Diels−Alder Reactions of Quinol Lactones: A Change of Regioselectivity with Stannic Chloride Catalysis

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Received June 3, 2002

Abstract: Lewis acid-mediated Diels−Alder reactions of quinol lactone **2** gave regioselectivity opposite to that of the uncatalyzed reaction. Compound **12** is proposed as the reactive intermediate generated by the reaction of **2** with stannic chloride.

In 2000, Takeya and co-workers isolated and determined the structure of the novel quassinoid dilactone eurycolactone A (**1**).[1] In view of our longstanding interest in biologically active quassionoids and the novel structure and activity of **1**, we embarked on the synthesis of eurycolactone A.[2] The retrosynthetic analysis led to quinol lactone **2** and diene **3**. Although quinol lactones such as **2** have not been reported to undergo Diels−Alder reactions, Houk and Liotta have utilized substituted quinols as dienophiles in the Diels−Alder reaction.[3]

Lactone **2** was readily prepared from benzopyrone **4** and phenyliodine diacetate in 97% yield in methanol at 25 °C.[4] Benzopyrone **4** was synthesized in one step from methylhydroquinone and ethyl acetoacetate.[5] Attempts to replace the methoxyl group in **2** with a methyl group were unsuccessful.

Diene **3** was synthesized by a Wittig−Emmons reaction between diacetyl and dimethyl carbomethoxymethyl phosphonate followed by reaction with TBSOTf and triethylamine.[6] This procedure led to a mixture of (*E*)- and (*Z*)-dienes, which were separable by silica gel chromatography. The reaction of the (*E*)-diene **3** with **2** at temperatures ranging from 110 to 250 °C led to recovered starting material. The Lewis-acid-catalyzed reaction with stannic chloride in methylene chloride from −78 to 25 °C led to adduct **5** in 41% isolated yield. The use of other Lewis acids led to decomposition of the diene ($TiCl_4$) or recovered starting materials (TMSOTf).

Initially, we believed that we had produced isomer **6**. The mass spectral data and IR supported that structure, but the NMR data, particularly the COSY and NOESY experiments, supported only structure **5**. In the COSY experiment, the methine multiplet centered around 3.33 correlated with the methyl doublet at 1.17 and the doublet of doublets centered around 2.85. The doublet of doublets centered around 2.85 also correlated with the methine doublet at 3.05. These observations defined the three contiguous methine protons in **5**. The COSY also identified an isolated AB quartet (representing the methylene group α to the ketone). These connections supported the assignment of structure **5**. The production of **5** was surprising, since we had expected that the ketone at C-6 in compound **2** would direct the regiochemistry. To better understand this outcome, we treated **2** with a more reactive diene. The reaction of Danishefsky's diene with **2** at 160 °C in toluene for 5 h followed by treatment with 6 N hydrochloric acid afforded adduct **7** in 80% yield.[7] The three-proton coupling pattern of the methylene group with the ring juncture methine proton was supportive of the assignment of **7**. The regiochemistry in this reaction was consistent with direction by the ketone. Unfortunately, Danishefsky's diene decomposed when subjected to the stannic chloride reaction conditions.

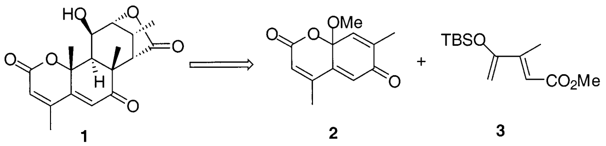

FIGURE 1.

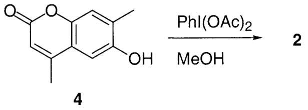

FIGURE 2.

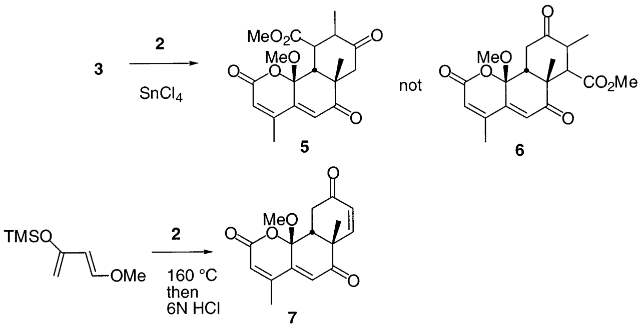

FIGURE 3.

