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Experimental and theoretical study of a Diels–Alder reaction between a sugar-derived nitroalkene and cyclopentadiene

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ABSTRACT

The Diels–Alder reaction of a pyranose-derived nitroalkene 1 with cyclopentadiene is described, and the unexpected facial selectivity of the cycloaddition is analyzed by a computational study.

1. Introduction

The Diels–Alder (DA) reaction is one of the most studied and widely used processes in organic synthesis. This transformation enables the formation of carbon–carbon bonds and carbon–heteroatom bonds in a regio- and stereocontrolled approach, yielding six-membered rings and a maximum of four stereogenic centers in one step.[1] The use of simple nitroalkenes as dienophiles in DA transformations has emerged as an attractive strategy in organic synthesis. The nitro group provides dienophile activating properties, high regio and stereoselectivity, and access to a wide range of functional groups, such as amides, hydroxylamines, amines, nitrones, oximes, nitriles, nitrile oxides, nitronates, and carbonyls.[2] In addition, it is well known that nitroalkenes can function either as dienophiles or heterodienes in Diels–Alder reactions. The competition between these cycloaddition types is an interesting subject, both from a theoretical[3] and a practical[4] point of view.

As part of our program on the enantiospecific synthesis of biologically important natural products using widely available carbohydrates,[5] we have synthesized methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-α-D-*erythro*-hex-2-enopyranoside (**1**) as a suitable precursor for carbocyclic systems bearing a quaternary center.[6] Nitroalkene **1** offers an excellent opportunity to determine the role of the nitro group in the reactivity and stereoselectivity in DA reactions using carbohydrate-derived dienophiles. The unexpected experimental results obtained, along with a computational study, are reported herein.

2. Results and discussion

The synthesis of **1** was accomplished in four steps and 77% overall yield from methyl α-D-glucopyranoside.[6] Treatment of nitroalkene **1** with freshly distilled cyclopentadiene in toluene at 70–80 °C afforded products **3** and **4** in a 1.5:1 ratio and 64% overall isolated yield after column chromatography (Scheme 1). The reaction temperature was optimized in order to compare the reaction outcome with other previously reported results[5d] and to minimize dimerization problems of the cyclopentadiene. It was also observed by TLC that above 100 °C undefined degradation byproducts were produced.

The structural assignments for both products were based on spectroscopic evidence obtained from homo and heteronuclear 2D NMR studies, as well as from NOE experiments. The signal correlations allowed us to assign all the protons and carbon atoms for each isomer.

Compound **3** (α-*exo*) showed the following relevant NMR data: the norbornene signals appeared at 1.38 and 1.60 ppm for the methylene protons (the first of them is in the *endo*-position), 3.03 and 3.86 ppm for the bridgehead protons, 6.18 and 6.44 ppm for the vinylic protons as two double doublets. The carbon signals of the norbornene system appeared at 48.0 ppm for the methylene, 45.5 and 51.4 ppm for the bridgehead carbons, and 130.9 and 141.9 ppm for the vinylic positions.

The stereochemical outcome was established through nuclear Overhauser effect (NOE) experiments (Fig. 1): A 2.53% signal enhancement between H-15*endo*/H-11 denoted the *exo* approach; a 1.37% signal enhancement between H-8/H-13 and 1.80% between H-8/H-14 showed the attack of the cyclopentadiene from the α-face of the dienophile in the *exo* mode.

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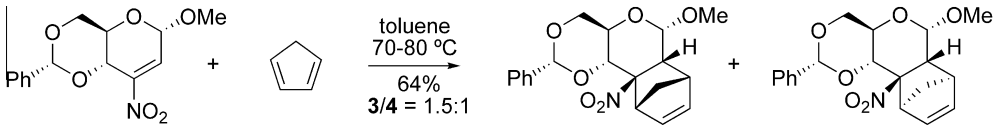
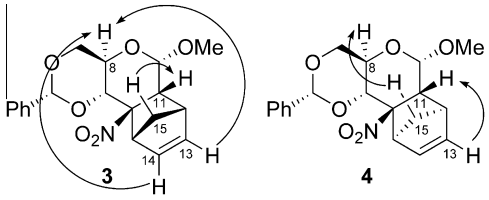


1 2 3 4

Scheme 1.



3 4

Figure 1.

