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Hetero Diels–Alder trapping of 3-methylene-1,2,4-[3*H*]naphthalenetrione: an efficient protocol for the synthesis of α- and β-lapachone derivatives

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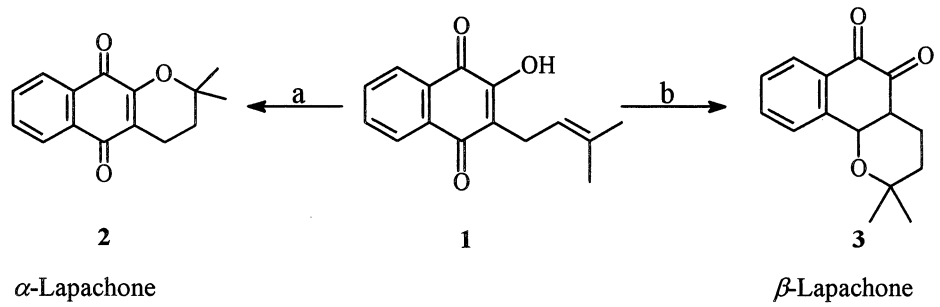
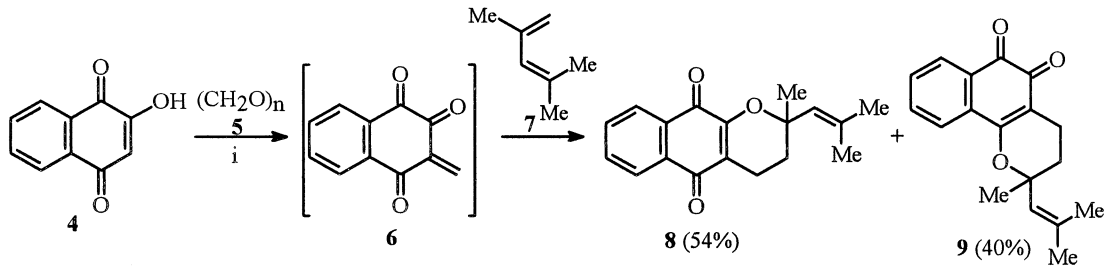
Abstract—3-Methylene-1,2,4-[3*H*]naphthalenetrione, generated by Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone with formaldehyde, undergoes facile hetero Diels–Alder reaction with various dienophiles affording derivatives of α- and β-lapachone. © 2001 Published by Elsevier Science Ltd.

Dihydronaphthopyrandiones comprise an important group of heterocyclic quinones. A number of these compounds exhibit a wide range of pharmacological activities.[1] For example, β-lapachone **3** induces apoptosis in human prostate cancer cells in vitro[2,3] and several of its derivatives are cytotoxic agents.[4,5] The common protocol for the synthesis of these pyran derivatives essentially rests on the acid-catalyzed cyclization of lapachol **1** and its derivatives[6] (Scheme 1) and the synthesis of the latter has been the subject of many investigations.[7]

As part of our research program focused on the cycloaddition reactions of quinonoid compounds,[8] we



Scheme 1. (a) HCl, 25°C, H_2O; (b) H_2SO_4, 25°C, H_2O.



Scheme 2. (i) Dioxane, 100°C, 6 h.

Keywords: Diels–Alder reactions; dienes; enol ethers; quinonoid compounds.
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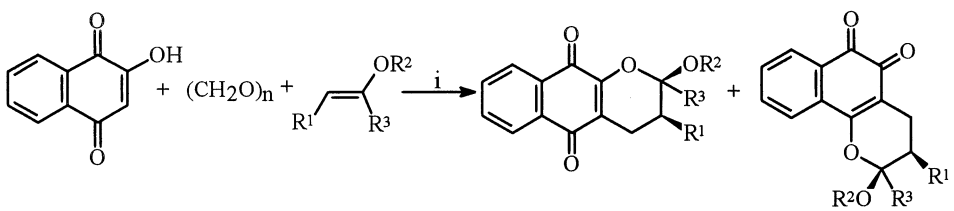
became interested in the construction of dihydronaphthopyrandiones (derivatives of α- and β-lapachone) by hetero Diels–Alder reactions of 3-methylene-1,2,4-[3*H*]naphthalenetrione, the quinone methide generated from 2-hydroxynaphthoquinone. To the best of our knowledge, there is no report of the generation and Diels–Alder reactions of this type of quinone methide. The preliminary results of our investigations are presented here.

Our studies commenced with the Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone and para-

Table 1. Cycloaddition of **6** with dienes

Entry	Diene	Time (h)	Product(s), (yield%)*
1	**10**	6	**11** (42%); 12 (23%)
2	**13**	6	**14** (78%)
3	**15**	6	**16** (30%)
4	**17**	3	**18** (90%)
5	**19**	6	**20** (30%); **21** (32%)

* Isolated yield; Reaction conditions: Dioxane, 100 °C.



4	5	22a-d	23a-d	24a-d
		22a, R^1 = Ph, R^2 = Me, R^3 = H	**23a** (75%)	**24a** (20%)
		22b, $R^1 = R^3$ = H, $R^2 = C_2H_5$	**23b** (50%)	**24b** (30%)
		22c, R^1 = H, $R^2 = R^3$ = Me	**23c** (60%)	nil
		22d, $R^1 = R^3$ = H, $R^2 = C_4H_9$	**23d** (50%)	nil

Scheme 3. (i) Dioxane, reflux, 4–9 h.

formaldehyde leading to the quinone methide **6** and its trapping in situ by 2,4-dimethyl-1,3-pentadiene **7**. The reaction proceeded smoothly to afford **8** and **9** in a total yield of 94% (Scheme 2).

