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Dehydrogenation by Air: Preparation of 1,3-Disubstituted-5,1-Dioxo-5,10-Dihydro-1H-Benzo[g] Isochromene Scaffold

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Abstract: Naphthaquinopyrans **5a-d, 10** and **12** have been converted to benzoisochromene **IIb** *via* base-promoted air oxidation. A mechanism is proposed to account for the observed results. Use of peroxide scavenger was found necessary for consistent yields. **IIb** proved to be a versatile scaffold for diversity expansion.

Herbarin and related classes, as defined by structure **I**, have been shown to exhibit interesting biological activities.[1,2] Comparatively, the 3,4-dehydro series **II** has received much less attention. In connection with our interest in quinone-based anticancer agents, **IIb** represents a novel template on which the introduction of various appendages shown by R_4 and R_5 for SAR study is expected. (**Figure 1**)

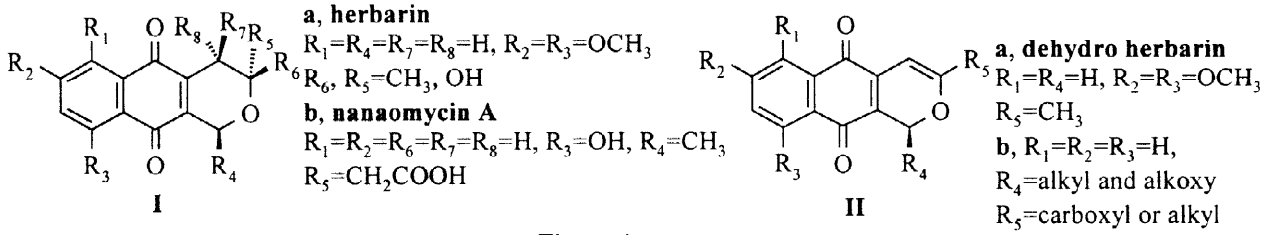
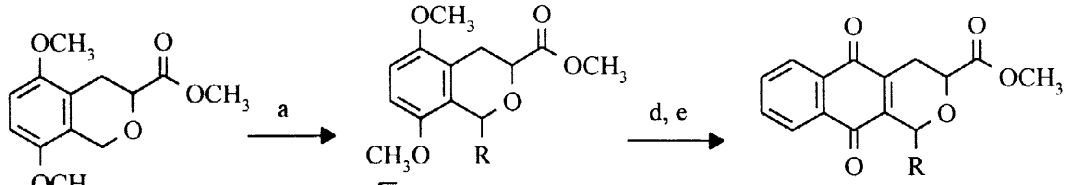


Figure 1

We envisaged that **IIb** could be oxidatively derived from its dihydro precursor **5** which should in turn be readily prepared from isochroman **1**[3] using conventional methods. As demonstrated in Scheme 1, several quinones (**5a-d**) carrying different R^4 have thus been efficiently prepared.



a, DDQ, methanol/CH_2Cl_2; b, allylsilane, $BF_3.Et_2O$; c, H_2, Pd/C; d, CAN/CH_3CN;
e,1-acetoxy-1,3-butadiene, then aromatization on SiO_2

Scheme 1

Numerous general dehydrogenation processes are available[5] but methods suitable for the conversion of **5** to **IIb** need to be carefully chosen. For example, DDQ has been used to oxidize an ester to its unsaturated analog,[6] but failed to effect any desired transformation in our system. Other common methods involving enolate entrapment by selenyl agents and subsequent oxidative cleavage would also appear problematic due to the existence of multiple reactive sites in the molecule.

