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Intramolecular site selectivity in cation radical Diels–Alder cycloadditions of difunctional and trifunctional dienophiles

Nathan L. Bauld* and Jingkui Yang

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

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ABSTRACT: The cation radical Diels–Alder reactions of several difunctional and trifunctional dienophiles with 1,3-cyclopentadiene, catalyzed by tris(4-bromophenyl)aminium hexachloroantimonate, were determined. When both of the reactive sites are of the 4-methoxystyrene type, reaction occurs smoothly at both styrene moieties to give the bis-adducts. However, when one reactive moiety is of the styrene type and one is of the enol ether type, reaction occurs exclusively at the styrene moiety to give a mono-adduct, even in the presence of a large excess of cyclopentadiene. When three potentially reactive moieties are included, two of them being of the styrene type and one of the 1,2-diaryloxyethene type, the reaction is again specific for the styrene moieties, giving only the bis-adduct. The high site selectivity observed in these reactions is especially noteworthy in view of the observation that monofunctional molecules containing all three of these moieties are found to be reactive toward Diels–Alder adduct formation under the same reaction conditions and that these adducts are relatively stable under the reaction conditions. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: Cation radical; radical cation; specificity; Diels–Alder; Aminium ion; conjugated systems

INTRODUCTION

Aminium salt-catalyzed cation radical Diels–Alder cycloadditions (For a review of the cation radical Diels–Alder reaction and references to the many contributors to this general area, see Ref. 1) of such readily ionized substrates as *trans*-anethole,[2] aryl propenyl ethers,[3] and 1,2-diaryloxyethenes[4] to 1,5-cyclopentadiene have all been observed (Scheme 1). However, relatively little research has been reported on cation radical Diels–Alder reactions of di- or polyfunctional substrates. The goal of the present research was to investigate the feasibility of multiple cation radical Diels–Alder reactions of a single substrate and more especially to establish the level of selectivity of such reactions when different potential dienophilic reaction sites are present in the same molecule. A further unique aspect of two of the substrate molecules chosen for this study is that the two (or three) functional groups constitute part of a continuous conjugated system, so that the preferred site of reactivity is not determined by the ionization step (presumably involving reaction with the aminium salt), but as an inherent preference of the extensively conjugated cation radical.

**Correspondence to:* N. Bould, Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA.
E-mail: bauld@mail.utexas.edu
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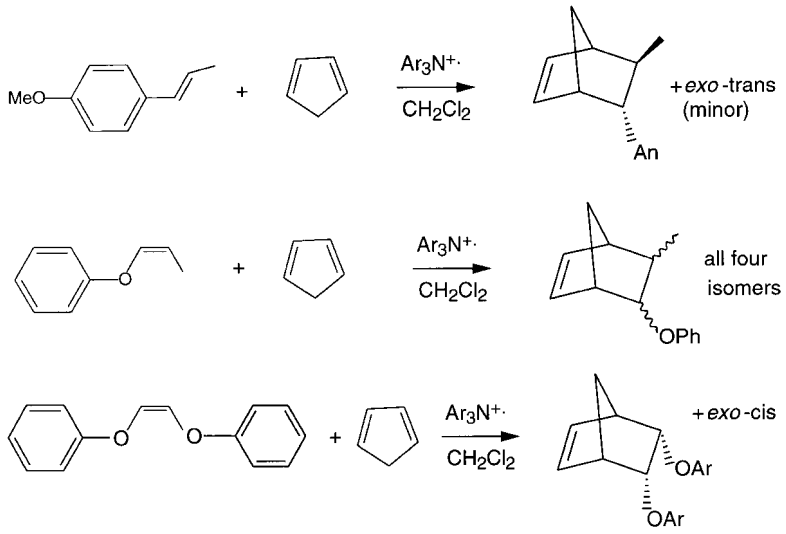
RESULTS AND DISCUSSION

The ionizable functionalities selected for the present study (Scheme 2) were precisely the ones mentioned above, the behavior of which in aminium salt-catalyzed cation radical Diels–Alder reactions is now well established. The linking conjugated system, in two cases, is the 1,4-benzenediyl (1,4-phenylene) moiety, which, in the present work, is not considered to be a further potential site of reactivity, since benzene and other aromatics have been found not to participate in the cation radical Diels–Alder reaction.