Compound **4** (α-*endo*) showed the following NMR signals: the norbornene signals appeared at 1.64 and 2.01 ppm for the methylene protons, 3.20 and 3.87 ppm for the bridgehead protons, and 6.10 and 6.39 ppm for the vinylic protons. In the ^{13}C NMR spectrum, the norbornene signals appeared at 48.1 ppm for the methylene carbon, at 44.2 and 47.5 ppm for the bridgehead positions, and at 138.0 and 140.5 ppm for the vinylic carbons.

Also in this case, the stereochemical result was determined by NOE effect: A 9.40% signal enhancement between H-15*endo*/H-8 established the approximation of cyclopentadiene from the α-face of the dienophile in an *endo mode*, and a 0.84% signal enhancement between H-13/H-11 corroborated the *endo* approach of the diene.

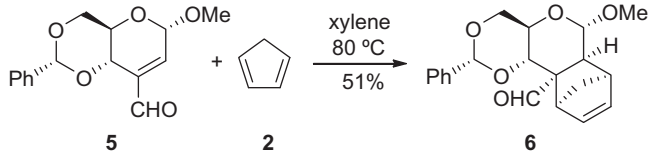
Based on these data, we could unequivocally identify the major and minor compounds **3** and **4** as the *exo*-α and *endo*-α adducts, respectively.

It is well documented that the π-facial selectivity observed in cycloaddition reactions of dienophiles structurally related to **1** is mainly governed by steric effects.[7,8] Typically, the anomeric alkoxy group serves as an element of stereocontrol, thus leading the diene to attack from the opposite face.[7,8] Since the bicyclic dienophile **1** is conformationally rigid, the steric hindrance produced by the anomeric methoxy group should preclude any addition from the α-face of the molecule, as we observed when using similar dienophiles.[5d] For instance, the reaction between aldehyde **5** with cyclopentadiene afforded *exo*-β cycloadduct **6** as the only detectable product (Scheme 2). Similar β cycloadducts were obtained with other sugar-derived dienophiles bearing different exocyclic electron-withdrawing groups.[7b]

However, in the DA reaction between **1** and **2**, α-face selectivity was observed, which constitutes a surprising and unexpected result.

We found precedents in the literature regarding the peculiar facial selectivity of this nitroalkene and also analogous vinyl sulfones that could not explain the intriguing facial selectivity when these compounds were used as Michael acceptors.[9]

These facts prompted us to undertake a theoretical investigation by performing several DFT calculations at the B3LYP/6-31G* level of theory[10] in order to understand the origins of the unexpected stereoselectivities observed in the cycloaddition reaction. The Diels–Alder reactions between cyclopentadiene (**2**) and



5 2 6

Scheme 2.

dienophiles **1** or **5** can take place through four reaction channels, depending on the approach and orientation of **2** toward the dienophile, namely **TS-Nα**, **TS-Nβ**, **TS-Xα**, and **TS-Xβ** (the transition structures were named as follows: the first and second numbers indicate the dienophile and diene, respectively; the **N** and **X** were used for *endo* and *exo* orientation, and α and β accounts for the facial approach of diene toward dienophile).[†]

Examination of the reaction surfaces allowed us to locate the transition structures corresponding for each mode of addition, as shown in Figure 2. In all cases, the C2–C1′ Wiberg bond indices (WBI) are higher than the respective C3–C4′ bond orders, and bond lengths between C2–C1′ are shorter than the C3–C4′ distances. Thus, in the transition structures we found that the C2–C1′ bonds are almost fully developed, while the second C3–C4′ bonds are only emerging. The computed synchronicities are, therefore, quite low (S_y ranging from 0.74 to 0.84).

IRC calculations yielded **TS-Nα**, **TS-Xα,** and **TS-Xβ** as the only saddle points connecting reactants and products. Therefore, these TSs correspond to a normal electron demand Diels–Alder path leading to the corresponding [4+2] cycloadduct in a concerted fashion. However, our calculations show that **TS-1+2-Nβ** and **TS-5+2-Nβ** lead to nitronate (**Int1**) and vinyl-dihydropyran (**Int2**) intermediates, respectively (Scheme 3).

Both **Int1** and **Int2** correspond to a [2+4] cycloadduct, resulting from a [2+4] heterocycloaddition. Further exploration of the potential energy surface (PES) allows one to find **TS-1+2-Nβ-2** and **TS-5+2-Nβ-2** that implies the conversion of formal [2+4] cycloadducts **Int1** and **Int2** into the formal [4+2] cycloadducts **P-1+2-Nβ** and **P-5+2-Nβ**, respectively. This conversion is associated with a Claisen rearrangement, which is a [3,3] sigmatropic shift. There are several examples in the literature of cross-[4+2] cycloaddition reactions, that is, a tandem hetero Diels–Alder cycloaddition/[3,3] sigmatropic shift.[3] It is also important to point out that all efforts to locate [4+2]-**Nβ** transition structures merged in their [2+4] counterpart. This could be attributed to the unfavorable steric interaction between H-5′α and H-4 that would arise in the (hypothetically) [4+2] TSs.