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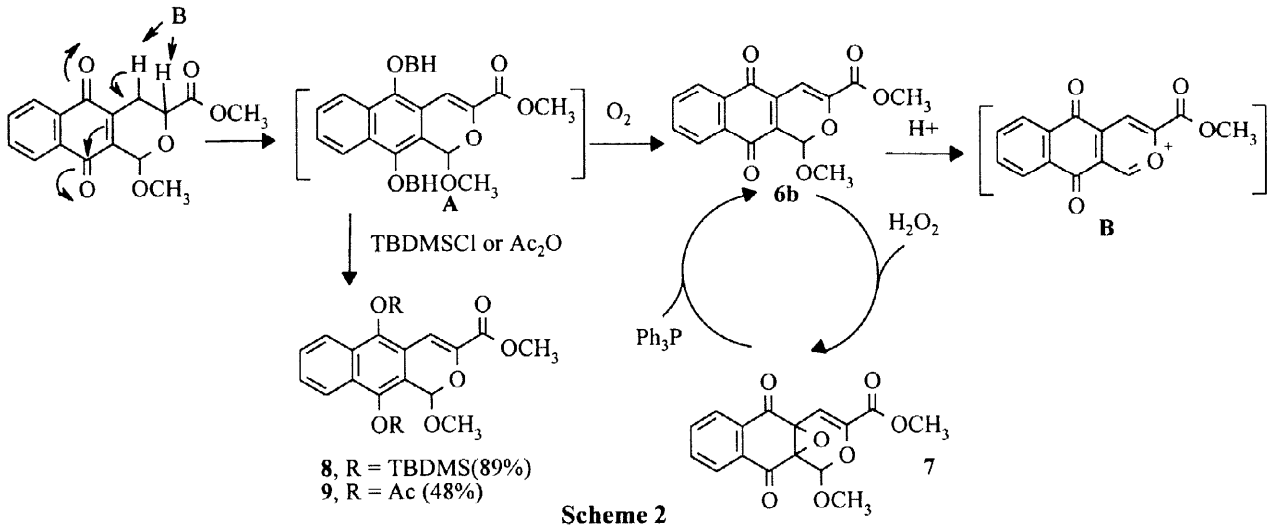
Here, we wish to report a simple yet highly effective method for the formation of **IIb** from **5** using only air under basic conditions.[7] The method was based on our initial observation that saponification of **5b** with sodium hydroxide resulted in partial formation of the 3,4-unsaturated acid. As the amount of unsaturated acid was greatly reduced under anaerobic conditions, it suggested that molecular oxygen played a major role in the oxidative transformation. We decided to look into the process more carefully and ultimately to develop conditions suitable for preparative purposes. Using **5b** as a standard framework, a rapid evaluation of bases and solvents was conducted. We found that amine bases such as triethyl amine or DABCO were superior to other bases such as sodium hydroxide or methoxide. The reaction was best run in solvent such as dichloromethane. As an example to show the effectiveness of the conditions, the desired product **6b** was obtained in up to 80% yield.

We soon realized, however, that the formation of **6b** even under our best conditions varied considerably from run to run. The product was accompanied by a major byproduct which was inseparable from **6b** and unstable to chromatographic conditions. Based on our hypothesis of the reaction pathway leading to the product, we proposed that intermediate **A** was formed initially. The air oxidation of **A** would take place to generate product **6b** with concomitant release of hydrogen peroxide. The byproduct epoxide **7** could then result from a further reaction of **6b** with hydrogen peroxide[8] and the proposed mechanism was supported by the experiments. In a study where the reaction was run in aerobic conditions, **6b** (soluble in dichloromethane) was formed efficiently, whereas under anaerobic conditions an insoluble material precipitated out and could be trapped as **8** and **9** with appropriate reagents. We also treated **6b** with hydrogen peroxide buffered by sodium bicarbonate and obtained an epoxide identical by ^{1}H NMR to **7** as observed in the air oxidation. Thus the identity of the byproduct from air oxidation was established. (**Scheme 2**)

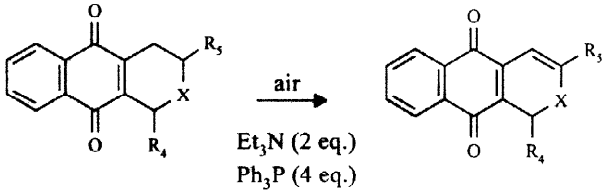


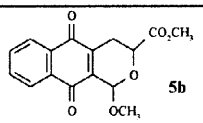
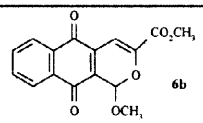
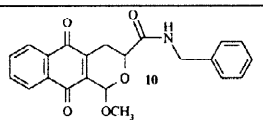
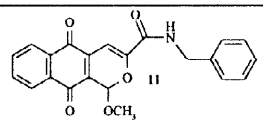
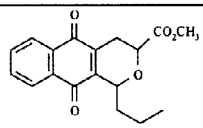
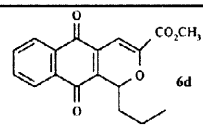
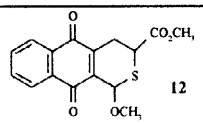
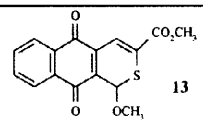
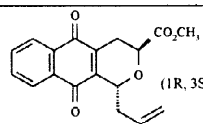
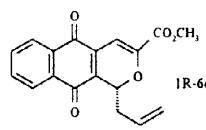
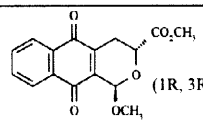
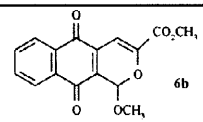
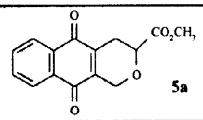
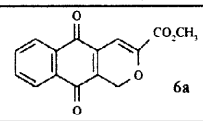
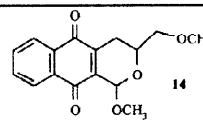
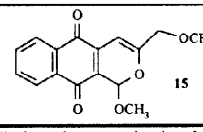
Scheme 2

