The Diels-Alder Reactions of Quinone Imine Ketals: A Synthesis of The Ergot Skeleton

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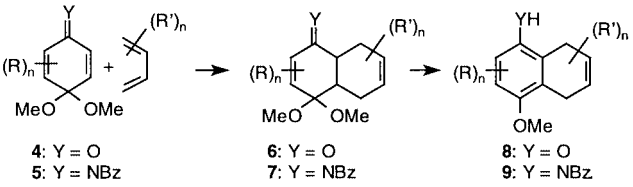
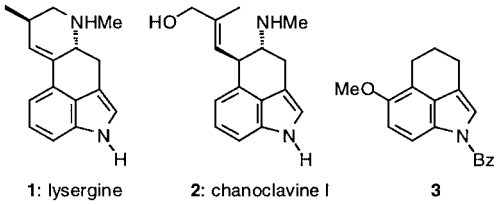
Abstract: The high pressure (13 kbar) Diels-Alder reaction of *N*-benzoyl-*p*-benzoquinone-mono-imine dimethyl ketal with an appropriate diene yields, after treatment with anhydrous acid, a dihydronaphthanilide. Conversion to the tricyclic skeleton of the ergot alkaloids is effected via a series of simple transformations.

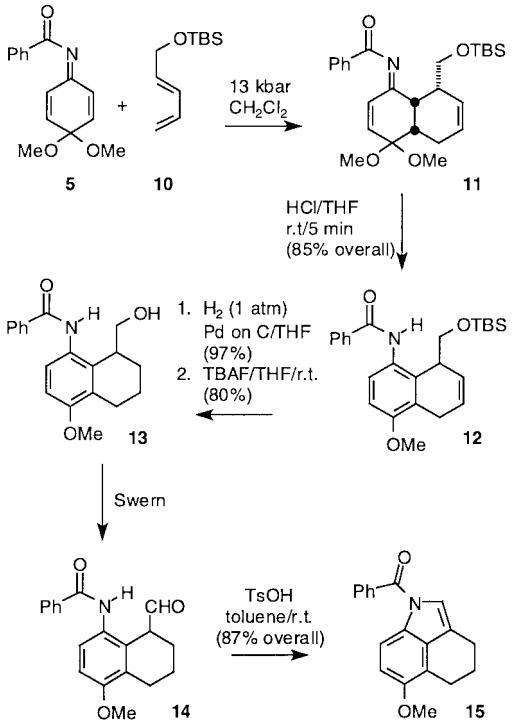
Key words: Diels-Alder reactions, quinones, alkaloids, cycloadditions



Scheme 1

There is arguably no more famous or notorious group of alkaloids than those belonging to the ergot class.[1] The fungus ergot has been used medicinally for centuries and the elucidation of the active compounds has been an ongoing challenge for almost 200 years. The bioactivity of the ergot alkaloids is significant, ranging from the infamous psychotropic effects of lysergic acid derivatives, to properties which include smooth muscle contraction, serotonin antagonism and various central nervous effects. Common to most members of the ergot alkaloids is a 1,3,4,5-tetrahydro-benzo[*c*,*d*]indole ring system. The ergolines (of which lysergine **1** is a representative example) possess an additional tetrahydropyridine ring not present in the seco-ergoline series (represented by chanoclavine I, **2**). In this letter we present a novel approach to the synthesis of the methoxy-1,3,4,5-tetrahydro-benzo[*c*,*d*]indole **3** using a Diels-Alder strategy.





