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SYNTHESIS OF LONAPALENE

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Abstract: An efficient and practical synthesis of the antipsoriatic drug Lonapalene is reported. This involves the thermal rearrangement of 4-(4-chlorophenyl)-4-hydroxy-2,3-dimethoxycyclobutenone to 6-chloro-1,4-dihydroxy-2,3-dimethoxynaphthalene which was converted to Lonapalene upon treatment with acetic anhydride/pyridine.

Lonapalene, **6**, is a selective 5-lipoxygenase inhibitor which is currently in Phase II clinical trials for the treatment of psoriasis.[1,2] The two syntheses of this compound which have been reported suffer some shortcomings. One of these starts with readily available precursors (chloroprene and 1,4-benzoquinone) but involves an overall lengthy procedure.[2] The other is more efficient but utilizes 2,3-dimethoxy-1,4-benzoquinone, a compound which is not easily obtained. [3]

Reported in this Letter is a practical synthesis of Lonapalene initiating from dimethyl squarate **1** and 4-bromochlorobenzene, both of which are readily available (Scheme 1).[4] This synthesis is based upon the recent observation that 4-aryl-4-hydroxycyclobutenones rearrange to annelated hydroquinones upon thermolysis in refluxing p-xylene (138°).[5,6] Scheme 1 provides a summary of this method as it applies to the synthesis of Lonapalene, **6**, and illustrates the intermediacy of the vinylketene, **4**. Specifically, the lithium reagent **2** was generated at -78° in THF upon treatment of 4-bromochlorobenzene (1.03 g, 5.39 mmol) with butyllithium (5.44 mmol). This was then added to a THF solution containing 0.75 g (5.28 mmol) of dimethyl squarate. After 15 min. the reaction was quenched by pouring the reaction mixture into a separatory funnel containing 10 ml of 5% NH_4Cl and 20 ml of diethyl ether. After an aqueous wash and concentration, the resulting oil was purified by column chromatography on silica gel (hexane/ethyl acetate) to give **3** as a white crystalline solid in 55% yield (0.74 g): mp, 93-95°; IR (KBr, cm^{-1}) 3321, 1769, 1602; ^1H NMR ($CDCl_3$, ppm) 3.21 (s, 1H), 4.01 (s, 3H),

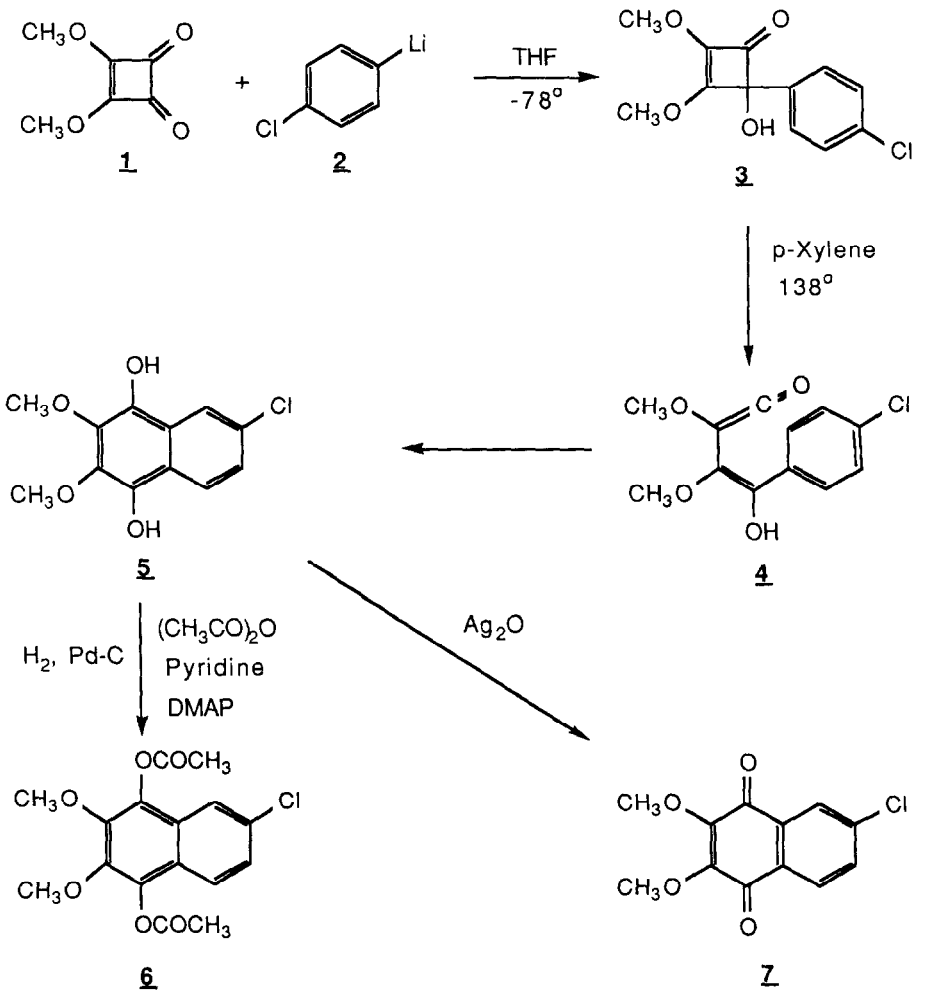
4.07 (s, 3H), 7.33 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7 Hz, 2H); Exact Mass Calcd. for $C_{12}H_{11}ClO_4$: 254.0346, found: 254.0327.

