EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Cyclic Nitronates via Sugar-Derived Nitroalkenes in a Hetero-Diels-Alder/[3,3]-Sigmatropic Rearrangement Pathway.

Authors: María Inés Mangione, Darián Vazquez, Rolando Ángel Spanevello, and Ariel Marcelo Sarotti

To be cited as: *Eur. J. Org. Chem.* **2024**, e202400650

Link to VoR: https://doi.org/10.1002/ejoc.202400650

WILEY VCH

10.1002/ejoc.202400650

WILEY VCH

RESEARCH ARTICLE

Cyclic Nitronates via Sugar-Derived Nitroalkenes in a Hetero-Diels-Alder/[3,3]-Sigmatropic Rearrangement Pathway

Darián Vazquez[a], Rolando A. Spanevello[a]; Ariel M. Sarotti[a] and María I. Mangione[a]*

[a] D. Vázquez, Prof. Dr. R. A. Spanevello, Prof. Dr. A. M. Sarotti, Prof. Dr. M. I. Mangione
Department of Organic Chemistry, Facultad de Ciencias Bioquímicas y Farmacéuticas
Instituto de Química Rosario (IQUIR-CONICET-UNR)
Suipacha 531, S2002LRK, Rosario, Argentina
E-mail: mangione@iquir-conicet.gov.ar

Supporting information for this article is given via a link at the end of the document.

Abstract: Diels-Alder between nitroalkenes derived from a sugar scaffold and cyclopentadiene were examined. Depending on chemical structure of nitroalkene and polarity of solvent used, the reaction proceeded via the formation of a nitronate intermediate. Cyclic nitronates highly functionalized were obtained as chemically stable and stereochemically pure-compounds. [3,3] sigmatropic shift of these ones afforded the Diels Alder cycloadducts in quantitative yield. Mechanistic aspects of reaction between nitroalkenes and cyclopentadiene has been studied using DFT computational methods. Nitronate derivatives are attractive intermediates and open the way for the construction of valuable compounds with potential applications.

Introduction

Since its first appearance in the scientific literature in 1928[1] the Diels-Alder reaction (DA) has become a universal method for obtaining carbocyclic and heterocyclic structures.[2] The DA reaction of nitroalkenes with conjugated dienes is a powerful synthetic tool for the construction of nitrocarbocyclic systems in high regio- and stereoselective manner.[3] Nevertheless, in the case of electron deficient nitroalkenes, the carbon DA reaction can compete with the hetero DA process (HDA) where one of the N=O bonds participates as part of the 4π electron functionality.[3a, 4] Under thermal conditions, nitroalkenes behave as electron-deficient dienophiles and react with dienes yielding 3-nitrocyclohexenes. They can also act as heterodienes under specific reaction conditions: the presence of Lewis acids and low temperatures, electron-withdrawing groups (EWG) adjacent to nitro group, or microwave irradiation, affording cyclic alkyl nitronates.[3a, 5] Moreover, the nitro group provides access to a wide range of functional groups, such as amides, hydroxylamines, amines, nitrones, oximes, nitriles, nitrile oxides, nitronates and carbonyls.[3b]

The use of nitroalkenes as heterodienes leads to high-yielding, and stereoselective method of achieving cyclic nitronic esters. These dipoles can undergo 1,3-dipolar cycloaddition reactions, however, synthetic applications of these two processes are scarce due to the lack of general procedures to prepare nitronates or to their instability. [3b, 6]

DA reaction are continuously subject of both experimental and theoretical studies. In addition to the concerted one step mechanism, it is known that the reaction can also proceed through a two-step zwiterionic or biradical mechanism, leading to more complex stereochemical results. In particular, such mechanisms have been observed in polar [4+2] cycloadditions. [6, 7]

In the present work, we describe the DA reaction of structurally related nitroalkenes, derived from a widely available carbohydrate precursor, as part of our program of enantiospecific synthesis of natural products and related derivatives.[8] Starting with methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-α-D-erythro-hex-2-enopyranoside **2**, which was prepared by an efficient synthetic protocol developed in our laboratory, we obtained a family of 2,3-dideoxy-3-*C*-nitro-α-D-erythro-hex-2-enopyranoside dienophiles. Thermal DA reactions of these ones with freshly cracked cyclopentadiene were assayed and studied. At room temperature and depending on the protective groups present, the cycloaddition proceeds selectively through a hetero Diels-Alder reaction. Surprisingly, chemically stable and enantiomerically pure nitronates were formed with each derivative. Subsequently, [3,3]-sigmatropic rearrangement of these nitronates, induced by temperature, leads to the major observed normal demand cycloadduct performed under heating. These experimental findings along with computational study have paved the way for a comprehensive mechanistic understanding of reactions involving related sugar-derived nitroalkenes.

