. *J. Org, Chem.* **1988**, *53*, 2308.

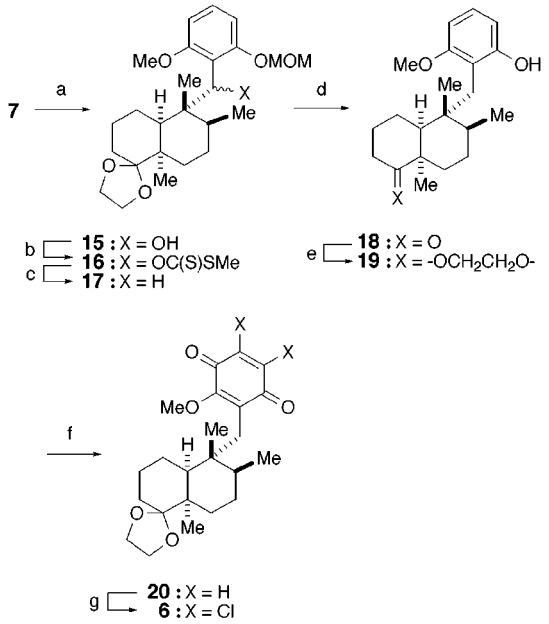
(9) Detailed experimental procedures for the synthesis of **7** starting from **10** are provided in the Supporting Information.

(10) Compound **8** was prepared from commercially available 3,4-dimethoxyphenol via a two-step sequence of reactions [(a) MOMCl, *i*-Pr_2-NEt, CH_2Cl_2, rt, 78% (b) *t*-BuLi, TMEDA, Et_2O, −78 °C; Br_2, −78→0 °C, 50%] (see the Supporting Information for experimental details).

(trimethylsilyl)amide [NaN(TMS)$_2$] followed by carbon disulfide and then iodomethane afforded the corresponding methyl xanthate **12** in 94% yield, which was further treated with tri-*n*-butyltin hydride and 2,2′-azobis(isobutyronitrile) (AIBN) in refluxing toluene, providing the desired deoxygenated product **13** in 77% yield. Compound **13** was then converted to the requisite phenolic segment **5** in 92% overall yield via a two-step sequence involving acid hydrolysis of both the MOM and ethylene acetal protecting groups in **13** followed by reprotection of the carbonyl functionality of the resulting ketone **14**.[12]

Next, the synthesis of the quinone segment **6** was conducted through the coupling reaction of the *cis*-decalin **7** with 1-bromo-2-methoxy-6-(methoxymethoxy)benzene (**9**)[13] as shown in Scheme 3. By employing a reaction sequence

Scheme 3. Synthesis of the Quinone Segment **6**[a]

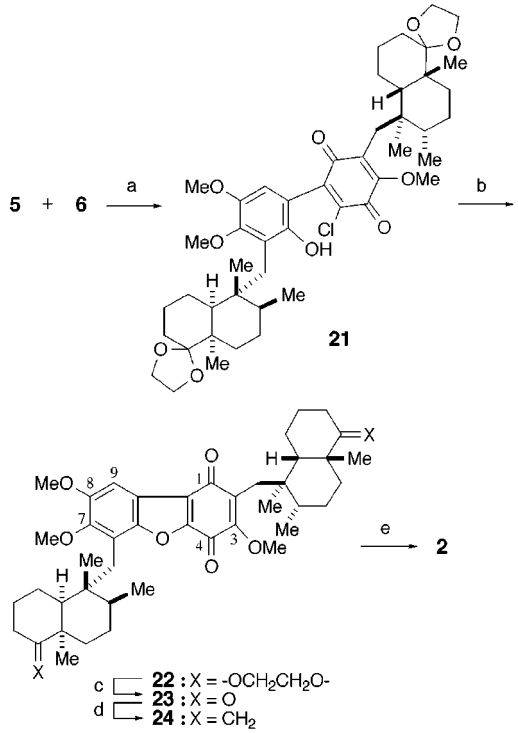


[a] Reagents and conditions: (a) 1-bromo-2-methoxy-6-(methoxymethoxy)benzene (**9**), *n*-BuLi, THF, −40 °C; **7**, −40 → −20 °C, 97%; (b) CS_2, THF, −78 °C; NaN(TMS)$_2$, −78 → −70 °C; MeI, −70 → −60 °C, 90%; (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 81%; (d) 12 M HCl, MeOH, 40 °C, 95%; (e) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux, 90%; (f) salcomine, O_2, DMF, rt, 85%; (g) $SOCl_2$, pyridine, benzene, reflux, 78%.