Calculated Gibbs free-energy activation barriers suggest that α-face addition should be strongly favored for the **1+2** reaction, while the β mode of addition should be preferred for the reaction between **5** and **2**. The computed *endo*/*exo* ratios are 30:70 (toluene) and 10:90 (toluene) for the **1+2** and **5+2** systems, respectively. It is also important to point out that the energy activation barriers computed for both systems under study are similar in magnitude; therefore, both **2** and **5** should display similar reactivity toward cyclopentadiene. Although these results are in excellent agreement with the experimental findings discussed above, we aimed to indentify the governing factors that influence the unusual selectivity in the reaction between **1** and **2**.

The proximity between oxygen atoms Oa and Ob (Fig. 2) leads to repulsive electrostatic interactions, which in turn might have a crucial effect in the relative stabilization of competitive transition

[†] A complete computational study of the Diels–Alder reaction between **5** and **2** had been already described using the semiempirical AM1 method.[7a] However, we have recalculated the **5+2** system at the B3LYP/6-31G* level of theory in order to obtain comparable results.

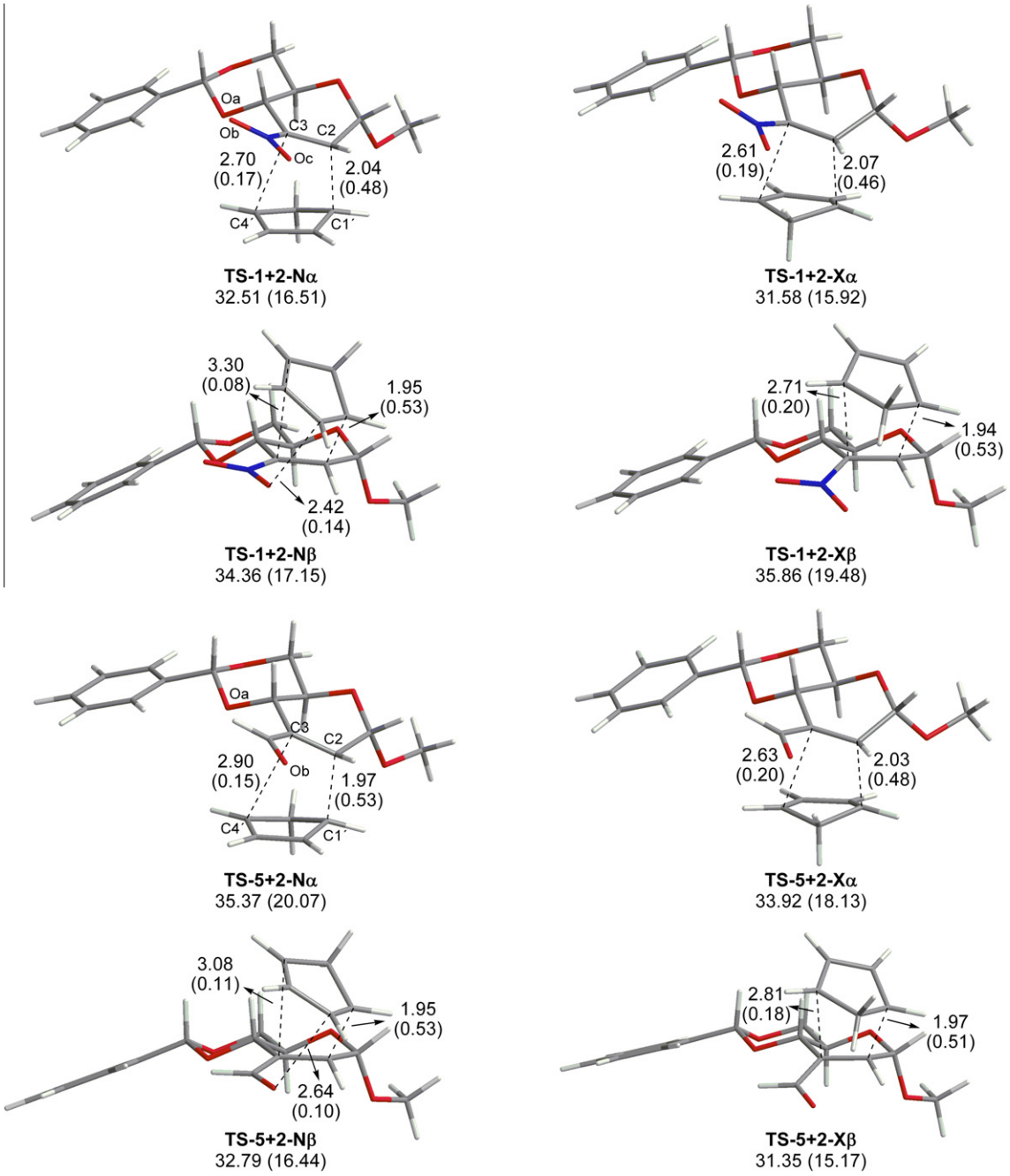


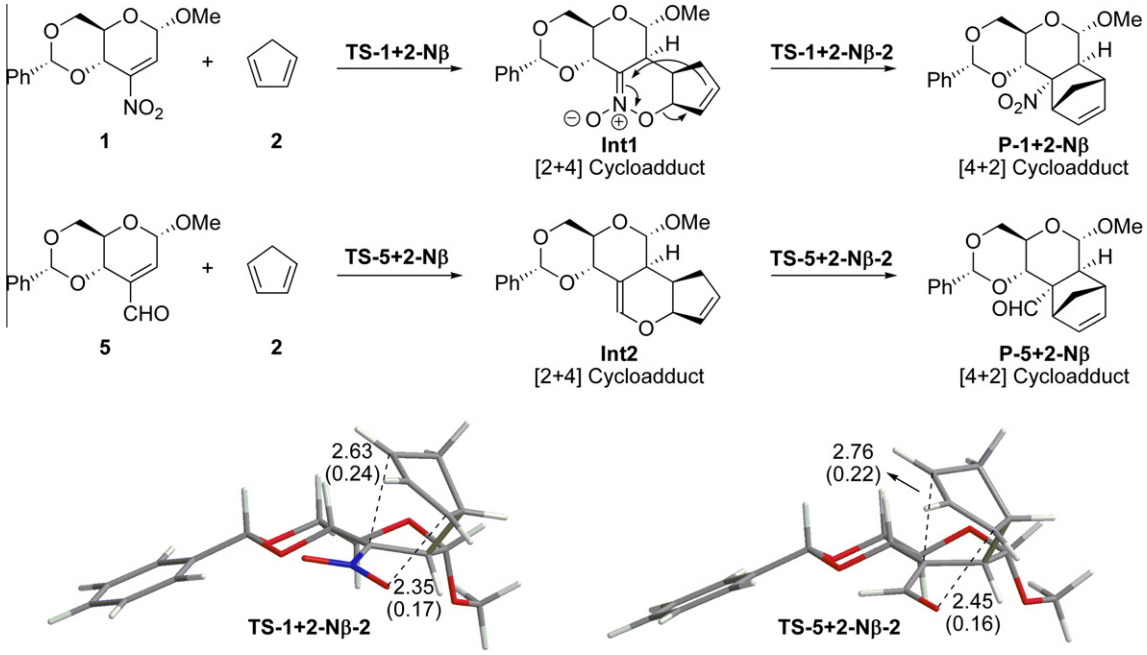
Figure 2. Optimized geometries for the TSs of the cycloaddition reaction of cyclopentadiene with **1** and **5** with selected distances in Å and Wiberg bond indices (in parentheses). Free energies relative to reactants in the gas phase and in solution (in parentheses) are shown in kcal mol^{-1}.

structures. The calculated Coulombic forces using the Mulliken partial charges were in good agreement with the relative energies between diastereomeric transition structures.[‡] For instance, the most stable transition structure (**TS-1+2-Xα** was found to exhibit the lowest Coulombic interaction of all TSs. It is important to point out that in the reaction between **5** and **2** the aldehyde moiety adopts a cisoid conformation in the most stable TS located for each mode of addition. As a consequence, the large distance between Oa and Ob prevails over any significant Coulombic repulsion; therefore, the observed β selectivity should be attributed to steric effects. However, in the transoid arrangement the α approach exhibits a lower Coulombic interaction as compared to that of the β approach; therefore, the energy barriers for both modes of addition are nearly the same.

