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Diels-Alder Cycloaddition of Cyclopentadiene to a Bis-naphthoquinone

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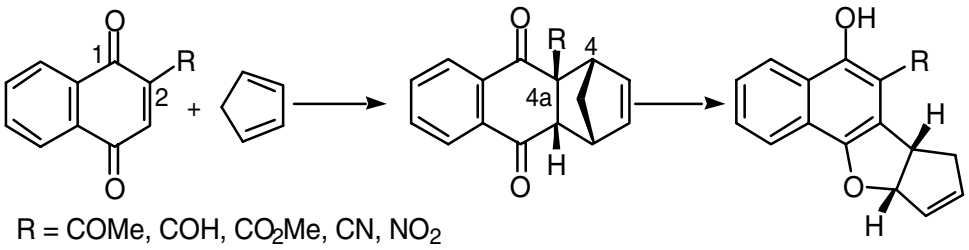
Abstract: Addition of cyclopentadiene to bis-naphthoquinone (**1**) afforded predominantly the *endo-endo* [4+2] cycloadduct (**2**).

Keywords: Diels-Alder, naphthoquinones, cyclopentannulation.

Introduction

Work in this research group has focussed on the addition of cyclopentadiene to naphthoquinone dienophiles bearing an electron withdrawing group at C-2 [1]. These dienes are of particular interest in that the Diels-Alder adducts can undergo selective fragmentation of the C-4/C-4a bond affording an electrophilic site which can then be trapped by a hydroxyl group to give a cyclopentannulated product (Scheme 1). Development of this Diels-Alder/fragmentation reaction in an asymmetric sense has also been the focus of recent investigations [2] using chiral Lewis acid catalysis.



Scheme 1.

As an extension to our earlier work in this area, bis-naphthoquinone (**1**) was perceived to be a bis-dienophile for a double [4+2] cycloaddition reaction with cyclopentadiene (Scheme 2). The Diels-Alder adduct (**2**) resulting from addition to the two quinonoid double bonds would undergo fragmentation at both ends of the molecule to afford a bis-cyclopentannulated product (**3**) (Scheme 3).

