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Synthesis of Various Model Compounds for the Central Tricyclic Ring System of Popolophuanone E

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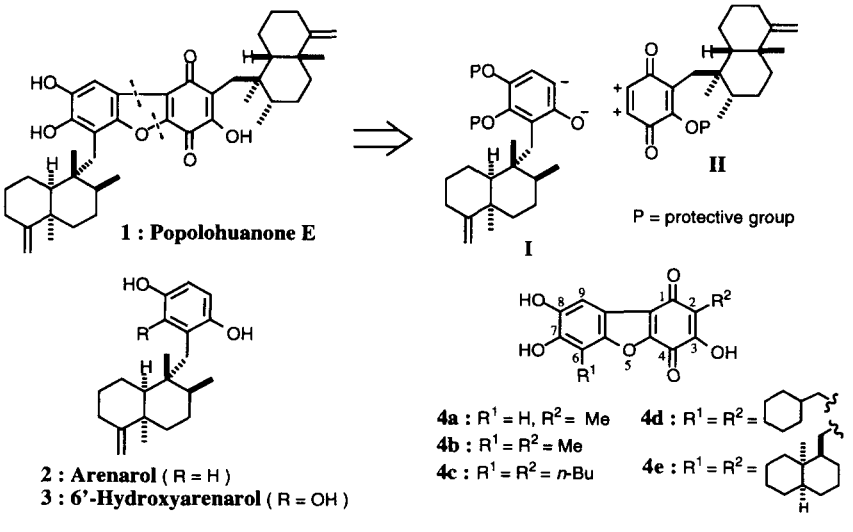
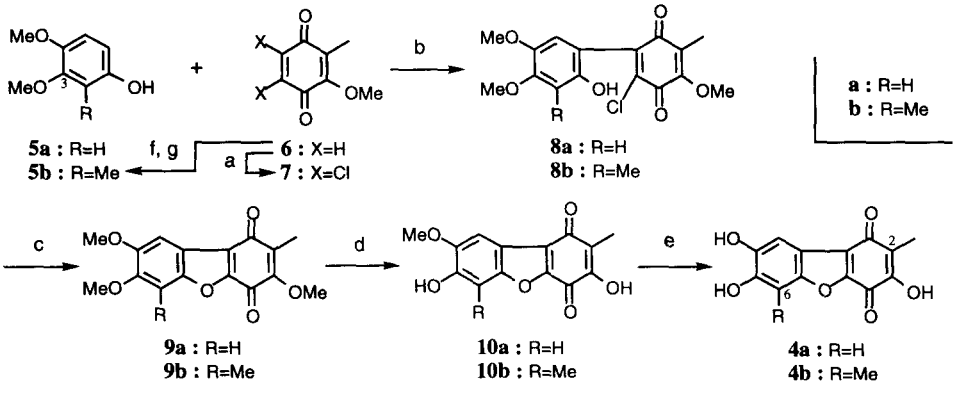
Abstract: *An efficient synthesis of various model compounds* ***4a-e*** *for the tricyclic core of popolophuanone E (**1**), a novel marine natural product, was accomplished ; the method features highly regioselective annulation of the phenols* ***5a-e*** *with the 2,3-dichloro-1,4-benzoquinones* ***7***, ***7c-e***. *Preliminary studies definitely demonstrated the feasibility of our designed synthetic strategy for* ***1*** *(the phenolic subunit* ***I*** *+ the quinone subunit* ***II*** *→* ***1*** *).* Copyright © 1996 Elsevier Science Ltd

Popolophuanone E (**1**) isolated from the Pohnpei marine sponge *Dysidea* sp. by Scheuer *et al.* in 1993, is a potent inhibitor of topoisomerase-II and exhibits a highly selective cytotoxicity against human non-small cell lung cancer cells.[2] The gross structure of **1** was revealed by means of extensive spectroscopic studies to have a unique 3,7,8-trihydroxydibenzofuran-1,4-dione nucleus which possesses two identical *cis*-fused decalin moieties the same as in arenarol (**2**).[2-4] Scheuer *et al.* proposed that **1** might be produced *in vivo* by oxidative dimerization of the as-yet-unreported 6'-hydroxyarenarol (**3**).[2,5] Its remarkable biological properties and unique structural features make **1** an exceptionally intriguing and timely target for total synthesis. We embarked on a project directed at the total synthesis of optically active **1** and its congeners with the aim of exploring the structure-activity relationships. Our synthetic strategy for **1** was designed as shown in **Scheme 1**, which features the biogenetic-type annulation of the phenolic subunit **I** with the quinone subunit **II** to regioselectively

Scheme 1. Synthetic Strategy for Popolophuanone E (**1**) and Structures of Its Related Compounds