Having defined the route in which the unwanted epoxide was formed, we included *triphenylphosphine* as an peroxide scavenger when the oxidation was conducted. We found that dehydrogenation then took place smoothly to produce the desired product in consistently good yields. The role of triphenylphosphine was not limited to just quenching the hydrogen peroxide generated *in situ*. We also observed that epoxide **7** could be converted back to **6** *even* at room temperature by triphenylphosphine. This observation was interesting that such a deoxygenation of a structurally similar epoxide lacking C3-C4 double bond required a much higher temperature.[9]

Typical procedure: A solution of **5b** in dichloromethane (0.1-0.05M), open to air through a drying tube, was stirred with triethylamine (2eq) and triphenylphosphine (4 eq) for 3 h (or longer) until the reaction was completed. Solvent was evaporated and the crude product was chromatographed (toluene/ethyl acetate) to give **6b** in 75% yield.

Table 1. Base-Catalyzed Dehydrogenation by Air



Entry	Reactant	Product	Yield[a]
1			75-80%
2			70%
3			70%
4			50-60%
5			75%
6			77%
7			75%[b](20%)
8			0%

a. Isolated yields; b. The yield was somewhat low (20%), but **6a** was obtained in better yield from **6b** (TFA/Et_3SiH).

As shown in **Table 1**, the oxidation conditions worked very well in systems carrying different function at either C1 or C3 position.(entries 1-3) The formation of the product was easily detected by the appearance of a bright yellow band on TLC. Interestingly, the thio compound **13** was also obtained from **12**[10] in good yield without oxidation occurring on sulfur atom. We have also studied the oxidation towards chiral templates such as (1R,3R)-**5b** ($[\alpha]_D$= -158.07, c=1.45, $CHCl_3$) and (1R, 3S)-**5c** ($[\alpha]_D$= -35.40, c=1.74, $CHCl_3$).[11] Oxidation proceeded smoothly with (1R, 3S)-**5c** to give 1R-**6c** which contained now only one stereogenic center and was optically active ($[\alpha]_D$= -200.00, c=0.36, $CHCl_3$). On the other hand, oxidation of (1R,3R)-**5b** resulted in complete racemization at C-1, as evidenced by rotation data ($[\alpha]_D$= +0.73, c=3, $CHCl_3$ as compared to the racemic compound **6b**, $[\alpha]_D$=+0.22, c = 0.93, $CHCl_3$) and ^1H NMR using $EU(fod)_3$ shifting agents (entry 6).

These results indicated that the momentary breakage of lactol methoxy at C-1, quite facile at the stage of **A**, might have been responsible for the observed racemization. In fact, the cleavage of glycosyl OMe of even quinone **6b** could be effected smoothly. Thus, the conversion of quinone **6b** to **6a** (but not **5b** to **5a**) was achieved cleanly using Et_3SiH in trifluoroacetic acid (entry 7), possibly *via* initial formation of benzoisochromenylium species **B**.[12] This was an example in which the reactive feature of **6b** at C-1 was advantageously captured, since direct oxidation of **5a** gave **6a** only in low yield. Finally, compound **14** carrying an electron-donating group at C-3 was subject to the standard conditions and found completely unreactive, confirming the crucial role played by C-3 electron-withdrawing group for the formation of the prerequisite intermediate **A**.(entry 8)

In conclusion, we have described a general approach starting from quinone **5** to benzoisochromene scaffold **IIb** *via* air oxidation protocol. Based on our mechanistic study, the use of triphenylphosphine was necessary to insure good yields. The procedure was simple yet suitable for large scale synthesis and could be tolerated by chiral templates with non-leaving group at C-1. The scaffold having simultaneously two functional handles proved suitable for diversity expansion. For example, **6b** have been hydrolyzed and effectively condensed with an array of amines or diamines *via* its acid chloride form.[13] On the other hand, the C-1 glycosyl linkage also displayed good potential for chemical modifications without affecting other functional groups in the molecule, as seen in entry 7. Further investigation of the chemistry related to this functional linkage is ongoing.

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References and Notes :

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11. These chiral templates were obtained from the respective chiral isochromans of **1** (resolved using Evan's auxiliary). The absolute configuration was determined by relating to the isochroman derived from commercially available chiral glycidol and 1,4-dimethoxyl benzene.
12. Formation of **B** type quinonoid cation was proposed previously : Aldersley, M. F. ; Dean, F. M. and Hamzah, S. *Tetrahedron Lett.* **1986**, *27*, 255-258.
13. Unpublished results.