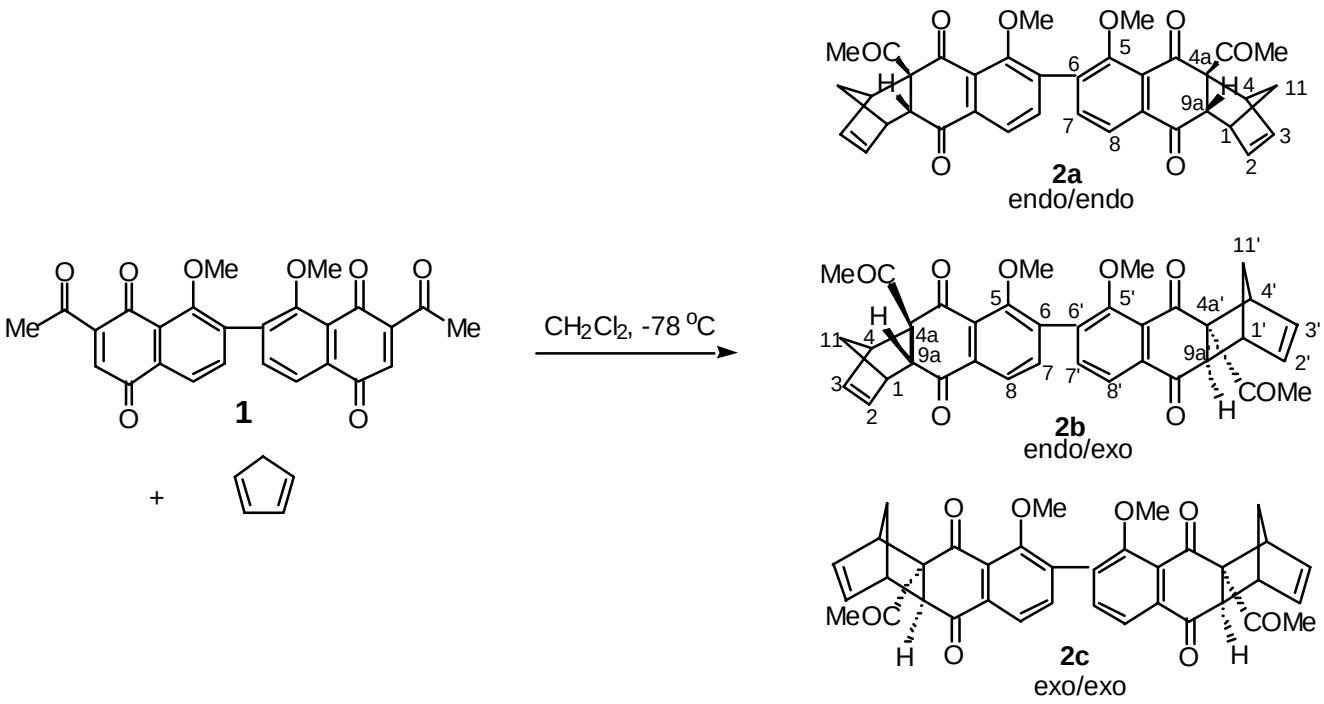
Results and Discussion

A study of the Diels-Alder addition of cyclopentadiene to bis-naphthoquinone was initiated. An excess of freshly distilled cyclopentadiene was added under nitrogen -78 ^{o}C to a dichloromethane solution of bis-naphthoquinone (**1**) which was prepared as reported previously [3]. After 10 min., no starting material remained and the formation of several new products of similar polarity was evident upon TLC analysis. ^{1}H nmr analysis of the reaction mixture displayed features consistent with formation of adduct (**2**). The presence of signals resonating at δ 6.0-6.5 were assigned to the vinylic protons whilst a resonance at δ 4.13 was characteristic of the bridgehead proton assigned to H-9a.

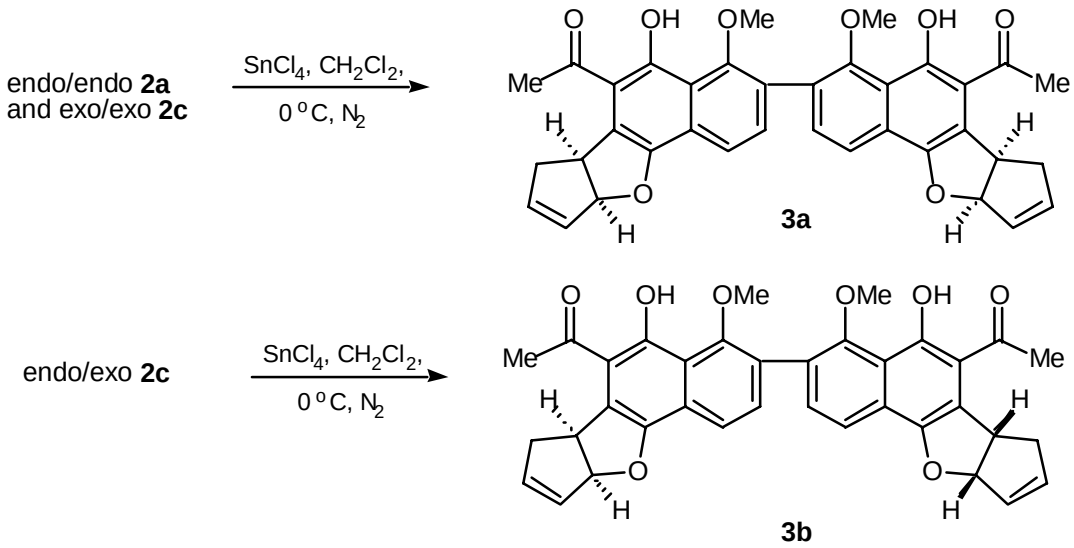
When using monomeric quinones as the dienophile exclusive formation of the *endo* cycloaddition adducts was observed [2]. However, the possibility of forming several diastereomeric adducts arises when bis-dienophile (**1**) is used. In bis-naphthoquinone (**1**) three modes of addition can potentially result, *endo-endo, endo-exo* and *exo-exo,* thus the possibility of diastereomeric adducts is not unexpected. The presence of multiple vinylic, bridgehead and methoxy signals in the ^{1}H nmr spectrum provided evidence for a mixture of products.