A sample of **3** was converted to the quinone **7** in 85% yield as outlined below. A p-xylene solution (20 ml) containing 156 mg (0.61 mmol) of **3** was refluxed (138°) under argon for 2 h. The solvent was removed and the residue was dissolved in benzene (20 ml). This solution was treated with solid K_2CO_3 (0.34g, 2.48 mmol) and Ag_2O (0.57g, 2.48 mmol) and stirred 1h. The reaction mixture was vacuum filtered through a bed of celite and rinsed with ether (40 ml). The filtrate was concentrated under reduced pressure which resulted in a yellow solid. Crystallization from ether afforded 132 mg (85%) of quinone **7** as yellow fluffy crystals: mp, 122-124°; lit.[2] mp, 125-126°; IR (KBr, cm-1) 1667, 1610; ^{1}H NMR ($CDCl_3$, ppm) 4.10 (s, 3H), 4.12 (s, 3H), 7.65 (dd, J=9.3 Hz, 2.1 Hz, 1H), 8.02 (m, 2H); Exact Mass Calcd. for $C_{12}H_9ClO_4$: 252.0189, found: 252.0183.

The synthesis of Lonapalene itself was accomplished without isolation of any of the intermediates. Specifically, the lithium reagent **2** was generated in the same manner as described above from 4-bromochlorobenzene (2.16 g, 11.3 mmol). This was then added to a solution containing 1.50 g (10.6 mmol) of dimethyl squarate **1**. The resulting crude cyclobutenone **3** was was dissolved in p-xylene (50 ml) and this solution was refluxed for 3 h. After cooling to ambient temperature the solution was placed under an atmosphere of hydrogen over a catalyst of Pd-C (10%, 0.27 g) for 3.5 h. These reduction conditions were employed to assure a maximum concentration of the hydroquinone **5**. Acetic anhydride (10.8 g, 106 mmol), pyridine (8.35 g, 106 mmol) and DMAP (0.13 g, 1.06 mmol) were added and stirred 10 h under a hydrogen atmosphere. After complete reaction, the reaction mixture was filtered and concentrated in vacuo. The residue was dissolved in diethyl ether (225 ml), washed with 1 M HCl (3 X 50 ml) and finally with brine. Following evaporation, the resulting semisolid was purified by flash chromatography (hexanes/ethyl acetate 7:1) followed by crystallization (ether/hexanes) to afford 1.84 g (52%) of pure Lonapalene **6**: mp, 87.5-89.5° (Lit[2] mp, 91-92°, Lit[3] mp, 83-85°); IR ($CDCl_3$) 1769 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.48 (s, 3H), 2.49 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 7.38 (dd, J=2.0, 8.9 Hz, 1H), 7.69 (d, 1H), 7.72 (d, 1H); Exact Mass Calcd. for $C_{16}H_{15}O_6Cl$: 338.0555, found: 338.0560.

In summary, we note that the synthesis of Lonapalene reported here can be accomplished on a reasonably large scale. Also, it is highly convergent and thus offers an attractive route to a variety of highly substituted annelated hydroquinones, some of which may be of further interest as possible antipsoriatic drugs. The only critical flaw in regards to the practicality of this synthesis concerns the current expense of squaric acid.

Scheme 1



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References and Notes

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4. Dimethyl squarate **1** was prepared from commercially available squaric acid. See, Cohn, S.; Cohen, S. G.; *J. Am. Chem. Soc.*, 1966, *88*, 1533. 4-Bromochlorobenzene is commercially available.

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