Scheme 2. Synthesis of the Model Compounds **4a - b**



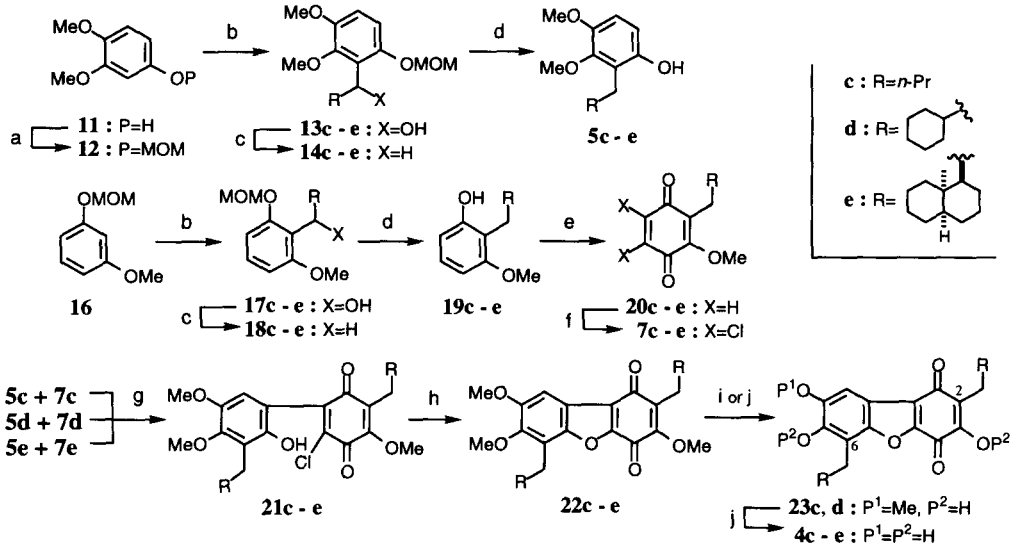
reagents and conditions: a) $MgCl_2$, conc HCl, 30% H_2O_2, 0°C, 66% b) NaH, THF, -78→-35°C, 67% for **8a**, 73% for **8b** c) Amberlite® IRA-900, $CHCl_3$, 0°C, 72% for **9a**, 83% for **9b** d) $AlCl_3$, CH_2Cl_2, reflux, 74% for **10a**, 89% for **10b** e) BBr_3, CH_2Cl_2, reflux, 49% for **4a**, 52% for **4b** f) H_2, 10%Pd-C, DMF, rt g) NaH, Me_2SO_4, -60°C→rt, 42% (2 steps)

construct the 3,7,8-trihydroxydibenzofuran-1,4-dione skeleton representing the tricyclic core of **1** as the key step. We wish to report here an efficient synthesis of 2-substituted- and 2,6-disubstituted-3,7,8-trihydroxydibenzofuran-1,4-dione derivatives **4a-e**[6] as model compounds for **1**, demonstrating the feasibility of our designed synthetic strategy.

At first, we pursued the synthesis of the model compound **4a** as shown in **Scheme 2**. In our preliminary studies, the known 2-methoxy-3-methyl-1,4-benzoquinone (**6**)[7] was first employed as **II** for the annulation with commercially available 3,4-dimethoxyphenol (**5a**) corresponding to **I**. However, neither the coupling products nor the cyclization products were found in the reaction mixture probably due to the poor electrophilicity of **6**. After experimentation, the 2,3-dichloro-1,4-benzoquinone **7** was found to behave as **II**. This compound **7**, mp 107-111°C, was readily prepared from **6** in one step by dichlorination.[8] The crucial regioselective annulation of **5a** with **7** to construct the requisite dibenzofuran-1,4-dione **9a** turned out to be effected by a two-step sequence.[9] Thus, the initial coupling reaction of **5a** with **7** in the presence of sodium hydride in tetrahydrofuran at -78°C followed by warming to -35°C proceeded smoothly to afford the *C*-substituted product **8a**,[10] mp 110-111°C, as a single regioisomer in 67% yield. The structure of **8a** was unambiguously established as depicted by its X-ray diffraction analysis.[11] Subsequent ring closure was carried out by exposure of **8a** to Amberlite® IRA-900 (OH^- form)[12] in chloroform at 0°C, leading to formation of **9a**, mp 217-218°C(dec), in 72% yield. The final phase remaining to complete the synthesis of **4a** was the full deprotection of the three methyl groups in **9a**.[13] Treatment of **9a** with aluminum chloride in refluxing dichloromethane afforded monomethyl ether **10a**, mp 212-215°C(dec), which was further allowed to react with boron tribromide in refluxing dichloromethane, giving rise to **4a**,[14] mp >300°C.