The structure of the products was established by spectroscopic methods.[†,‡] Although the product distribution was found to vary from diene to diene, the reaction was found to be general. The results of these experiments are summarized in Table 1. It may be mentioned that the theoretical calculations performed using PC SPARTAN Graphical Interface Package for Molecular Mechanics and Molecular Models[9] are in accord with the observed reactivity pattern.

Subsequently, the hetero Diels–Alder reaction of **6** with enol ethers was investigated and the results are summarized in Scheme 3.

In conclusion, we have shown that the generation of a quinone methide from 2-hydroxynaphthoquinone and its hetero Diels–Alder reactions provide an efficient protocol for the one-pot synthesis of α- and β-lapachone derivatives. The strategy employed here appears to be amenable to the synthesis of a variety of pyranoquinone derivatives.

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[†] Experimental procedure and data for **8** and **9**: Treatment of **4** (174 mg, 1 mmol), **5** (240 mg, 8 mmol) and **7** (288 mg, 3 mmol) in dioxane under reflux conditions (6 h), followed by work-up with Na_2CO_3 solution and water, followed by chromatography, afforded the adduct **8** (152 mg, 54%) as a yellow solid and **9** (113 mg, 40%) as a red semi-solid. Data for **8**: IR (KBr) $\nu_{(max)}$: 1678, 1642, 1612, 1381, 1337, 1306, 1297, 1202, 1101, 959 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.08–8.04 (m, 2H), 7.68–7.65 (m, 2H), 5.10 (s, 1H), 2.72–2.62 (m, 1H), 2.55–2.44 (m, 1H), 2.05–1.97 (m, 1H), 1.81 (s, 3H), 1.76–1.70 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR: δ 184.11, 179.47, 154.39, 137.59, 133.60, 132.70, 132.14, 131.15, 126.70, 126.16, 125.90, 121.17, 79.47, 32.10, 27.15, 26.98, 18.86, 16.80; HRMS calcd for $C_{18}H_{18}O_3$: 282.1255. Found: 282.1246. Data for **9**: IR (neat) $\nu_{(max)}$: 1698, 1644, 1603, 1572, 1450, 1389, 1327, 1306, 1179, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, $J=7.3$ Hz, 1H), 7.82 (d, $J=7.6$ Hz, 1H), 7.63 (t, $J=7.3$ Hz, 1H), 7.49 (t, $J=7.3$ Hz, 1H), 5.21 (s, 1H), 2.63–2.58 (m, 1H), 2.53–2.47 (m, 1H), 2.04–2.01 (m, 1H), 1.88–1.85 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR: δ 179.64, 178.42, 161.68, 137.50, 134.65, 132.68, 130.52, 129.04, 128.76, 127.14, 123.91, 113.81, 80.69, 32.52, 31.66, 27.19, 26.97, 22.72; HRMS calcd for $C_{18}H_{18}O_3$: 282.1255. Found: 282.1257.

[‡] The other possible regioisomeric structure was discarded on the basis of ^1H NMR analysis. In the ^1H NMR spectrum of the possible regioisomeric structure, there will be three protons (two olefinic protons and one proton on the sp^3 carbon adjacent to the pyran oxygen) in the olefinic region (δ 6.00–4.50). However, the ^1H NMR spectrum of **8** and **9** showed only one proton in the region δ 7.00–3.00. The number of methylenic protons also will be different in the other regioisomer.

References

1. Thomson, R. H. *Naturally Occurring Quinones III, Recent Advances*; Chapman and Hall: London, 1987; pp. 609–633.
2. Planchon, S. M.; Wuerzberger, S.; Frydman, B.; Witiak, D. T.; Hutson, P.; Church, D. R.; Wilding, G.; Boothman, D. A. *Cancer Res.* **1995**, *55*, 3706.
3. Li, C. J.; Wang, C.; Pardee, A. B. *Cancer Res.* **1995**, *55*, 3712.
4. Frydman, B.; Marton, L. J.; Sun, J. S.; Neder, K.; Witiak, D. T.; Liu, A. A.; Wang, H.-M.; Mao, Y.; Wu, H.-Y.; Sanders, M. M.; Liu, L. F. *Cancer Res.* **1997**, *57*, 620.
5. Dolan, M. E.; Frydman, B.; Thompson, C. B. *Anti-Cancer Drugs* **1998**, *9*, 437.
6. Hooker, S. C. *J. Chem. Soc.* **1892**, *61*, 611–650.
7. (a) Schaffner-Sabba, K.; Schmidt-Ruppin, K. H.; Wehrli, N.; Schurch, A. R.; Wasley, J. W. *J. Med. Chem.* **1984**, *27*, 990 and references cited therein; (b) Sun, J. S.; Geiser, A. H.; Frydman, B. *Tetrahedron Lett.* **1998**, *39*, 8221.
8. (a) Nair, V.; Kumar, S. *Synlett* **1996**, 1143; (b) Nair, V.; Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 443; (c) Thomas, A.; Anilkumar, G.; Nair, V. *Tetrahedron* **1996**, *52*, 2481; (d) Nair, V.; Mathew, B. *Tetrahedron Lett.* **2000**, *41*, 6919; (e) Nair, V.; Maliakal, D.; Treesa, P. M.; Rath, N. P.; Eigendorf, G. K. *Synthesis* **2000**, 850.
9. AM1 calculations using PC SPARTAN Graphical Interface Package for Molecular Mechanics and Molecular Orbital Models by Wavefunction Inc. 18401, von Karman, suite 370, Irvine, CA, USA.