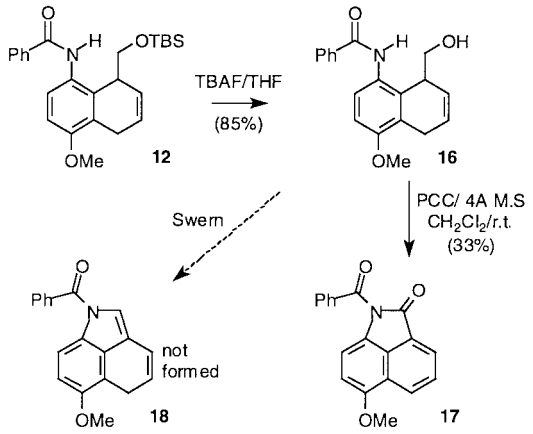
Scheme 2

Recently we reported that the use of pressures on the order of 13 kbar were effective in promoting the reactions of relatively unreactive quinoid species such as p-quinone-mono-ketals[2] **4** and benzoylated quinone imine ketals **5**[3] (Scheme 1). The reaction products **6** and **7** are characterized by high regio- and diastereocontrol. Aromatization can be effected by treament with anhydrous acid resulting in an annulated phenol **8** or anilide **9**. It occurred to us that by judicious selection of the appropriate diene, the adducts could be transformed expeditiously to the 6-methoxy-1,3,4,5-tetrahydro-benzo[*c*,*d*]indole (**3**). The methoxy group, while not common in naturally occurring ergot alkaloids, could be used as a handle toward further functionalizing the molecule and may be removed by hydrogenolysis of the corresponding triflate at a later stage.[4] Herein, we report our initial findings which show the feasibility of this protocol for the formation of the 6-methoxy-1,3,4,5-tetrahydro-benzo[*c*,*d*]indole ring system.

The synthesis of the target skeleton (Scheme 2) was initiated by treatment of quinone-imine-ketal **5**[5] with diene **10** at 13 kbar to produce the adduct **11** which could be isolated and purified[3] but was typically left crude, taken up in

THF and treated with a drop of concentrated HCl to yield the aromatized compound **12** in 85% overall yield.[6] Hydrogenation followed by treatment with fluoride yielded the alcohol **13**[7] which when treated under Swern[8] conditions produced a mixture of aldehyde **14** and indole **15**. Typically the crude material isolated from the Swern oxidation was treated with p-toluenesulfonic acid in toluene to effect complete conversion to **15** in 87% overall yield.[9] The overall yield of **15** from **5** was 57% over the six steps.

If the double bond was left intact prior to desilylation the alcohol **16** was produced, which when oxidized with PCC gave, not unexpectedly the fully oxidized compound **17** (Scheme 3).[10] If, instead, the oxidation was performed using Swern conditions, the reaction yielded a complicated mixture and not the expected product **18**. Interestingly, structures such as **17** have been shown to reduce rectal temperatures in rats and have stimulated interest for their potential as fever reducing agents.[11]



Scheme 3

In summary, we have shown that the tricyclic subunit present in most of the ergot alkaloids can be prepared in high overall yield by the cycloaddition of a quinone mono ketal with an appropriate diene, followed by several simple transformations. In future reports we intend to show the generality of this method for the formation of more sophisticated compounds related to the natural products and unusually substituted indoles in general.

Acknowledgement

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References and Notes

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(6) Procedure for the preparation of Diels-Alder adduct **12**: The quinone imine ketal **5** (0.259 g, 1.0 mmol) and the diene **10** (0.609 g, 3.1 mmol) were taken up in dry methylene chloride (0.5 mL) in a dry 10 mL pear shaped flask. This solution was transferred with the aid of an additional 0.5 mL CH_2Cl_2, to a ~7 cm length of heat shrinkable Teflon tubing which was pinched and sealed at one end with a brass screw clamp. Excess air was squeezed from the tube and it was sealed with a brass screw clamp. The vessel was then pressurized in a LECO Tempres HPC 200 system at 13 kbar for a period of 7 days, after which time the reaction mixture was concentrated and taken up in THF (20 mL). Concentrated HCl (1 drop) was added and the mixture was stirred for 5 min and diluted with water. Extractive workup with diethyl ether yielded crude **12**, which was purified by column chromatography on silica gel (elution with 25% EtOAc/hexane). The yield was 0.360 g (85%) as a white gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.53 (s, 1H), 7.98 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 1H), 7.54-7.45 (m, 3H), 6.83 (d, J = 8.8 Hz, 1H), 6.11-6.01 (m, 1H), 5.86-5.81 (m, 1H), 3.96 (AB of ABX, 2H), 3.85 (s, 3H), 3.55 (dd, J = 21.9, 5.1 Hz, 1H), 3.35 (t, J = 11.1 Hz, 1H), 3.04 (d, J = 21.9 Hz, 1H), 0.73 (s, 9H), -0.10 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4, 154.0, 135.1, 131.6, 131.3, 128.9, 128.4, 127.9, 127.3, 124.6, 123.6, 123.4, 108.0, 69.1, 55.5, 38.3, 25.8, 24.3, 18.6, -5.6, -5.7; IR (thin film) ν = 3337, 1672 cm^{-1}; HRMS (EI 70 eV) - calcd for $C_{25}H_{33}NO_3Si$: 423.2230, found: 423.2211.