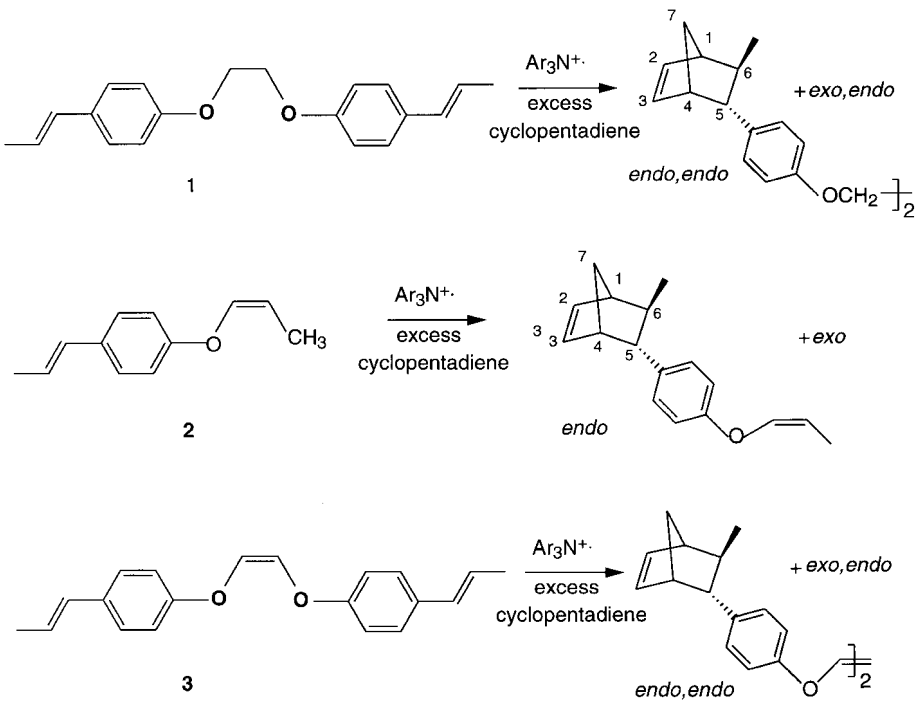
The feasibility of consecutive cation radical Diels–Alder additions to a substrate having two equivalent unconjugated reactive sites was demonstrated by the reaction of substrate **1** (Scheme 2) with a fivefold excess of 1,3-cyclopentadiene in dichloromethane solvent at 0–5 °C. After a reaction time of only 15 s, the bis-adducts are generated in 47% yield. The isolated yield in the corresponding monofunctional reaction of *trans*-anethole was 52%.[2] The ratio of *endo* to *exo* Diels–Alder linkages was found from the proton NMR spectrum to be 5.2:1, but the percentage composition of the three diastereoisomeric Diels–Alder adducts could not be directly determined from the NMR (the *endo* moieties in the *endo, endo* and *endo, exo* isomers are NMR equivalent, as are the *exo* moieties in the *exo, exo* and *endo, exo* diastereomers) or by GC (because of the instability of the bis adducts at the high temperatures required for its elution). The monoadduct of **1** with 1,3-cyclopentadiene could not be isolated because the bis-adduct was the



Scheme 1

major product even at very short reaction times or when only one mole of 1,3-cyclopentadiene was employed. This interesting observation is consistent with the hypothesis that, at least in part, intramolecular hole transfer occurs in the initially formed monoadduct cation radical to generate a cation radical site at the second *trans*-anethole-like moiety, which then reacts with another molecule of the diene to yield the bis-adduct without proceeding through the neutral mono-adduct.[5]

Selectivity in the context of non-equivalent, conjugated reaction sites was then investigated in the reaction of substrate **2** with cyclopentadiene. Because enol ether functionalities have been found to be sensitive to the strong acids which are generated during aminium salt-catalyzed reactions, the two-phase dichloromethane–water solvent mixture which had previously been shown in this laboratory to work especially well for acid sensitive groups was employed.[3] The reaction is highly site selective for the *trans*-anethole-like moiety in preference to the enol ether moiety, the alternative mono-adducts not being detectable by either GC or NMR. Further, bis-adducts were also absent from the reaction mixture. The predominant *endo* isomer of the mono-adduct was isolated in pure form in 32% yield, but