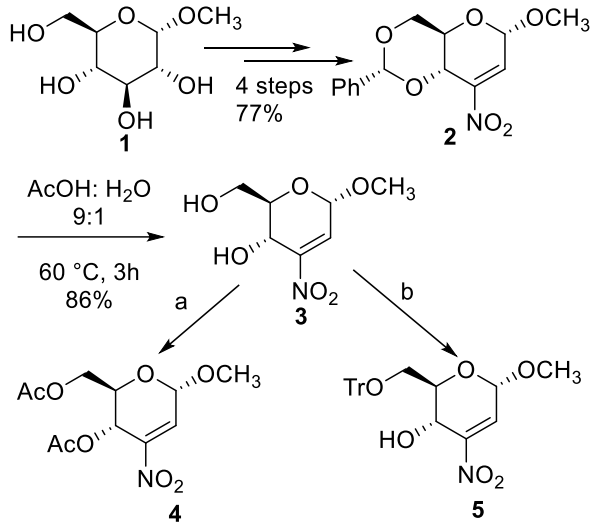
Results and Discussion

Cycloaddition studies

Synthesis of structurally nitroalkenes related is depicted in Scheme 1. Compound **2** was obtained by an optimized procedure in a 77% overall yield from methyl-α-D-glucopyranoside **1**.[9] Deprotection of benzylidene acetal under acidic conditions afforded diol **3** in very good yield.[10] Compound **3** was fully acetylated[11] to obtain **4**, also treated with trityl chloride[12] to afford monoprotected derivative **5**.

10.1002/ejoc.202400650

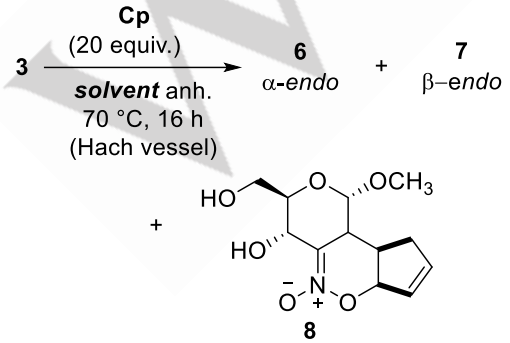
RESEARCH ARTICLE



Conditions: a) Ac_2O, $BF_3.Et_2O$ (cat.), -20 °C, 8 min., 100%; b) TrCl, Et_3N, 0 °C to rt, 3h, 68%

Scheme 1. Synthesis of structurally related dienophiles **2** – **5**.

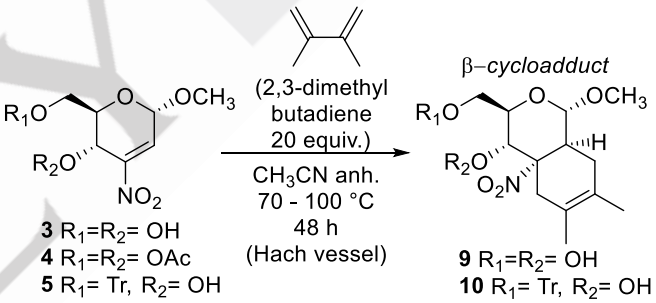
In order to compare our previous results[8], dienophile **3** was submitted to a thermal DA reaction with freshly distilled cyclopentadiene (**Cp**) in toluene at 70 °C in a closed vessel. Products **6** and **7** were formed in a 1:2 ratio approx. and 60% overall isolated yield after column chromatography (Scheme 2). Exhaustive NMR spectroscopic characterization allowed us to determine that **6** and **7** were the α-*endo* and β-*endo* nitronorbornene cycloadducts, respectively (NMR studies and NOE experiments are described in the Supporting Information). Both cycloadducts arise from an *endo*-approximation of **Cp** to nitroalkene, in accordance with Alder's rule.[13] Comparing these results with the conformationally rigid system **2**, no *exo*-adducts were observed. Previous publications demonstrate that face selectivity in structurally related dienophile systems was governed by steric factors.[14] The methoxy group could act as a stereocontrol element generating the attack of the diene from the opposite β-face. Consequently, a higher proportion of the β-*endo* cycloadduct was observed.