similar to that described for the synthesis of the phenolic segment **5**, the phenol derivative **19** was prepared starting with **7** in five steps in 60% overall yield via the coupling product **15**, methyl xanthate **16**, deoxygenated product **17**, and ketone **18**. The subsequent crucial formation of the quinone system was successfully carried out by reaction of **19** with molecular oxygen in the presence of salcomine [*N*,*N*-bis(salicylidene)ethylenediiminocobalt(II)][14] in DMF at ambient temperature, which provided the corresponding quinone **20** in 85% yield. Finally, dichlorination of **20** was achieved by treatment with thionyl chloride in the presence of pyridine in refluxing benzene,[15] leading to the formation of the desired quinone segment **6** in 78% yield.

With the phenolic segment **5** and the quinone segment **6** in hand, we turned our attention toward the proposed biogenetic-type annulation to construct the central tricyclic ring system of the targeted compound **1** as depicted in Scheme 4. The critical annulation of **5** with **6** was ac-

Scheme 4. Synthesis of 8-*O*-Methylpopolohuanone E (**2**)[a]



[a] Reagents and conditions: (a) **5**, NaH, THF, rt; **6**, −78 °C, 94%; (b) Amberlite IRA-900, THF, rt, 80%; (c) 1.0 M HCl, MeOH, rt, 100%; (d) CH_2Br_2, Zn, $TiCl_4$, THF, rt, 26%; (e) *n*-BuSLi, HMPA, 110 °C, 34%.

complished in a completely regioselective manner via a two-step sequence of reactions. Thus, the initial coupling reaction of **5** with **6** in the presence of sodium hydride in THF at −78 °C proceeded smoothly to provide the coupling

(11) Barton, D. H. R.; McCombie, S. W.*J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(12) Direct conversion of compound **13** to the requisite phenolic segment **5** by chemoselective deprotection of the MOM protecting group met with failure.

(13) Compound **9** was prepared from commercially available 3-methoxyphenol via a two-step sequence of reactions [(a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 91% (b) *t*-BuLi, TMEDA, Et_2O, −78 °C.; Br_2, −78→0 °C, 73%] (see the Supporting Information for experimental details). Compound **9** has been previously prepared from the same starting material using 1,2-dibromotetrafluoroethane as the bromine source, see: Rice, J. E.; Cai, Z.-W. *J. Org. Chem.* **1993**, *58*, 1415.

(14) (a) Wakamatsu, T.; Nishi, T.; Ohnuma; T.; Ban, Y. *Synth. Commun.* **1984**, *14*, 1167. (b) Yoshida, K.; Nakajima, S.; Ohnuma, T.; Ban Y.; Shibasaki, M.; Aoe, K.; Date, T. *J. Org. Chem.* **1988**, *53*, 5355. (c) Saito, N.; Obara, Y.; Aihara, T.; Harada, S.; Shida, Y.; Kubo, A. *Tetrahedron* **1994**, *50*, 3915. (d) Miyata, F.; Yoshida, S.; Yamori, T.; Katoh, T. *Heterocycles* **2001**, *54*, 619.

(15) Shi, S.; Katz, T. J.; Yang, B. V.; Liu, L. *J. Org. Chem.* **1995**, *60*, 1285.