With completion of the synthesis of **4a**, the explored synthetic scheme was next applied to the synthesis of various model compounds **4b-e** possessing two identical methyl, *n*-butyl, cyclohexymethyl, and *cis*-decalin-1-ylmethyl groups at the C-2 and C-6 positions, respectively (**Schemes 2** and **3**). Towards this end, preparation of the phenols **5b-e** and the 2,3-dichloro-1,4-benzoquinones **7c-e** was first attempted. Hydrogenation of the benzoquinone **6** followed by monomethylation furnished **5b**, mp 105-106°C. The other phenols **5c-e** were accessible from commercially available 3,4-dimethoxyphenol (**11**) *via* a four-step sequence

Scheme 3. Synthesis of the Model Compounds **4c - e**



reagents and conditions: a) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 90% for **19**, 83% for **25** b) *t*-BuLi, hexane, 0°C; RCHO (**c** series: butyraldehyde, **d** series: cyclohexanecarbaldehyde, **e** series: (4a*R*, 8a*R*)-1-formyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-8a-methyl-naphthalene), 0°C, 44% for **13c**, 41% for **13d**, 24% for **13e**, 62% for **17c**, 87% for **17d**, 74% for **17e** c) H_2, 10%Pd-C, MeOH, rt, 78% for **14c**, 49% for **14d**, 82% for **14e**, 92% for **18c**, 91% for **18d**, 81% for **18e** d) conc HCl, MeOH, rt, 100% for **5c**, 86% for **5d**, 100% for **5e**, 100% for **19c**, 92% for **19b**, 93% for **19e** e) salcomine, O_2, DMF, rt, 67% for **20c**, 73% for **20d**, 73% for **20e** f) $SOCl_2$, pyridine, benzene, reflux, 57% for **7c**, 62% for **7d**, 62% for **7e** g) NaH, THF, -78→-35°C, 98% for **21c**, 85% for **21d** ,94% for **21e** h) Amberlite® IRA-900, $CHCl_3$, 0°C, 99% for **22c**, 88% for **22d**, 82% for **22e** i) $AlCl_3$, CH_2Cl_2, reflux, 69% for **23c**, 70% for **23d** j) BBr_3, CH_2Cl_2, reflux, 75% for **4c**, 53% for **4d**, 77% for **4e** (from **22e**)

involving protection of **11** as its methoxymethyl (MOM) ether, coupling reaction[15] of the aryl lithium *in situ* generated from **12** with various types of the aldehydes,[16] reductive removal of the secondary hydroxy group in **13c-e**, and final deprotection of the MOM group in **14c-e**. On the other hand, the 2,3-dichloro-1,4-benzoquinones **7c-e** were prepared in five steps from the known 3-methoxy-1-(methoxymethoxy)benzene (**16**).[15] Thus, **16** was converted to the phenols **19c-e** *via* alcohols **17c-e** and MOM ethers **18c-e** by a reaction sequence similar to that described for the preparation of **5c-e** from **12**. Further conversion of **19c-e** to **7c-e** was carried out by sequential oxidation with salcomine[17] and dichlorination[18] of the resulting 1,4-benzoquinones **20c-e**.

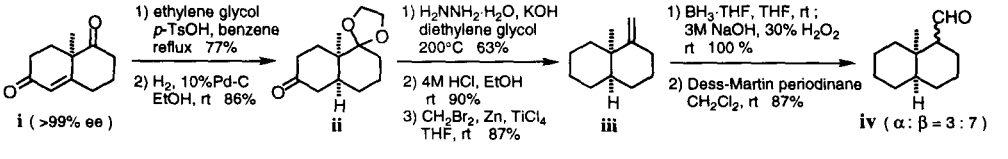
With the requisite phenols **5b-e** and 2,3-dichloro-1,4-benzoquinones **7**, **7c-e** in hand, we next focused our attention on construction of the dibenzofuran-1,4-diones **9b** and **22c-e** (**Schemes 2** and **3**). By employing a reaction sequence similar to that described for the preparation of **9a** from **5a** and **7**, the requisite dibenzofuran-1,4-diones **9b**, mp 182-183.5°C, and **22c-e** (**22c**: mp 101-103°C, **22d**: mp 133-135°C, **22e**: mp 251-253.5°C) were prepared from **5b-e** and **7**, **7c-e** in good yields (74-97%, 2 steps) *via* the coupling products **8b** and **21c-e**. It is noteworthy that the entire crucial two-step annulation (**5b+7→8b→9b**, **5c+7c→21c→22c**, **5d+7d→21d→22d**, and **5e+7e→21e→22e**) took place with a high regioselectivity similar to that of **5a** with **7** (**5a+7→8a→9a**). Complete removal of the three methlyl groups in **9b** and **22c,d** according to the same procedure as described for **9a** afforded the requisite model compounds **4b-d**[14] (**4b**: mp >300°C, **4c**: mp 258-262°C(dec), **4d**: mp 286-289°C) *via* monomethyl ethers **10b**, mp 262-266°C(dec),

and **23c,d** (**23c**: mp 224-226°C, **23d**: mp 242-244.5°C(dec)). In the case of **22e**, full deprotection was effected upon treatment with boron tribromide in refluxing dichloromethane, directly providing the model compound **4e**,[14] mp >300°C, in good yield.

