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

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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 dialactone eurycolactone A (1). In view of our longstanding interest in biologically active quassinoids and the novel structure and activity of 1, we embarked on the synthesis of eurycolactone A. 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 quinol lactone 4 as dienophiles in the Diels–Alder reaction. 3

Lactone 2 was readily prepared from benzopyrone 4 and phenylidine diacetate in 97% yield in methanol at 25 °C. Benzopyrone 4 was synthesized in one step from methylhydroquinone and ethyl acetoacetate. 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 carbomethoxyethyl phosphonate followed by reaction with TBSOTf and triethylamine. 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 (TiCl4) 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. 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.

We next reacted quinol lactone 2 with diene 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 with 2 was also catalyzed by stannic chloride and produced adduct 11 in 41% yield. This adduct was crystalline, and

(6) Alibes, R.; Busque, F.; De March, P.; Figueredo, M.; Font, J.; Parella, T. Tetrahedron 1998, 54, 10857–10878. The (E)-stereochemistry was assigned on the basis of the NOESY spectrum.
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 observation that only a single ring junction methoxyl group on the exo-face of the cis-decalin system.

**Experimental Section**

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/E to afford the product.

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

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