To examine whether additional electronic factors contribute toward the relative stabilization between competing transition structures, a natural bonding analysis was performed. Interestingly, the lowest energy transition structure **TS-1+2-Xα** exhibits improved delocalization over that of the corresponding **TS-1+2-Xβ** in accordance with the predicted selectivity. In the case of **TS-5+2-Xα** and **TS-5+2-Xβ**, the analogous NBO analysis reveals similar electronic delocalization for both TSs.

In summary, we have presented an appealing effect of inversion of π-facial selectivity in a Diels–Alder reaction between a sugar-derived nitroalkene and cyclopentadiene compared with other previously studied dienophilic systems. DFT calculations have shown that differential electrostatic interactions and electronic

[‡] In an effort to establish the magnitude of these interactions, we carried out further calculations that are described in detail in the Supplementary data.



Scheme 3.

delocalization operating in the diastereomeric transition structures may be invoked, at least in part, as the origins of this unexpected result. Finally, calculations based on Gibbs free energies of the competing TSs correctly reproduced the experimentally observed *endo*/*exo* and π-facial selectivities.

3. Experimental

3.1. General

Melting points were taken on a Leitz Wetzlar Microscope Heating Stage, Model 350 apparatus and are uncorrected. Optical rotations were recorded with a Jasco DIP 1000 polarimeter. 1D and 2D NMR spectra were recorded on a Bruker AC-200 spectrometer with TMS as the internal standard and $CDCl_3$ as the solvent. Reactions were monitored by TLC on 0.25 mm E. Merck Silica Gel 60 F254 plates using UV light (254 nm) and anisaldehyde–H_2SO_4–HOAc as the developing agent. Flash column chromatography using E. Merck Silica Gel 60H was performed by gradient elution of mixture of *n*-hexane with increasing volumes of EtOAc. Reactions were run under an argon atmosphere with dry, freshly anhyd distilled solvents. Yields refer to chromatographically and spectroscopically homogeneous materials.

3.2. Preparation of cycloadducts 3 and 4

Nitroalkene **1** (70.3 mg, 0.24 mmol) was dried azeotropically with anhyd benzene and dissolved in anhyd toluene (2.4 mL) under an argon atmosphere at room temperature. To this solution freshly cracked cyclopentadiene (0.2 mL, 2.4 mmol) was added, and the mixture was heated at 70–80 °C for 3 days. The organic solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography. Both products were crystallized from EtOAc–hexanes.

3.2.1. (1*R*,2*R*,3*S*,5*R*,8*R*,10*S*,11*R*,12*S*) 10-Methoxy-2-nitro-5-phenyl-4,6,9-trioxatetracyclo[10.2.1.$0^{2,11}$.$0^{3,8}$]pentadec-13-ene (3)

Compound **3** (36.6 mg, 43%); white crystalline solid; mp 160.0–160.5 °C; $[\alpha]_D^{22}$ 99.6 (*c* 1.55, $CHCl_3$); IR (KBr, ν_{max} cm^{-1}): 760, 912, 997, 1047, 1219, 1344, 1458, 1530 (NO_2), 1541, 2363, 2859, 2994; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.38 (d, 1H, J_{gem} = 9.4 Hz, H-15β), 1.60 (d, 1H, J_{gem} = 9.4 Hz, H-15α), 3.03 (br s, 1H, H-12), 3.33 (s, 3H, OCH_3), 3.56 (dd, 1H, J_{gem} = $J_{8,7ax}$ = 9.6 Hz, H-7ax), 3.62 (m, 1H, H-8), 3.71 (dd, 1H, $J_{10,11}$ = 8.2 Hz, $J_{11,12}$ = 3.7 Hz, H-11), 3.86 (d, 1H, $J_{1,14}$ = 3.2 Hz, H-1), 4.05 (d, 1H, $J_{3,8}$ = 9.6 Hz, H-3), 4.21 (dd, 1H, J_{gem} = 9.6 Hz, $J_{7eq,8}$ = 4.2 Hz, H-7eq), 5.12 (d, 1H, $J_{10,11}$ = 8.2 Hz, H-10), 5.52 (s, 1H, H-5), 6.18 (dd, 1H, $J_{13,14}$ = 5.3 Hz, $J_{1,14}$ = 3.2 Hz, H-14), 6.44 (dd, 1H, $J_{13,14}$ = 5.3 Hz, $J_{12,13}$ = 3.0 Hz, H-13), 7.35–7.53 (m, 5H, aromatics); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 45.5 (C-12), 48.0 (C-15), 50.4 (C-11), 51.4 (C-1), 55.1 (OCH_3), 60.6 (C-8), 69.9 (C-7), 82.5 (C-3), 97.7 (C-10), 99.4 (C-2), 102.0 (C-5), 126.1 (2C aromatics, C-*ortho*), 128.2 (2C aromatics, C-*meta*), 129.0 (1C aromatic, C-*para*), 130.9 (C-13), 137.1 (1C aromatic, C-*ipso*), 141.9 (C-14); HRFABMS: calcd for $C_{19}H_{21}NO_6$ [M+H$^+$] *m*/*z* 360.14458; found *m*/*z* 360.14490.