Direct fragmentation of the product mixture using $SnCl_4$ in dichloromethane was then examined in order to simplify product analysis (Scheme 3). After stirring for 10 min. at 0 ^{o}C several new products of lower polarity were evident upon TLC analysis, however, rapid decomposition of the crude reaction mixture in $CDCl_3$ occurred. The addition of the Lewis acid catalyst ($SnCl_4$) to bis-naphthoquinone (**1**) prior to addition of cyclopentadiene afforded baseline material due to decomposition of bis-naphthoquinone (**1**) by the Lewis acid.

Partial characterisation of the original Diels-Alder product mixture (5 mg) was accomplished using preparative HPLC affording four separate products in low yield (0.6-2 mg). Formation of the *endo-endo* adduct (**2a**) as the major product was confirmed upon spectroscopic analysis. High resolution mass spectrometry established the molecular formula $C_{36}H_{30}O_8$ whilst two bands in the IR spectrum at 1725 cm^{-1} and 1678 cm^{-1} were attributed to the carbonyls of the ketone and ene-dione respectively. The ^{1}H nmr spectrum displayed two singlets at δ 2.42 and δ 3.50 assigned to the methyl groups of the acetyl and methoxy, whilst multiplets at δ 3.58-3.60 and δ 3.80-3.82 were assigned to H-1 and H-4 respectively. A two proton multiplet at δ 6.24-6.26 was assigned to the vinylic protons H-2 and H-3, whilst a doublet at δ 4.13 with coupling constant $J_{9a,1}$ 3.9 Hz was assigned to the bridgehead proton H-9a. The coupling constant $J_{9a,1}$ 3.9 Hz is consistent with formation of the bis-*endo* adduct (**2a**) [2].



Scheme 2.



Scheme 3.

A second product (1 mg) displayed features consistent with *endo-exo* adduct (**2b**) formation, most noticeably three vinylic multiplets were observed which integrated for one, two and one proton(s) respectively. The two proton multiplet at δ 6.25-6.27 was assigned to the *endo* ring vinylic protons H-2 and H-3. These protons resonated at a similar chemical shift to those reported for the analogous pro-

tons in the *endo-endo* adduct (**2a**). The remaining one proton multiplets at δ 6.41-6.44 and δ 6.11-6.13 were thus assigned to the vinylic protons of the *exo* adduct portion of the molecule, H-2' and H-3'. Two singlets at δ 2.30 and δ 2.42 were assigned to the acetyl group of the *exo* and *endo* rings respectively, whilst multiple aromatic signals provided further evidence for the unsymmetrical diastereomer (**2b**).

The two remaining products (<1.5 mg) exhibited complex ^{1}H nmr spectra and the structures to date have not been elucidated. It is not unreasonable to assume that the formation of unsymmetrical dimers arising from reaction of only one half of bis-naphthoquinone (**1**) may well result in a complicated mixture. A poor mass recovery was obtained from the Diels-Alder addition of bis-naphthoquinone (**1**) to cyclopentadiene thereby precluding a synthetically useful approach to the bis-cyclopentannulated products (**3**).

Experimental

General

^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM 400 NMR and were recorded at 400 and 10 MHz respectively. Liquid secondary ion mass spectrometry (LSIMS) high resolution mass spectra were recorded at a nominal resolution of 5000 using 4-nitrobenzyl alcohol (NBA) and a 5:1 mix (v/v) of dithiothreitol : dithioerythritol as matrix. High performance liquid chromatography (HPLC) was carried out using a Waters Associates system consisting of, a mdel M-6000A pump, a millipore model U6K injector, a model 440 ultra-violet detector at 256 nm and a R401 differential refractometer. Separation was carried out using the indicated solvents on a Partisil 10 M9 semipreparative column of the following dimensions: outer diameter 12.80 mm, inner diameter 9.40 mm, length 500.0 mm, and particle size 10.0 μm. Cyclopentadiene was obtained from Aldrich Chemical Company (USA) and was cracked immediately prior to use.