Scheme 2

the minor, *exo* isomer was difficult to separate from the neutral triarylamine. Although the higher reactivity of a conjugated cation radical containing both a *trans*-anethole moiety and an arylpropenyl ether moiety seems not unreasonable based upon the lower oxidation potential of *trans*-anethole than of simple aryl propenyl ethers and the consequently higher hole density (cation radical character) on the former moiety, it is at least somewhat surprising that, in the presence of such a large excess of the diene (10-fold), the aryl propenyl ether moiety of the mono-adduct is essentially unreactive. Evidently, intramolecular hole transfer is not operative in this instance, possibly because hole transfer to the enol ether moiety is less energetically favorable than to the *trans*-anethole moiety involved in the reaction of **1**. We suggest that the short reaction time (3 min) along with retardation of the subsequent cycloaddition to the enol ether moiety by the neutral triarylamine generated in the initial stage of the reaction[6] could account for the failure to observe any bis-adducts. In any case, the selectivity for the *trans*-anethole moiety is impressive. It is important to note that, although the yield in this reaction is not especially high, the possibility that alternative adducts corresponding to addition to the enol ether moiety could have been formed and subsequently decomposed is rendered highly unlikely by the demonstrable stability of the corresponding adducts derived from the monofunctional enol ether under the same reaction conditions.

Substrate **3** provides a novel opportunity to probe, simultaneously, multiple Diels–Alder reactivity and site selectivity. The reaction of this trifunctional substrate with an excess of 1, 3-cyclopentadiene in dichloromethane for 3 min yields the bis-Diels–Alder adducts corresponding to reaction exclusively at the two *trans*-anethole sites in 56.7% yield. The diastereoisomeric adduct mixture consisted predominantly of the *endo, endo* diastereomer, but smaller amounts of the *endo, exo* isomer were evident in the NMR spectra. Once again, the diaryloxyethene moiety, although reactive in the simple monofunctional context, shows no sign of reactivity toward cation radical cycloaddition, since neither the appropriate bis-adducts nor a tris-adduct could be detected.

CONCLUSIONS

Double cation radical Diels–Alder reactions of substrates containing two *trans*-anethole-type moieties are found to be relatively facile and even difficult to arrest at the stage in which a single molecule of the diene is incorporated. In contrast, corresponding reactions of difunctional substrates containing one *trans*-anethole moiety and one of the enol ether type are highly selective for the *trans*-anethole moiety and no bis-adducts are formed. Similarly, a substrate containing two *trans*-anethole moieties and one of the enediol diether type are highly selective for reaction at the *trans*-anethole moities, yielding bis-adducts, but no tris-adducts.

EXPERIMENTAL

Equipment. Proton NMR spectra were recorded on a Bruker AC250 or a Varian UNITY INOVA 500 spectrometer. Carbon spectra were recorded on the Bruker AC250 machine. COSY and NOESY spectra were recorded on the Varian UNITY INOVA 500 spectrometer. High-resolution mass spectra were recorded on a VG ZAB-2E mass spectrometer.

Chemicals. All chemicals used as starting materials were purchased from Aldrich and used as received. The catalyst, tris(4-bromophenyl)aminium hexachloroantimonate, was also obtained from Aldrich. The dichloromethane solvent was dried by refluxing it over calcium hydride.

*Reaction of **1** with 1,3-cyclopentadiene.* To 1,2-bis(4-*trans*-propenylphenoxy)ethane (**1**, 50 mg, 0.17 mmol)[7] and 1,3-cyclopentadiene (56 mg, 0.85 mmol) in anhydrous dichloromethane (10 ml) at 0–5 °C were added, all at once, 21 mg (0.25 mmol) of tris(4-bromophenyl)aminium hexachloroantimonate dissolved in 5 ml of anhydrous dichloromethane. After a reaction time of 15 s, the mixture was quenched with saturated potassium carbonate–methanol solution and water was added. The dichloromethane layer was then dried and the solvent removed by a vacuum aspirator, followed by column chromatography on silica gel. The adduct mixture was eluted with 4:1 hexanes–dichloromethane, yielding 34 mg (47%) of the *endo, endo* isomer admixed with smaller amounts of the *endo, exo* and, perhaps, the *exo, exo* isomer. The ratio of *endo* to *exo* linkages in the diastereoisomer mixture was found to be 5.2:1. However, the *endo* linkages of the predominant *endo, endo* isomer were indistinguishable from those of the *endo, exo* isomer, and the *exo* linkages of the *exo, exo* and *endo, exo* isomers were also indistinguishable. ^{1}NMR (250 MHz, $CDCl_3$, *endo* linkages), δ 1.19 (d, 6H, J = 6.57 Hz), 1.45–1.51 (m, 2H, C7-*anti* proton on the bicycloheptadiene ring), 1.61–1.70 (m, 4H, C7-*syn* proton plus C6 proton), 2.49 (s, 2H, C1 proton), 2.67–2.70 (t, 2H, J = 4.02, C4 proton), 2.95 (s, 2H, C5 proton), 4.24–4.28 (m, 4H, ether methylenes), 5.84–5.88 (m, 2H, C2 proton), 6.28–6.32 (m, 2H, C3 proton), 6.77–6.81 (d, 4H, J = 8.67, aromatic), 7.05–7.08 (d, 4H, J = 8.49); *exo* linkages: 0.93–0.96 (d, 6H, J = 6.57), 1.74–2.10 (m, 6H, C7 *syn* and *anti* and C6 protons), 2.73–2.77 (m, 6H, C1, C4, and C5 protons), 4.24–4.28 (m, 4H, ether methylenes), 6.09–6.11 (m, 2H, C2 proton), 6.28–6.32 (m, 2H, C3 proton), aromatic protons same as in the *endo* diastereoisomer.