Scheme 2. Solvent effect in Diels-Alder reaction of **3** with cyclopentadiene.

To determine the reactivity of our nitroalkenes with other dienes we evaluated the reaction of **3**, **4** and **5** with dienes like 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene. The reactions were carried out in acetonitrile at 70 °C and 100 °C.

Reaction of **3**, **4** and **5** with 1,3-cyclohexadiene, did not afford any product, neither normal nor inverse demand cycloadditions even under heating for 16h at 100 °C. It can be assumed that the lower reactivity of cyclohexadiene affected these reactions. Cycloaddition with 2,3-dimethyl-1,3-butadiene could only be observed after heating from 70 to 100 °C for 48h, no reaction was observed at lower temperatures. Dienophiles **3** and **5** afforded normal β-cycloadducts **9** and **10** in 42 and 69% yield respectively (Scheme 3). Unfortunately, nitroalkene **4** decomposed with heating and no product could be isolated. During NMR studies the trityl group of **10** underwent hydrolysis, generating the cycloadduct **9**. This confirms that **10** resulted from the β-approximation of diene on **5**. These experimental results showed that our systems act as dienophiles under thermal Diels-Alder cycloaddition conditions, with limited reactivity towards other dienes. The reactions did not achieve complete consumption of the starting material, even with an excess of diene. The facial selectivity was preserved, consistent with the results observed with **Cp**.



Scheme 3. Solvent effect in Diels-Alder reaction of **3** with cyclopentadiene.

In order to evaluate solvent effects, the DA reaction of nitroalkene **3** and **Cp** was repeated in various polar protic and aprotic solvents (Scheme 2). The influence of solvent polarity on the mechanism of DA adduct formation, and the resulting stereochemical outcome, is well documented in the literature [4, 7b, 15]. The observed results are presented in Table 1. The DA reactions of compound **3** with **Cp** afforded both α- and β-*endo* cycloadducts, namely **6** and **7**, in the diverse solvents examined.

With an increase in solvent polarity, a new adduct, nitronate **8**, was isolated (Entries 2, 5, and 6). The solvent polarity also influenced the ratio between products **6** and **7**, with the proportion of the latter favored in more polar reaction media. Notably, the major proportion of **8** was observed in anhydrous acetonitrile, along with a quantitative overall yield of the DA reaction (Entry 6). It is worth mentioning that in solvents with similar polarity, such as nitromethane (Entry 7), no formation of **8** was observed, and only cycloadducts **6** and **7** were detected. Among the different solvents tested, the polar protic solvent (Entry 5) exhibited the highest

10.1002/ejoc.202400650

RESEARCH ARTICLE

Entry	Solvent	μ	6 (α–*endo*) %	7 (β–*endo*) %	Nitronate 8 %	Yield (%)
1	Toluene	0.43	20	40	-	60
2	1,4-dioxane	0.45	22	44	11	77
3	^{i}PrOH	1.66	18	56	-	74
4	1,2-DCE	1.86	17	70	-	87
5	HFIP	2.05	3	82	10	95
6	CH_3CN	3.45	9	49	42	100
7	CH_3NO_2	3.54	12	67	-	79

Table 1. Diels-Alder reaction of **3** with **Cp** in solvents with different polarity.

stereoselectivity, yielding 3% of product **6** and 82% of product **7**, along with 10% of **8**. Based on these results, it can be inferred that the formation of cycloadduct **7** is likely driven by a polar mechanism. Nitronate **8** was the result of the [2+4] HDA reaction between nitroalkene **3** and **Cp**. It is worth to mention that, cyclic nitronate **8** was formed under thermal conditions as a chemically stable compound derived from a sugar moiety and without using Denmark Diels-Alder reaction, usually needed for another examples of simple *O*-allyl nitronic esters.[4, 16]

The structure elucidation of **8** was achieved by performing 1D and 2D NMR experiments as well as from NOE experiments. Also, nitronic ester **8** was analyzed using X-ray crystallography.

An interesting spectroscopical data was the difference in chemical shifts between primary and secundary OH groups. The first appeared at 2.01 ppm as a broad singlet and the second one, at 4.65 ppm as a sharp singlet. This observation could be attributed to the posibility of a hydrogen bonding interaction between the OH group in C-4 with O atom of the adyacent cyclic nitronate **8**.