Method

To a solution of 7-(2'-acetyl-8'-methoxy-1',4'-dioxonaphthalen-7'-yl)-2-acetyl-8-methoxy-1,4-naphthoquinone (**1**, 25 mg, 0.055 mmol) in dichloromethane (2 ml) cooled to 0 ^{o}C under nitrogen was added freshly distilled cyclopentadiene (0.018 ml, 0.22 mmol). After stirring for 10 min., the reaction mixture was poured into aqueous sodium hydrogen carbonate solution (5 ml) and extracted with dichloromethane (4 x 5 ml). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a dark oil. Purification by flash chromatography using hexane-ethyl acetate (6:4) as eluent afforded a yellow oil which was further purified by HPLC on a Partisil 10 M9 semipreparative column using hexane-ethyl acetate (75:15) as eluent to afford: (1S,4R,4aR,9aR,1'S,4'R,4'aR,9'aR)-4a-Acetyl-6-[4a'-acetyl-1',4',4a',9a'-tetrahydro-1',4'-methano-5'-methoxy-9',10'-dioxoanthracen-6-yl]-1,4,4a,9a-tetrahydro-1,4-methano-5-methoxy-9,10-anthra-

cenedione **2a** (1.6 mg, 5%) as a yellow oil and (1S,4R,4aR,9aR,1'R,4'S,4a'S,9a'S)-4a-Acetyl-6-[4a'-acetyl-1',4',4a',9a'-tetrahydro-1',4'-methano-5'-methoxy-9',10'-dioxoanthracen-6-yl]-1,4,4a,9a-tetrahydro-1,4-methano-5-methoxy-9,10-anthracenedione **2b** (1 mg, 3%) as a yellow oil.

Spectral Data for Adduct **2a**

IR (CH_2Cl_2 solution) cm^{-1}: 1725 (C=O, acetyl), 1678 (C=O, ene-dione), 1190, 1025.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.36-1.39 (1H, m, 11-H_B), 1.47 (obscured, 11-H_A), 2.42 (3H, s, COMe), 3.50 (3H, s, OMe), 3.58-3.60 (1H, m, 1-H), 3.80-3.82 (1H, m, 4-H), 4.13 (1H, d, $J_{9a,1}$ 3.9 Hz, 9a-H), 6.24-6.26 (2H, m, 2-H and 3-H), 7.62 (1H, d, $J_{7,8}$ 8.0 Hz, 7-H), 7.72 (1H, d, $J_{8,7}$ 8.0 Hz, 8-H).

MS (LSIMS): 591 (MH^+, 13%), 525 (M-C_5H_6, 20), 207 (45) and 176 (100).

HRMS (LSIMS) for $C_{36}H_{31}O_8$ (MH^+): Calcd 591.2019; Found 591.2044.

Spectral Data for Adduct **2b**

IR (CH_2Cl_2 solution) cm^{-1}: 1725 (C=O, acetyl), 1679 (C=O, ene-dione), 1193, 1024.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.31-1.48 (4H, m, 11-H_A, 11-H_B, 11'-H_A and 11'-H_B), 2.30 (3H, s, 4a'-$COCH_3$), 2.42 (3H, s, 4a-$COCH_3$), 3.45 (1H, m, 1'-H), 3.51 (3H, s, OMe), 3.52 (3H, s, OMe), 3.59-3.61 (1H, m, 1-H), 3.67-3.69 (1H, m, 4'-H), 3.80-3.83 (1H, m, 4-H), 4.12-4.15 (2H, m, 9a-H and 9a'-H), 6.11-6.13 (1H, m, 2'-H or 3'-H), 6.25-6.27 (2H, m, 2-H and 3-H), 6.41-6.44 (1H, m, 3'-H or 2'-H), 7.62-7.66 (2H, m, 7-H and 7'-H), 7.72 (1H, d, J_{ortho} 8.1 Hz, 8-H or 8'-H), 7.75 (1H, d, J_{ortho} 8.0 Hz, 8'-H or 8-H).

MS (LSIMS): 591 (MH^+, 13%), 525 (M-C_5H_6, 16), 207 (55) and 176 (100).

HRMS (LSIMS) for $C_{36}H_{31}O_8$ (MH^+): Calcd 591.2019; Found 591.2041.

References and Notes

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Samples Availability: Available from the authors.