*Synthesis of cis-(1-propenyl) 4-(trans-1-propenyl)phenyl ether (**2**).* To a mixture of 4-propionylphenol (50.35 g, 0.335 mol) and potassium carbonate (55.61 g, 0.40 mol) in acetone (250 ml) was added allyl bromide (101 g, 0.83 mol). The solution was heated to 75–90 °C and vigorously stirred for 6 h. After allowing the reaction mixture to cool, the inorganic solids were removed by filtration and the solvent was removed by rotary evaporation. Water and dichloromethane were then added, the dichloromethane layer was separated and dried with sodium sulfate and the solvent dichloromethane was evaporated to obtain 56.8 g (89.4%) of the product, allyl 4-propionylphenyl ether. ^{1}H NMR (250 MHz, $CDCl_3$), δ 1.12–1.19 (t, 3H, J = 7.25 Hz), 2.84–2.29 (q, 2H, J = 7.26), 4.52–4.55 (d, 2H, J = 7.26), 5.23–5.30 (dt, 1H, J = 10.59, 1.46), 5.32–5.42 (dt, 1H, J = 17.37, 1.59), 5.92–6.05 (m, 1H), 6.85–6.09 (m, 2H), 7.85–7.91d (m, 2H); ^{13}C NMR (250 MHz, $CDCl_3$), δ 8.283, 31.248, 68.703, 114.232, 117.969, 129.946, 130.034, 132.410, 162.153, 199.291; HRMS, calculated for $C_{12}H_{14}O_2 + H$ (M + 1), 191.107205; found, 191.1107770.

To allyl 4-propionylphenyl ether (the product of the previous reaction, 49.94 g, 0.26 mol) dissolved in 50 ml of ethanol was added 5.28 g (0.14 mol) of sodium borohydride. The solution was stirred for 4 h and then quenched with 50 ml of water and the solvents were removed by a vacuum aspirator. Water and dichloromethane were then added and the latter layer was separated, dried and the solvent removed, providing 36.82 g (0.192 mol, 73.7%) of the oily alcohol product, allyl 4-(1-hydroxypropyl)phenyl ether. ^{1}H NMR (250 MHz, $CDCl_3$), δ 0.87 (t, 3H, J = 7.38), 1.65–1.82 (m, 2H, J = 7.21), 4.46–4.52 (m, 3H), 5.24–5.30 (dd, 1H, J = 10.49, 1.35), 5.34–5.44 (dd, 1H, 17.34, 1.61), 5.96–6.10 (m, 1H), 6.84–7.24 (m, 4H); ^{13}C NMR (250 MHz, $CDCl_3$), δ 10.142, 31.688, 68.768, 75.528, 114.521, 117.550, 127.123, 133.261, 136.908, 157.925; HRMS, calculated for $C_{12}H_{16}O_2 + H$ (M + 1), 193.122855; found, 193.122719.