X-ray crystallography of compound **8** revealed the presence of an intramolecular hydrogen bonding interaction between these two atoms, consistent with spectroscopic observations (Figure 1).[17]

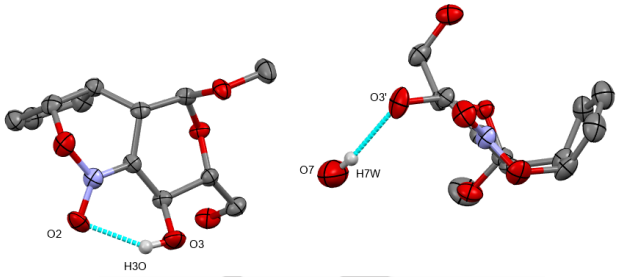


Figure 1. Hydrogen bonding intramolecular interaction. Hydrogen bonds as dashed lines: H1B(O3)···O2: 2.01(6) Å, H7W(O7)···O3': 2.21(2) Å. H atoms not involved in this interactions are omitted for clarity

This interaction would justify the observed chemical stability and the absence of a full rearrangement to the normal demand cycloadduct in the reaction conditions.

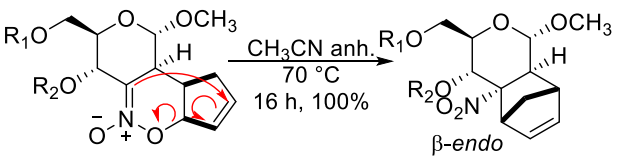
Protecting groups effect

Considering acetonitrile as the solvent to evaluate the DA cycloaddition, dienophiles **2**, **4** and **5** reacted with **Cp** under thermal conditions. Scheme 4 describes the results observed. Nitroalkene **2** afforded only a mixture of **11** and **12**, the same products observed in toluene, but in lower yields, no nitronate were detected. Bis-acetylated derivative **4** afforded 69% of global yield. Considering products distribution, normal cycloadducts **13** and **14** were isolated as an inseparable mixture, representing 53% of the mixture and 16% correspond to nitronate **15**.

Comparison of ^{1}H NMR spectrum of the mixture with the fully acetylated derivative of **7**, let us to determine that the compound **14** was the β-*endo* cycloadduct. Complete spectroscopical characterization of the **13**+**14** mixture enable us to established that product **13** was the α-*endo* cycloadduct. DA reaction of **5** afforded three products: normal cycloadducts **16** and **17** and nitronate **18** in quantitative global yield. Considering the stabilizing hydrogen bonding interaction observed for **8**, the higher proportion of nitronate for the trityl derivative could be attributed to this interaction. These findings underscore the significance of both steric factors and the presence of hydroxyl groups in influencing the outcome of the reactions. The results indicate that the reaction products are not solely dependent on the electronic properties of the components but are also affected by the spatial arrangements and potential interactions between the reacting species. Nitronate formation occurs under thermal conditions and its ratio is related not only to solvents effects but also to changes in the protective groups of the nitroalkene system.

[3,3]-Sigmatropic rearrangement

In polar DA reactions, cyclic nitronates were proposed as intermediates from a [2+4] heterocycloaddition. Subsequently, these intermediates were converted by a Claisen rearrangement, a [3,3] sigmatropic shift, into the normal electron demand adducts. Actually, intense scientific research, both theoretical and experimental, takes place on this sequence HDA/ [3,3] sigmatropic shift.[6, 18, 19] One of the main experimental difficulties is the isolation and characterization of the cyclic nitronate because most of them need special conditions to be obtained or rearrange spontaneously in the reaction medium and cannot be detected. [7b] To ascertain whether our nitronates were products of cycloaddition or intermediates, nitronates **8**, **15** and **18** were heated in acetonitrile at 70 °C. β-*endo* cycloadducts **7**, **14** and **17** respectively, were obtained as pure samples in quantitative yields (Scheme 5). Spectroscopical analysis of these samples were in agreement with adducts isolated from normal DA reaction.