We next reacted quinol lactone **2** with diene **8**.[8] Although this reaction did not proceed under uncatalyzed conditions, the stannic chloride-catalyzed reaction provided diketone **9** in 40% yield via a Michael addition reaction. Its structure assignment was supported by two isolated AB quartets. The reaction of diene **10**[7] with **2** was also catalyzed by stannic chloride and produced adduct **11** in 41% yield. This adduct was crystalline, and

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10.1021/jo020366p CCC: $22.00

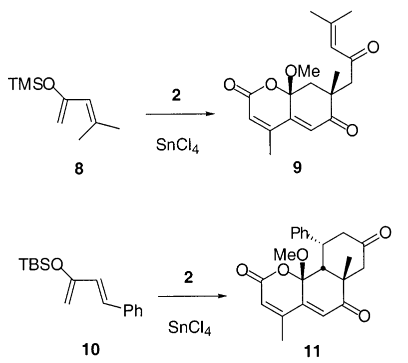

FIGURE 4.

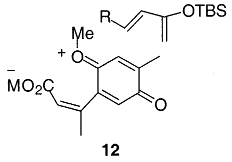

FIGURE 5.

its structure was determined by X-ray crystallography. The observation that only a single ring junction methoxyl substituent was produced in this reaction may be rationalized by equilibration during the workup to place the methoxyl group on the exo- face of the *cis*-decalin system.

The opposite regiochemical direction in the uncatalyzed reaction of **2** with Danishefsky's diene versus the Lewis-acid-catalyzed reactions of **2** with dienes **3** and **10** can be rationalized by the reactive intermediate **12**. This intermediate would be produced by coordination of the Lewis acid with the lactone moiety followed by an alkoxy-assisted opening. Despite the cis ring junctures in the products, the reaction could proceed via a stepwise mechanism.[10] Interestingly, the reaction of **2** with allyltrimethylsilane and stannic chloride did not result in the introduction of the allyl group. This type of regiochemical outcome does not appear to have been reported in the Diels–Alder reactions of quinone monoketals,[11,12] a structurally similar class of compounds.

Lewis-acid-mediated activation of **2** may lead to reactive intermediate **12**, which could react readily with enol silyl ethers to afford products resulting from either a Diels–Alder reaction or a Michael addition reaction. Recognition of this novel reactivity allows the preparation of highly functionalized adducts not accessible via the uncatalyzed pathway.

Experimental Section

6,8a-Dihydro-8a-methoxy-4,7-dimethyl-1-benzopyran-2,6-dione 2. To a mixture of **4** (5.69 g, 30 mmol) and 60 mL of CH_3OH was added $PhI(OAc)_2$ (10.61 g, 33 mmol) at room temperature. The mixture was stirred for 30 min. The mixture was concentrated and purified by silica gel flash chromatography (sgc) using 2:1 hexanes/EtOAc to afford product **2** (6.4 g, 97% yield) as yellow solid with mp = 97–99°C: ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3 H), 2.17 (s, 3 H), 3.39 (s, 3 H), 6.08 (s, 1 H), 6.40 (s, 1 H), 6.81 (s, 1 H); ^{13}CNMR ($CDCl_3$) δ 15.6, 17.8, 52.1, 95.3, 120.8, 125.8, 136.6, 138.0, 145.7, 147.5, 161.8, 185.5; IR (film) 1738, 1674, 1654, 1262 cm^{-1}; MS (*m*/*z*) 220, 192, 189, 161, 105; HRMS for $C_{12}H_{12}O_4$ calcd, 220.0736; found, 220.0739.

General Procedure for the Lewis Acid-Catalyzed Diels–Alder Reaction. To a stirred solution of enone **2** (110 mg, 0.50 mmol) and diene (111 mg, 0.65 mmol) in 5 mL of dry ether at −40 °C was added dropwise 30 μL of stannic chloride. The mixture was allowed to slowly warm to room temperature. After 6 h, 5 mL of cold water was added and the layers were separated. The aqueous phase was extracted twice with methylene chloride. The combined organic layers were dried, concentrated, and evaporated in vacuo. The residue was purified by sgc with 2:1 H/EA to afford the product.

6,6a,7,8,9,10,10a,10b-Octahydro-10b-methoxy-4,6a,9-trimethyl-10-(1-oxo-2-oxapropyl)-2*H*-naphtho[1,2-b]pyran-2,6,8-trione 5: light yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, J = 6 Hz, 3H), 1.31 (s, 3H), 2.20 (s, 3H), 2.25 (d, J = 12 Hz, 1H), 2.85 (dd, J = 3, 9 Hz, 1H), 3.05 (d, J = 3 Hz, 1H), 3.09 (d, J = 12 Hz, 1 H), 3.18 (s, 3H), 3.29–3.38 (m, 1H), 3.86 (s, 3H), 6.20 (s, 1H), 6.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 18.0, 24.9, 42.9, 46.9, 47.1, 47.7, 51.0, 52.4, 52.7, 102.2, 122.1, 126.8, 145.1, 148.3, 159.3, 172.3, 199.3, 209.6; IR (film) 1741, 1722, 1672, 1268, 994 cm^{-1}; HRMS for $C_{19}H_{22}O_7$ calcd, 362.1366; found, 362.1372.