(7) Physical data for **13**: ^{1}H NMR (400 MHz, DMSO) δ = 10.23 (s, 1H), 8.03 (d, J = 7.4 Hz, 2H), 7.67-7.58 (m, 3H), 7.36 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 5.42-5.40 (m, 1H), 3.85 (s, 3H), 3.68-3.63 (m, 1H), 3.58-3.52 (m, 1H), 3.21-3.19 (m, 1H), 2.83 (dd, J = 18.0, 5.1 Hz, 1H), 2.10 (d, J = 13.0 Hz, 1H), 1.79-1.75 (m, 2H), 1.57-1.51 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 165.2, 154.7, 134.9, 134.5, 131.4, 129.2, 128.5, 127.3, 125.4, 124.4, 107.5, 65.0, 55.3, 35.5, 23.7, 22.8, 16.6; IR (thin film) ν = 3275, 1645 cm^{-1}; HRMS (EI 70 eV) - calcd for $C_{19}H_{21}NO_3$: 311.1521, found: 311.1519.

(8) The insoluble nature of the alcohol **13** required the use of DMSO as a co-solvent. See: Swern, D.; Mancuso, A.J. *Synthesis* **1981**, 165-185.

(9) Procedure for the formation of indole **15**: The crude product from the Swern reaction was purified by column chromatography on silica gel (elution with 30% EtOAc/hexane to yield a mixture of the aldehyde **14** (25 mg) and the indole **15** (16 mg). The aldehyde was taken up in dry toluene (5 mL) and treated with 1 crystal of *p*-toluenesulfonic acid monohydrate. After 10 min the mixture was diluted with EtOAc and washed successively with H_2O, saturated $NaHCO_3$, and brine before drying over $MgSO_4$. Evaporation of the solvent yielded pure indole **15** (24 mg). m.p. = 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (br d, 1H), 7.71

(dd, J = 7.9, 0.9 Hz, 2H), 7.59-7.49 (m, 3H), 6.94 (br s, 1H), 6.92, (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 2.85 (t, J = 6.2 Hz, 2H), 2.72 (t, J = 6.2 Hz, 2H), 2.00 (dt, J = 6.2, 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 152.3, 135.1, 131.3, 131.2, 129.3, 128.8, 128.4, 121.2, 119.7, 118.8, 114.2, 109.3, 56.3, 23.4, 21.5, 21.4; IR (thin film) ν = 1675.0, 1495.0 cm^{-1}; HRMS (EI 70 eV) - calcd for $C_{19}H_{17}NO_2$: 291.1260, found: 291.1254.

(10) Physical data for **17**: ^{1}H NMR (400 MHz, DMSO) δ = 8.40 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 7.0 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.79-7.76 (m, 3H), 7.62 − 7.58 (m, 1H), 7.52-7.48 (m 2 H), 6.85 (d, J = 8.2 Hz, 1H), 4.05 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ = 169.7, 166.5, 153.2, 134.6, 132.2, 129.1, 129.0, 128.2, 128.0, 128.0, 127.9, 125.7, 124.2, 122.5, 113.8, 105.4, 55.8; IR (thin film) ν = 1741, 1674, 1308 cm^{-1}; HRMS (EI 70 eV) - calcd for $C_{19}H_{13}NO_3$: 303.0895, found: 303.0890.

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