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Ultrasound-Promoted Synthesis of Substituted Phenanthrene-1,4-quinones; The Structure of Plectranthon D

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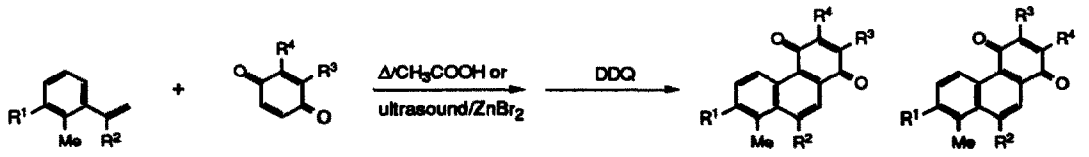
Abstract: *A series of tanshinone-type diterpenoids was prepared by ultrasound-promoted and Lewis acid catalyzed, highly regioselective cycloadditions of styrenes with substituted 1,4-benzoquinones as the key step.*

During phytochemical investigations on abietanoid diterpenes from *Coleus*- and *Plectranthus*-species (*Labiatae*) we isolated a series of substituted phenanthrene-1,4-quinones, plectranthons A-D[1,2]. Synthesis by photocyclization of the appropriately substituted stilbenes confirmed the structures of the plectranthons A, B, and C, whereas plectranthon D was shown to have been assigned erroneously as 3-hydroxy-7,8,10-trimethyl-2-(2-propenyl)phenanthrene-1,4-dione[3,4]. As a consequence, the natural compound D was tentatively formulated as the 7,8,9-trimethyl isomer **8**, but it could not be prepared by the above route[3].

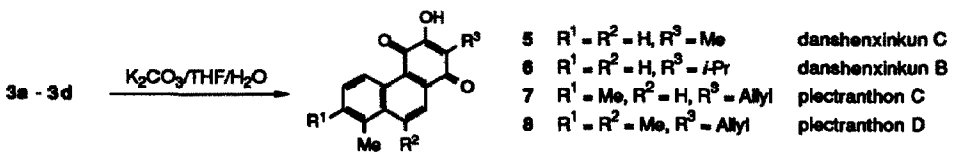
Recent advances in high-pressure[5,6] and ultrasound-promoted[6] Diels-Alder reactions between 1,2-or 1,4-benzoquinones and aliphatic dienes prompted us to study comparable cycloadditions using substituted styrenes **1** as the diene components. Besides establishing that the structure of plectranthon D was **8**, the method was intended to provide a simple, general access to phenanthrene-quinonoid tanshinone-type (nor)diterpenoids, which continue to be of current interest[7].

Refluxing 2-methoxy-1,4-benzoquinones **2**[8] with an excess of the styrenes **1**[8] (3-5 eq.) in AcOH or sonication[9] in the presence of $ZnBr_2$, followed by complete dehydrogenation of the tetrahydro cycloadducts and the dihydro intermediates with DDQ in toluene and purification by chromatography yielded the compounds **3a-d** and **4a-d**.



1a $R^1 = R^2 = H$ **2a** $R^3 = Me, R^4 = OMe$
1b $R^1 = Me, R^2 = H$ **2b** $R^3 = i\text{-}Pr, R^4 = OMe$
1c $R^1 = R^2 = Me$ **2c** $R^3 = Allyl, R^4 = OMe$

3a/4a $R^1 = R^2 = H, R^3 = Me, R^4 = OMe$
3b/4b $R^1 = R^2 = H, R^3 = i\text{-}Pr, R^4 = OMe$
3c/4c $R^1 = Me, R^2 = H, R^3 = Allyl, R^4 = OMe$
3d/4d $R^1 = R^2 = Me, R^3 = Allyl, R^4 = OMe$



5 $R^1 = R^2 = H, R^3 = Me$ danshenxinkun C
6 $R^1 = R^2 = H, R^3 = i\text{-}Pr$ danshenxinkun B
7 $R^1 = Me, R^2 = H, R^3 = Allyl$ plectranthon C
8 $R^1 = R^2 = Me, R^3 = Allyl$ plectranthon D

After deprotection of the 3-hydroxy group, the danshenxinkuns[10] B (6), C (5), and plectranthons C (7) and D (8) were obtained. All of the physical data[11] of the natural products were fully consistent with those reported[1,3,10], hence confirming that the structure of plectranthon D was indeed 8.