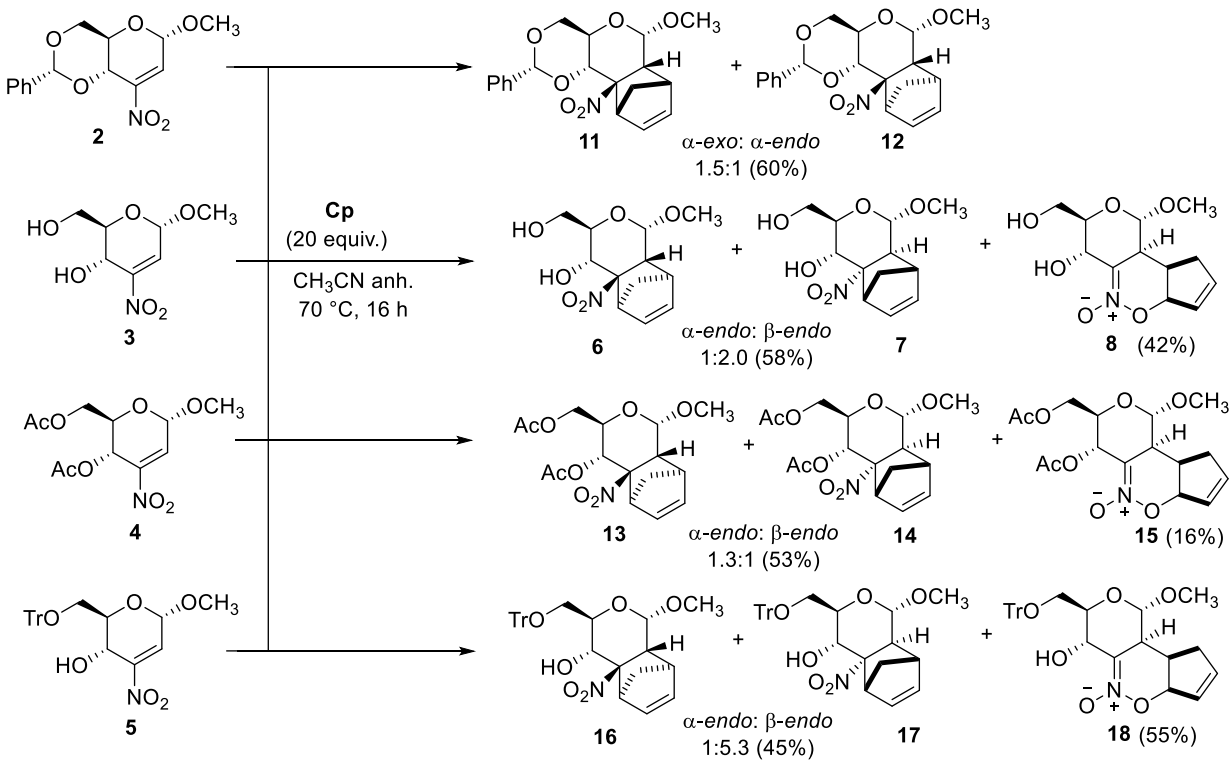


8: $R_1 = R_2 = H$ **7**: $R_1 = R_2 = H$
15: $R_1 = R_2 = Ac$ **14**: $R_1 = R_2 = Ac$
18: $R_1 = Tr$, $R_2 = H$ **17**: $R_1 = Tr$, $R_2 = H$

Scheme 5. [3,3]-sigmatropic rearrangements of nitronates **8**, **15** and **18**.

10.1002/ejoc.202400650

RESEARCH ARTICLE



Scheme 4. Comparative thermal Diels-Alder reactions of nitroalkenes **2** – **5** with **Cp**.

No other cycloadducts were detected. Sigmatropic rearrangement were carried out under mild temperature conditions. It could be assumed that this clean rearrangement may be due to the fact that the β-*endo* adducts are thermodynamically more stable than their respective nitronates.

Mechanistic observations

To establish whether there is competition between the normal demand DA and HDA reactions in these cycloadditions, and to identify the predominant reaction mechanism, the reactions of **3**, **4** and **5** were conducted at room temperature under inert atmosphere in a closed vessel (Hach vessel). Monitoring was performed at specific time intervals using thin-layer chromatography and ^{1}H NMR spectroscopy. Reactions at room temperature were slower than at 70 °C, and after 48 hours starting material was not completely consumed. The first cycloadduct formed was the product of the HDA reaction, the nitronic ester. Nitroalkenes **3**, **4** and **5** behave as hetero-dienes with **Cp**. In the case of compound **4** along with the formation of the nitronate **15**, the α-*endo* cycloadduct **13** was observed after 16 hours of reaction. Also, after overnight reaction, sigmatropic rearrangement from nitronates to β-*endo* adducts began started to be observed. At 48 hours, nitronates proportion followed the order **18** > **8** > **15**, which is in agreement with reaction conducted at 70 °C. The results of the monitoring by ^{1}H NMR are summarized in Table 2.