To the product of the previous reaction, allyl 4-(1-hydroxypropyl)phenyl ether (32.7 g, 0.169 mol), dissolved in 50 ml of anhydrous dichloromethane was added 56.5 ml of a 1.0 M solution of phosphorus tribromide in dichloromethane. After stirring the reaction mixture overnight, 50 ml of water were added, the dichloromethane layer was separated and dried and the solvent removed. Then, a solution of potassium *tert*-butoxide (20 g, 0.18 mol) dissolved in 30 ml of dimethyl sulfoxide was added and the reaction mixture was heated under reflux (120–140 °C) for 4 h. After cooling, 100 ml of water were added and the organic product was extracted into dichloromethane solvent. The product, allyl 4-(*trans*-1-propenyl)phenyl ether, was obtained in 56% yield (16.5 g) after silica gel chromatography using hexanes as the eluent. ^{1}H NMR (250 MHz, $CDCl_3$), δ 1.82–1.85 (dd, 3H, J = 6.51, 1.45), 4.48–4.51 (d, 2H, J = 6.75), 5.23–5.29 (d, 1H, J = 10.53), 5.34–5.43 (d, 1H, J = 17.21), 5.95–6.11 (m, 2H), 6.28–6.35 (d, 1H, J = 15.78), 6.80–6.85 (d, 2H, J = 6.87), 7.20–7.24 (d, 2H, J = 6.70); ^{13}C NMR (250 MHz, $CDCl_3$), δ 18.390, 68.817, 114.733, 117.581, 123.535, 126.827, 130.307, 130.957, 133.332, 157.577; HRMS, calculated for $C_{12}H_{14}O + H$ (M + 1), 175.112290; found, 175.111787.

To allyl 4-(*trans*-1-propenyl)phenyl ether (14.58 g, 83.7 mmol) dissolved in 150 ml of dry dimethyl sulfoxide was added potassium *tert*-butoxide (9.32 g). The reaction mixture was heated at 120–140 °C for 6 h, followed by cooling and addition of 300 ml of water. The organic product was extracted into dichloromethane and, after drying and removal of the solvent, the desired product, 1-propenyl 4-(*trans*-1-propenyl)phenyl ether (**2**), was obtained in 82% yield (12.0 g) as a mixture of *cis*/*trans*-propenyl isomers (*cis*:*trans* = 2.5:1). A small amount (0.175 mg, 1.2% yield) of the pure *cis*-1-propenyl ether was then obtained by column chromatography on silica gel (hexanes eluent). ^{1}H NMR (250 MHz, $CDCl_3$), δ 1.68–1.72 (dd, 3H, J = 5.96,1.70), 1.84–1.87 (dd, 3H, J = 6.56,1.53), 4.82–4.88 (m, 1H), 6.09–6.15 (m, 1H), 6.32–6.38 (m, 2H), 6.89–7.27 (m, 4H); ^{13}C NMR (250 MHz, $CDCl_3$), δ 9.350,18.404, 107.275, 116.157, 124.272, 126.895, 130.195, 132.432, 140.935, 156.458; HRMS, calculated for $C_{12}H_{14}O + H$ (M + 1), 174.104465; found, 174.105042.

*Reaction of cis-(1-propenyl) 4-(trans-1-propenyl)phenyl Ether (**2**) with 1,3-cyclopentadiene.* The title compound (**2**, 61 mg, 0.35 mmol) and 1, 3-cyclopentadiene (245 mg, 3.5 mmol) were dissolved in a solvent mixture consisting of 8 ml of dichloromethane and 2 ml of water and the solution was cooled to 0 °C. Tris(4-bromophenylaminium hexachloroantimonate (60 mg, 0.074 mmol) was then added and the reaction mixture stirred for 3 min prior to quenching with saturated methanolic potassium carbonate. After workup with additional water and dichloromethane and drying, the product was chromatographed on silica gel [hexanes–dichloromethane (50:1)] to yield 27 mg (32%) of the *endo* Diels–Alder adduct corresponding to addition to the anisyl moiety. ^{1}H NMR (250 MHz, $CDCl_3$), δ 1.16–1.25 (d, 3H, J = 6.89), 1.43–1.49 (m, 1H), 1.50–1.54 (m, 1H), 1.61–1.72 (m, 4H), 2.48 (s, 1H), 2.67–2.71 (t, 1H, J = 4.29), 2.94 (s, 1H), , 4.76–4.87 (m, 1H), 5.83–5.87 (m, 1H), 6.30–6.34 (m, 2H), 6.80–7.10 (m, 4H); HRMS, calculated for $C_{17}H_{20}O$, 241.159240; found, 241.160156.