Compared with thermal reactions, the ultrasound-promoted cycloadditions effected improved yields and high regioselectivities, favouring the natural isomer. Selected results[12] from our studies are summarized in the Table.

TABLE

	Styrene	Quinone	Cycloadducts	Yield (%)[a]	Regioisomers[b]
thermal ultrasound	**1a**	**2a**	**3a/4a**	-[c] 17	- 5:1
thermal ultrasound	**1a**	**2b**	**3b/4b**	6.5 26	2:1 100:0
thermal ultrasound	**1b**	**2c**	**3c/4c**	6 28	7:3 100:0
thermal ultrasound	**1c**	**2c**	**3d/4d**	<1 5	2:1 100:0

[a] % based on the quinone; crystalline products, after dehydrogenation with DDQ and chromatography.
[b] Ratio determined by HPLC and ^{1}H-NMR. [c] Not applicable due to sublimation of **2a**.

Although the reaction conditions were optimized for each experiment, the chemical yields are far from those expected. When using aprotic solvents, either no reaction (benzene, toluene) or decomposition (higher boiling solvents) was observed under thermal conditions, whereas the role of the solvent in ultrasound-promoted reactions remains unclear (see also ref.[6e]). Lewis acid catalysis in thermal reactions resulted in decomposition, but it was shown to be indispensable in the ultrasound-promoted reactions. Moreover, only the unfavourable ratio of **1** and **2** (the quinone partially acting as dehydrogenating agent) permitted a significant reaction[13]. This fact is probably due to the pronounced instability of the dienophiles **2**.

The reluctance of the reaction **1c** + **2c** → **3d/4d** can be explained by the lack of coplanarity between the involved frontier orbitals, which is a prerequisite. Theoretical considerations[12b] showed the rotational barrier to be >60kJ/mol in **1c**[14], a fact which is corroborated by the UV-spectrum of **1c**, in which the characteristic styrene absorption at *ca.* 250 nm (α-band) is absent. Hence, the preferred conformation adopts a perpendicular arrangement of the exocyclic π-orbital relative to the aromatic system. Additionally, the thermodynamic equilibria for this reaction have been calculated to be highly unfavourable[14].

In summary, we have described a simple, direct route to highly substituted phenanthrene-1,4-quinones which proceeds with excellent regioselectivity. Pure plectranthon D could be prepared for the first time.

Acknowledgement. We thank the Swiss National Foundation for financial support.

References and notes:

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2. Natural plectranthons C and D could only be isolated as an inseparable mixture (*ca.* 3:1) and their structures were assigned according to ^{1}H-NMR data.
3. Kaliakoudas, D.; Eugster, C.H.; Rüedi, P. *Helv. Chim. Acta* **1990**, *73*, 48.
4. The straightforward Diels-Alder appraoch was expected to give both low yields and regioselectivity; see *e.g.*: (a) Lora-Tamayo, M. *Tetrahedron* **1958**, *4*, 17. (b) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 563. The problem was discussed again recently: Engler, Th. A.; Letavic, M.A.; Combrink, K.D.; Takusagawa, F. *J. Org. Chem.* **1990**, *55*, 5810.
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6. (a) Lee, J. Snyder, J.K. *J. Am. Chem. Soc.* **1989**, *111*, 1522. (b) Lee, J.; Snyder, J.K. *J. Org. Chem.* **1990**, *55*, 4995. (c) Haiza, M.; Lee, J.; Snyder, J.K. *J. Org. Chem.* **1990**, *55*, 5008. (d) Lee, J.; Mei, H.S.; Snyder, J.K. *J. Org. Chem.* **1990**, *55*, 5013. (e) Lee, J.; Li, J.-H.; Oya, S. Snyder, J.K. *J. Org. Chem.* **1992**, *55*, 5301.
7. For an excellent overview concerning the high medical and chemical significance of these constituents of the Chinese traditional drug *"DAN SHEN"* (*Salvia miltiorrhiza*, Bunge) see: Chang, H.M.; Cheng, K.P.; Choang, T.F.; Chow, H.F.; Chui,K.Y.; Hon, P.M.; Tan, F.W.L.; Yang, Y.; Zhong, Z.P.; Lee, C.M.; Sham, H.L.; Chan, C.F.; Cui, Y.X.; Wong, H.C. *J. Org. Chem.* **1990**, *55*, 3537.
8. Preparation of the starting materials: **1c** from 2,3-dimethylbenzoic acid *via* 2-(2,3-dimethylphenyl)-2-propanol and dehydration. EIMS m/z=146 $[M]^+$, M=$C_{11}H_{14}$, 131 $[M\text{-}Me]^+$; UV (hexane) λ 199 (ε=13,800); ^{1}H-NMR (300MHz, $CDCl_3$) δ 2.05 (3H,dd, ^4J=1.5, <1Hz), 2.24, 2.31 (each 3H, s), 4.85, 5.20 (each 1H, dq, ^2J=2.5, ^4J=1.5Hz), 6.99 (1H, t, ^3J=4.5Hz), 7.09 (2H, br.d, ^3J=4.5Hz). **2a** from 2,6-dimethoxytoluene, partial ether cleavage with NaSEt/DMF and oxidation with $(KSO_3)_2NO$. **2a** according to ref.[5]. **2c** from 1,3-dimethoxybenzene *via* 1,3-dimethoxy-2-(2-propenyl)benzene[3], then analogous to **2a**. EIMS m/z=180 $[M+2]^+$, 178 $[M]^+$, M=$C_{10}H_{10}O_3$; ^{1}H-NMR (300MHz, $CDCl_3$) δ 3.20 (2H, dt, ^3J=6.5, ^4J=1.5Hz), 4.04 (3H, s), 5.03 (1H, dq, ^3J=10, ^2J=^4J=1.5Hz), 5.08 (1H, dq, ^3J=17, ^2J=^4J=1.5Hz), 5.91 (1H, ddt, ^3J=17, 10, 6.5Hz), 6.65, 6.69 (each 1H, AB system, ^3J=10Hz).
9. In a representative experiment the quinone (40mg) was sonicated (20kHz, 250W; Heat Systems Inc., N.Y., Ultrasonic Processor W-375; Cup Horn, mod. 413A) at r.t. in the presence of $ZnBr_2$ (20mg) and abs. EtOH (1-2ml). All of our attempts to reproduce thermal reactions according to literature procedures were unsuccessful, whereas the ultrasound protocol[6d] was easily reproducible in every respect.
10. Isolation: Fang, C.; Chang, P.; Hsu, T. *Acta Chimica Sinica* **1976**, *34*, 197. Synthesis: Danheiser, R.L.; Casebier, D.S.; Loebach, J.L. *Tetrahedron Lett.* **1992**, *33*, 1149. No spectroscopic data of **6** have been reported previously. The names of compounds **5** and **6** are given here according to the correct translation of the Chinese *"HAN YU PIN"* (*Dan Shen* quinones); unfortunately, several misspellings are found in the current literature, sometimes inconsistent within the same paper, *e.g.*: (a) Ikeshiro,Y.; Hashimoto, I.; Iwamoto, Y.; Mase, I.; Tomita, Y. *Phytochemistry* **1991**, *30*, 2791. (b) Luo, H.; Wu, B.; Yong, Z.; Ji, J. *Acta Pharm. Sinica* **1985**, *20*, 542.