21 as the single regioisomer in 94% yield. Subsequent ring closure was performed by exposure of **21** to Amberlite IRA-900 (OH^- form) in THF at ambient temperature, resulting in the formation of the desired cyclized product **22**[16] in 80% yield. To forward the synthesis, the two ethylene acetal moieties in **22** were deprotected by acid hydrolysis to furnish the corresponding diketone **23** in quantitative yield. Simultaneous olefination of the two carbonyl functionalities present in **23** was best achieved by employing a combination of dibromoethane, zinc powder, and titanium(IV) chloride developed by Takai et al.,[17] giving rise to popolohuanone E trimethyl ether (**24**) (26%).[18] The final task was the full deprotection of the three methyl groups in **24**. Considering the chemical instability of the *exo*-olefin moieties present in this type of decalin system under acidic conditions,[19] demethylation of **24** was investigated using a nonacidic alkylthiolate reagent. Thus, treatment of **24** with lithium *n*-butylthiolate[20] (30 equiv) in HMPA at 110 °C for 2 h, resulted in the formation of the partial demethylated product, 8-*O*-methylpopolohuanone E (**2**) (34%),[21] whose structure was determined by extensive spectroscopic analysis including NOESY experiment.[22] In this reaction, unfortunately, none of the desired completely deprotected product **1** was detected; the harsh reaction conditions including longer reaction time and/or higher reaction temperature led to only unidentified decomposition products. Several attempts to produce the targeted compound **1** by cleavage of the remaining methyl ether in **2** using the same reagent under a variety of conditions were also unsuccessful. Further efforts are underway to complete the synthesis of the marine natural product itself.

In summary, we have succeeded in developing a highly convergent synthetic pathway to 8-*O*-methylpopolohuanone E (**2**), which features a biogenetic-type annulation of the phenolic segment **5** and the quinone segment **6** to regioselectively construct the central tricyclic ring system of **2** as the key step. The explored synthetic method should hold promise for the preparation of various structural types of popolohuanone E congeners with useful in vivo antitumor activity.

Acknowledgment. We are grateful to Professor P. J. Scheuer, University of Hawaii at Manoa, for providing the ^1H and ^{13}C NMR spectra of natural **1**, which were instrumental in the structural determination of **2**.

Supporting Information Available: Detailed experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Signals at 184.4 (C-1) and 172.5 (C-4) in the ^{13}C NMR spectrum of **22** definitely established the annulation pattern of the quinone and the aromatic rings through the furan ring for the 3,7,8-trihydroxydibenzofuran-1,4-dione system. The related assignment has been reported for the structural determination of **1**.

(17) Takai, K.; Hotta, Y.; Ohsima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.

(18) In this reaction, the starting material **23** could not be recovered and unidentified more polar compounds were simultaneously produced. The olefination of **23** by reaction with Wittig reagent ($Ph_3P^+CH_3Br^-$/*t*-BuOK, toluene, 100 °C) or Tebbe reagent (THF, −45 °C → rt) gave none of the desired olefination product **24** and resulted in almost complete decomposition of **23**. Peterson reaction of **23** using $LiCH_2TMS$ in THF at −78 °C → rt resulted in complete recovery of the starting material.

(19) It is reported that the *exo*-olefin moiety present in this type of decalin system is unstable under acidic conditions (e.g., *p*-TsOH, $CHCl_3$, rt) and easily isomerizes to the corresponding *endo*-olefin, see: Piers, E.; Breau, M. L.; Han, Y.; Plourde, G. L.; Yeh, W.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 963.

(20) (a) Bartlett, P. A.; Johnson, W. S.*Tetrahedron Lett*. **1970**, 4459. (b) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem*. **1972**, *25*, 1719. (c) Welch, S. C.; Pao, A. S. C. P. *Tetrahedron Lett*. **1977**, 505. (d) Aristoff, P. A.; Harrison, A. W.; Huber, A. M. *Tetrahedron Lett*. **1984**, *25*, 3955. (e) Taishi, T.; Takechi, S.; Mori, S. *Tetrahedron Lett*. **1998**, *39*, 4347.

(21) In this reaction, disappearance of the starting material **24** could be ascertained by TLC analysis, while unidentified decomposition products of **24** and/or **2** were generated along with **2**.

(22) The structure of the 8-*O*-methyl regioisomer **2** was proven by NOESY experiment in the 500 MHz ^1H NMR spectrum; thus, clear NOE interactions between the signals due to C-8 methoxy protons (δ 4.03) and C-9 aromatic proton (δ 7.43) were observed.