6,7,8,8a-Tetrahydro-8a-methoxy-4,7-dimethyl-7-(2-oxo-4-methyl-3-pentenyl)-1-benzopyran-2,6-dione 9: colorless solid with mp = 144–145°C; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.84 (s, 3H), 2.06 (s, 3H), 2.13 (s, 3H), 2.33 (d, J = 14 Hz, 1H), 2.60 (d, J = 18 Hz, 1H), 2.63 (d, J = 15 Hz, 1 H), 3.24 (d, J = 18 Hz, 1H), 3.38 (s, 3H), 6.00 (s, 1H), 6.07 (s, 1H), 6.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 18.5, 21.2, 21.3, 224.4, 28.0, 37.5, 42.6, 50.1, 55.1, 60.6, 100.3, 120.9, 122.9, 127.6, 144.7, 148.4, 157.4, 161.7, 197.4, 202.0; IR (film) 1724, 1674, 1619, 1275, 734 cm^{-1}; MS (*m*/*z*) 318, 300; HRMS for $C_{18}H_{22}O_5$ calcd, 318.1467; found, 318.1473.

6,6a,7,8,9,10,10a,10b-Octahydro-10b-methoxy-4,6a-dimethyl-10-phenyl-2*H*-naphtho[1,2-b]pyran-2,6,8-trione 11: colorless solid with mp = 222–224°C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.71 (s, 3H), 2.21 (d, J = 12 Hz, 1H), 2.66 (brd, J = 9 Hz, 1H), 2.78 (dd, J = 10, 12 Hz, 1H), 3.29 (d, J = 4 Hz, 1H), 3.47 (s, 3H), 3.59 (brd, J = 12 Hz, 1H), 3.94–3.97 (m, 1H), 5.49 (s, 1H), 5.93 (s, 1H), 6.69 (d, J = 6 Hz, 2H), 6.99–7.06 (m, 3H); IR (film) 1717, 1675, 1265 cm^{-1}.

6,6a,9,10,10a,10b-Hexahydro-10b-methoxy-4,6a-dimethyl-2*H*-naphtho[1,2-b]pyran-2,6,9-trione 7. A sealed tube was charged with enone (11.21 g, 51 mmol), Danishefsky's diene (9.3 g, 54 mmol), and toluene (20 mL). The mixture was stirred at 160 °C for 5 h. After the mixture was cooled, toluene was evaporated under reduced pressure. The residue was dissolved in 250 mL of THF and cooled to 0 °C. To the solution was slowly added 250 mL of 6 N HCl. The mixture was stirred at room temperature for 24 h. The mixture was neutralized by carefully adding K_2CO_3 (100 g). The two layers that formed were separated. The aqueous phase was washed with 3 × 200 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by sgc (2:1 hexanes/EtOAc), affording the product (12.4 g, 80%) as a yellow solid with mp = 169–170°C: ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 3 H), 2.20 (s, 3 H), 2.16–2.24 (m, 1 H), 2.81 (dd, J = 3, 12 Hz, 1 H), 3.12 (dd, J = 3, 12 Hz, 1 H), 3.44 (s, 3 H), 6.10 (d, J = 9 Hz, 1 H), 6.19 (s, 1 H), 6.35 (s, 1 H), 6.89 (d, J = 9 Hz, 1 H); ^{13}CMR ($CDCl_3$) δ 15.9, 18.4, 26.6, 37.8, 43.6, 47.9,50.5, 101.4, 122.1, 127.3, 128.3, 144.4, 148.0, 153.8, 160.5, 196.0, 198.4; IR (film) 1723, 1688, 1664, 1272 cm^{-1}; MS (*m*/*z*) 288, 256, 228, 180,152, 124; HRMS for $C_{16}H_{16}O_5$ calcd, 288.0998; found, 288.1002.

Acknowledgment. We thank Iowa State University for partial support of this research.

Supporting Information Available: ^{1}H NMR spectra for compounds **2**, **3**, **5**, **7**, **9**, and **11**, X-ray data for **11**, and COSY for **5**.

JO020366P

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