11. All compounds were characterized by m.pts., UV/VIS-, IR-, ^{1}H-NMR, ^{13}C-NMR, and MS. **Selected Spectroscopic Data**: 3-Methoxy-7,8,9-trimethyl-2-(2-propenyl)phenanthrene-1,4-dione (**3d**): m.pt.=136-138° (Et_2O); ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.49, 2.74, 2.97 (each 3H, s), 3.34 (2H, dt, ^{3}J=6.5, ^{4}J=1.5Hz), 4.13 (3H, s), 5.04 (1H, dq, ^{3}J=8.5, ^{2}J=^{4}J=1.5Hz), 5.15 (1H, dq, ^{3}J=17, ^{2}J=^{4}J=1.5Hz), 5.88 (1H, m), 7.47 (1H, d, ^{3}J=9Hz), 7.95 (1H, s), 9.19 (1H, d, ^{3}J=9Hz). 2-Methoxy-7,8,9-trimethyl-3-(2-propenyl)phenanthrene-1,4-dione (**4d**): ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.48, 2.73, 2.97 (each 3H, s), 3.39 (2H, dt, ^{3}J=6.5, ^{4}J=1.5Hz), 4.11 (3H, s), 5.06 (1H, dq, ^{3}J=8.5, ^{2}J=^{4}J=1.5Hz), 5.17 (1H, dq, ^{3}J=17, ^{2}J=^{4}J=1.5Hz), 5.92 (1H, m), 7.45 (1H, d, ^{3}J=9Hz), 7.91 (1H, s), 9.31 (1H, d, ^{3}J=9Hz). 3-Hydroxy-2,8,-dimethylphenanthrene-1,4-dione (*danshenxinkun C*, **5**): m.pt. 216-218° (Et_2O); UV/VIS (Et_2O) λ (ε) 213 (15,850), 245 (13,500), 253 (14,100), 280sh (2,000), 289 (7,800), 330 (2,000), 380 (650), 440 (320). ^{1}H-NMR (300MHz, $CDCl_3$) δ 2.11, 2.74 (each 3H, s), 7.46 (1H, d, ^{3}J=7Hz), 7.50 (1H, s, D_2O exch.), 7.60 (1H, dd, ^{3}J=9, 7Hz), 8.28, 8.42 (each 1H, AB-system, ^{3}J=8.8Hz), 9.46 (1H, d, ^{3}J=9Hz). 3-Hydroxy-7,8,9-trimethyl-2-(2-propenyl)phenanthrene-1,4-dione (*plectranthon D*, **8**): m.pt.=175-177° (Et_2O); CIMS m/z=307 $[M+1]^+$, M=$C_{20}H_{18}O_3$; ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.49 (3H, s), 2.74 (3H, s), 2.99 (3H, s), 3.36 (2H, dt, ^{3}J=6.5, ^{4}J=1.5Hz), 5.06 (1H, dq, ^{3}J=10, ^{2}J=^{4}J=1.5Hz), 5.19 (1H, dq, ^{3}J=17, ^{2}J=^{4}J=1.5Hz), 5.94 (1H, ddt, ^{3}J=17, 10, 6.5Hz), 7.51 (1H, d, ^{3}J=9Hz), 7.82 (1H, s, D_2O exch.), 8.03 (1H, s), 9.41 (1H, d, ^{3}J=9Hz); ^{13}C-NMR (150MHz, $CDCl_3$) δ 20.5, 21.6, 27.7 (each q), 29.7 (t), 115.5 (t), 116.1, 117.8 (each d), 125,0 (s), 126.7 (d), 131.9 (s), 133.6 (d), 133.5, 134.1, 135.4, 136.8, 136.9, 138.0, 153.7, 183.2, 185.2 (each s).
12. Details of comparative studies concerning thermal, high-pressure and ultrasound-promoted cycloadditions of model compounds are described: (a) Zhang, Z. *PhD Thesis*, University of Zurich, 1993. (b) Flachsmann, F. *MSc Thesis*, University of Zurich 1993.
13. Considering that the tetrahydro adducts and the dihydro intermediates are completely dehydrogenated by the dienophile itself, the yield would not exceed 33% (based on 2); in fact, partial dehydrogenation by oxygen occurs.
14. (a) Dewar, M.J.S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (b) Thiel, W. *Program MNDO 91, version 3.3*. The following thermodynamic parameters resulted: ΔG^o = +68,4kJ/mol, $K^o = 1.0 \cdot 10^{-12}$; ΔG_{400K}= +93,2kJ/mol, $K_{400K} = 6.7 \cdot 10^{-13}$. (Compare the cycloaddition between butadiene and ethene: ΔG^o = -115.4kJ/mol, $K^o = 1.7 \cdot 10^{20}$). For details see ref.[12b].

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