*Synthesis of cis-1,2-bis(4-trans-propenylphenoxy)-ethene (**3**).* A solution of *cis*-1,2-bis(4-bromophenoxy)-ethene (3.1 g, 8.37 mmol)[8] in 100 ml of anhydrous diethyl in ether was cooled to −20 to −25 °C and treated with 18.3 ml of 1.6 M butyllithium in hexane). After stirring the reaction mixture for 2 h, propionaldehyde (2.61 g, 45 mmol) was added and the resulting mixture stirred for another 2 h at the same temperature before

quenching with water. Aqueous workup then afforded, after chromatography on alumina (dichloromethane eluent), the corresponding diol, *cis*-1,2-bis[4-(1-hydroxypropyl)phenyoxy]ethene, in 47% yield (1.28 g). ^{1}H NMR (250 MHz, $CDCl_3$), δ 0.84–0.89 (t, 6H, J = 7.41), 1.66–1.82 (m, 4H), 4.51–4.56 (t, 2H, J = 6.63), 6.12 (s, 2H), 7.01–7.29 (m, 8H); ^{13}C NMR (250 MHz, $CDCl_3$), δ 10.075, 31.843, 75.462, 116.059, 127.251, 128.351, 139.041, 156.704; HRMS, calculated for $C_{20}H_{22}O_4 + 2H$ (M + 2), 328.167460; found, 328.167084.

This diol (205 mg, 0.625 mmol) was dissolved in 25 ml of anhydrous dichloromethane and treated with phosphorus tribromide (0.4 ml of a 1 M solution in dichloromethane) and allowed to react at room temperature for 1 h. After evaporating the solvent, triethylamine (50 ml) was added and the solution refluxed for 2 h. After removal of the triethylamine, water and dichloromethane were added and the organic layer was separated, dried and the solvent removed. Following chromatography on alumina [hexanes–dichloromethane (6:1)] the desired compound (**3**) was isolated in 52% yield (95 mg). ^{1}NMR (250 MHz, $CDCl_3$), δ 1.83–1.86 (d, 6H, J = 6.51), 6.07–6.16 (m, 2H), 6.10 (s, 2H), 6.30–6.37 (d, 2H, J = 17.1), 6.98–7.02 (d, 4H, J = 6.73), 7.24–7.28 (d, 4H, J = 6.78); ^{13}C NMR (250 MHz, $CDCl_3$), δ 18.405,116.252, 124.601, 126.915, 128.290, 130.114, 132.914, 156.298; HRMS, calculated for $C_{20}H_{20}O_2 + H$ (M + 1), 293.154155; found, 293.153920.

*Diels–Alder reaction of cis-1,2-bis(trans-4-propenylphenoxy)ethene (**3**) with 1,3-cyclopentadiene.* To cyclopentadiene (23 mg, 0.35 mmol) and the substrate **3** (17 mg, 0.058 mmol) dissolved in anhydrous dichloromethane (10 ml) were added 9.5 mg (0.0116 mmol) of tris(4-bromophenyl)aminium hexachloroantimonate in 5 ml of dichloromethane at 0 °C. The reaction was quenched after 3 min with saturated methanolic potassium carbonate and the organic phase worked up in the usual way. Silica gel chromatography yielded 10 mg (56.7%) of the bis-Diels–Alder adduct, corresponding to reaction at the two propenyl groups, predominantly as the *endo, endo* isomer, but with a minor amount of the *endo, exo* isomer, which could not be readily separated. The spectroscopic data are given for the predominant *endo, endo* isomer. ^{1}H NMR (250 MHz, $CDCl_3$), δ1.19–1.23 (d, 6H, J = 6.85), 1.46–1.53 (m, 2H, *anti*-C7 proton on the norbornane ring), 1.65–1.67 (m, 4H, *syn*-C7 and C6 protons), 2.49 (s, 2H, bridgehead proton at C1), 2.68–2.71 (m, 2H, bridgehead proton at C4), 2.96 (s, 2H, benzylic proton at C5), 5.84 (m, 2H, olefinic proton at C2), 6.06–6.08 (s, 2H, olefinic protons on the central double bond), 6.29–6.32 (m, 2H, olefinic protons at C3), 6.91–6.95 (d, 4H, aromatic protons, J = 8.69), 7.08–7.11 (d, 4H, aromatic protons, J = 8.52); ^{13}C NMR (250 MHz, $CDCl_3$), δ 21.053, 41.366, 46.870, 49.198, 49.492, 52.579, 115.526, 128.320, 128.806, 133.475, 138.089, 139.122, 155.603; HRMS, calculated for $C_{30}H_{32}O_2 + H$ (M + 1), 425.248056; found, 425.247317.

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