In summary, we have succeeded in developing an efficient synthetic pathway to various model compounds **4a-e** for the 3,7,8-trihydroxydibenzofuran-1,4-dione system of **1**.[19] The key feature of the synthesis consists of highly regioselective annulation of the phenols **5a-e** with the 2,3-dichloro-1,4-benzoquinones **7**, **7c-e** to construct the dibenzofuran-1,4-dione systems **9a-b** and **22c-e** representing the tricyclic core of **1**. Our successful synthesis of **4a-e** obviously suggests that the total synthesis of **1** would be accomplished by employing the proposed synthetic strategy (*vide supra*). Studies on the total synthesis of optically active **1** are in progress and will be reported shortly.

References and Notes:

1. Visiting scientist from Research Laboratories, Sumitomo Pharmaceuticals Co. Ltd.
2. Carney, J. R., Scheuer, P. J., *Tetrahedron Lett.*, **1993**, *34*, 3727-3730.
3. Arenarol (**2**) was also isolated from the same Pohnpei sponge *Dysidea* species together with **1**.[2]
4. Quite recently, Wiemer *et al.* reported the first total synthesis of racemic **2**, see, Watson, A. T., Park, K., Wiemer, D. F., Scott, W. J., *J. Org. Chem.*, **1995**, *60*, 5102-5106.
5. 6'-Hydroxyarenarol (**3**) has not been isolated to date because this putative compound seems to be unusually unstable and/or prone to oxidation.[2]
6. To our best knowledge, there have been no reports on the synthesis of these compounds.
7. Rashid, A., Read, G., *J. Chem. Soc. (C)*, **1967**, 1323-1325.
8. Lübbecke, H., Boldt, P., *Tetrahedron*, **1978**, *34*, 1577-1579.
9. In order to directly obtain the requisite cyclization product **9a**, the annulation of **5a** with **7** was examined under a variety of reaction conditions. However, only the coupling product **8a** was produced as an isolable product instead of **9a**.
10. The electron-donating methoxy group present at the C-3 position in **5a** plays an important role in this coupling reaction to afford the *C*-substituted product **8a**. If 4-methoxyphenol was employed for the coupling reaction with **7** instead of **5a**, the corresponding *O*-substituted product was produced as a single isomer in 48% yield.
11. To be published in a separate paper.
12. When **8a** was treated with other bases such as LiHMDS, NaH, KH, Et_3N, pyridine, DBU, K_2CO_3, Cs_2CO_3, etc., **9a** was generated in poor yields (< 20%).
13. A number of attempts to achieve the full deprotection of **9a** in one step to complete the synthesis of **4a** resulted in failure.
14. The ^{13}C-NMR spectrum(spectra) of this(these) compound(s) definitely established the annulation pattern(s) 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**.[2]
15. Winkle, M. R., Ronald, R. C., *J. Org. Chem.*, **1982**, *47*, 2101-2108.
16. The *cis*-fused decalin aldehyde **iv** was prepared as an inseparable mixture of epimers from the optically pure (–)-Wieland-Miescher ketone **i** as shown below. The epimers could be readily separated after the coupling with the aromatic portion **12** or **16**. The conversion of **i** to the *cis*-fused decalin **ii** was carried out according to the reported procedures, see, a) Corey, E. J., Ohno, M., Mitra, R. B., Vatakencherry, P. A., *J. Am. Chem. Soc.*, **1964**, *86*, 478-485. b) McMurry, J. E., *ibid.*, **1968**, *90*, 6821-6825.



17. Wakamatsu, T., Nishi, T., Ohnuma, T., Ban, Y., *Syn. Commun.*, **1984**, *14*, 1167-1173.
18. Shi, S., Katz, T. J., Yang, B. V., Liu, L., *J. Org. Chem.*, **1995**, *60*, 1285-1297.
19. *In vitro* cytotoxicity of **4a-e** as well as their synthetic intermediates (**8a,b**, **9a,b**, **10a,b**, **21c-e**, **22c-e**, and **23c,d**) against murine leukemia cell (P388), human leukemia cells (CEM and HSB2), and human non-small cell lung cancer cells (A549 and QG56) will be reported in a full account along with their inhibitory activity against topoisomerase-II.

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