3.2.2. (1*S*,2*R*,3*S*,5*R*,8*R*,10*S*,11*R*,12*R*) 10-Methoxy-2-nitro-5-phenyl-4,6,9-trioxatetracyclo[10.2.1.$0^{2,11}$.$0^{3,8}$]pentadec-13-ene (4)

Compound **4** (18.3 mg, 21%) white crystalline solid; mp 132.0–133.0 °C; $[\alpha]_D^{20}$ −51.0 (*c* 0.39, $CHCl_3$); IR (KBr, ν_{max} cm^{-1}): 745, 812, 1088, 1348, 1450, 1533, 1541 (NO_2), 2365, 2855, 2969; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.64 (ddd, 1H, J_{gem} = 9.9 Hz, $J_{15β,12}$ = 1.7 Hz, $J_{15β,1}$ = 1.5 Hz, H-15β), 2.01 (br d, 1H, J_{gem} = 9.9 Hz, H-15α), 3.11 (dd, 1H, $J_{10,11}$ = 7.9 Hz, $J_{11,12}$ = 2.8 Hz, H-11), 3.20 (br s, 1H, H-12), 3.41 (s, 3H, OCH_3), 3.71 (dd, 1H, J_{gem} = $J_{7ax,8}$ = 9.8 Hz, H-7ax), 3.83 (ddd, 1H, $J_{8,7ax}$ = $J_{8,3}$ = 9.8 Hz, $J_{8,7eq}$ = 4.0 Hz, H-8), 3.87 (br s, 1H, H-1), 4.07 (d, 1H, $J_{3,8}$ = 9.8 Hz, H-3), 4.36 (dd, 1H, J_{gem} = 9.8 Hz, $J_{7eq,8}$ = 4.0 Hz, H-7eq), 5.15 (d, 1H, $J_{10,11}$ = 7.9 Hz, H-10), 5.59 (s, 1H, H-5), 6.10 (dd, 1H, $J_{13,14}$ = 5.6 Hz, $J_{1,14}$ = 2.7 Hz, H-14), 6.39 (dd, 1H, $J_{13,14}$ = 5.6 Hz, $J_{12,13}$ = 3.3 Hz, H-13), 7.35–7.56 (m, 5H, aromatics); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 44.2 (C-12), 46.3 (C-11), 47.5 (C-1), 48.1 (C-15), 55.5 (OCH_3), 60.8 (C-8), 70.1 (C-7), 81.9 (C-3), 98.0 (C-10), 99.4 (C-2), 102.1 (C-5), 126.0 (2C aromatics, C-*ortho*), 128.2 (2C aromatics, C-*meta*), 129.0 (1C aromatic, C-*para*), 136.9 (1C aromatic, C-*ipso*), 138.0 (C-13), 140.5 (C-14); HRFABMS: calcd for $C_{19}H_{21}NO_6$ [M+H$^+$] *m*/*z* 360.14458; found *m*/*z* 360.14630.

3.3. Computational methods

All density functional theory (DFT) calculations were carried out with the B3LYP[10] functional and the 6-31G* basis set,[11] using GAUSSIAN 03.[12] Geometries for all structures were fully optimized, and frequency calculations were used to confirm the nature of the stationary points. All transition structures were confirmed to have only one imaginary frequency corresponding to the formation of the expected bonds. Intrinsic reaction coordinate (IRC) calculations were performed to determine the connections between stationary points. To analyze the formation and breaking of bonds, Wiberg bond indices (WBIs) were calculated by using the natural bond orbital (NBO) program[13] as implemented in GAUSSIAN 03. Reported thermochemical properties include zero-point energies (ZPEs) without scaling and were calculated at 1 atm and 298.15 K. Free energies in solution were computed on the structures optimized in the gas phase with the polarizable continuum model (PCM) as implemented in GAUSSIAN 03 with toluene as the solvent.[14]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.12.006.

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