According to published literature, periselectivity in cycloadditions of nitroalkenes mainly depends on specific protocol for preparation and temperature.[20] There are only few examples of nitroalkenes structures that are prone to act as hetero-dienes in DA reaction under thermal conditions, for example, indole and pyrrole derivatives with EWG,[21] activated nitroethylene derivatives substituted with $PhSO_2$, PhCO, 4-aza-6-nitrobenzofuroxan.[22]

Table 2. Monitoring cycloaddition reactions by ^{1}H NMR.

Nitroalkene	Compounds[a]	δ (ppm)[b]	Relative mixture composition (%)[c]		
			4 h	16 h	48 h
3	**3**	7.05	100	47	26
	8[l]	4.78	0	44	58
	6	4.28	0	0	0
	7	6.36	0	9	16
4	**4**	7.17	94	43	8
	15	4.78	6	31	47
	13	5.17	0	11	19
	14	6.35	0	16	25
5	**5**	7.07	95	40	8
	18	4.81	5	47	69
	16	6.46	0	0	0
	17	4.65	0	13	23

10.1002/ejoc.202400650

[a] Nitroalkene and cycloadducts. [b] Singlets consider for relative integration. [c] Relative ratio of nitroalkene and cycloadducts expressed in relative percentajes.

Conformational fixed nitroalkene **2** only behaves as dienophile with cyclopentadiene. Flexible compounds **3**, **4** and **5** are hetero-dienes in the cycloaddition with **Cp**. But also, in these nitroalkenes the OH group at C-4 appears to have an influence favouring the formation of the nitronic ester, as observed in the monitored cycloaddition reactions with **Cp**.

When OH at C-4 is protected, such as in compound **4**, the competition of the normal demand DA reaction begins to emerge. Consequently, these nitroalkenes prove to be novel systems that act as heterodienes under thermal conditions, enabling the generation of functionalized poly- and heterocyclic systems as promising starting materials for the preparation of molecules of higher structural complexity.

Theoretical Studies

Based on the experimental results discussed above, it became evident that the nature of the protecting group at C4-OH and C6-OH has strong impact on the reactivity and selectivity of the reactions.[20b] To shed light on this issue, we carried out a comprehensive theoretical study using system **4** as case study at the B3LYP/6-311+G** level of theory, which was successfully explored by Houk and co-workers in related reactions. As the experimental results obtained with compounds **3-5** are qualitatively similar, the choice of **4** was based to avoid potential energy biases caused by the possible overestimation of DFT for the intramolecular hydrogen bonding interactions present in systems with free OH groups.[23] To validate the results, the **2** system (previously studied at the B3LYP/6-31G* level of theory) was recomputed at the B3LYP/6-311+G** level.[8] Four possible reaction channels are possible depending on the approach and orientation of the diene towards the dienophile, namely **TS-N-α**, **TS-N-β**, **TS-X-α**, and **TS-X-β**, where **N** and **X** accounts for the *endo* and *exo* orientations, respectively, and α and β indicate the facial approach of the diene. All the transition states (TSs) found are highly asynchronous, with the forming C2-C1' bond distances being considerably shorter than C3-C4', consistent with the higher electrophilicity of C2 due to resonance effects. Intrinsic reaction coordinate (IRC) calculations identified **TS-X** as the only saddle point connecting reactants and products (see Supporting Information), compatible with a polar Diels-Alder mechanism (pDA). However, the *endo* TSs present a different scenario, with greater asynchronicity and a significant interaction between the oxygen of the nitro group (namely, O_b) and the C2' carbon of the cyclopentadiene. In **TS-2+cp-N-β**, **TS-4+cp-N-α**, and **TS-4+cp-N-β** (Figure 2) there is a very advanced C2-C1' bond (r_A 1.94, 1.95, and 1.95 Å, respectively) and the preference towards the hetero-Diels-Alder nitronate (**Int**) is evidenced with the shorter C2'-O_b bonds lengths (r_C 2.42, 2.62, and 2.48 Å, respectively) relative to the C3-C4' (r_B 3.35, 3.34, and 3.29 Å, respectively).[20b]

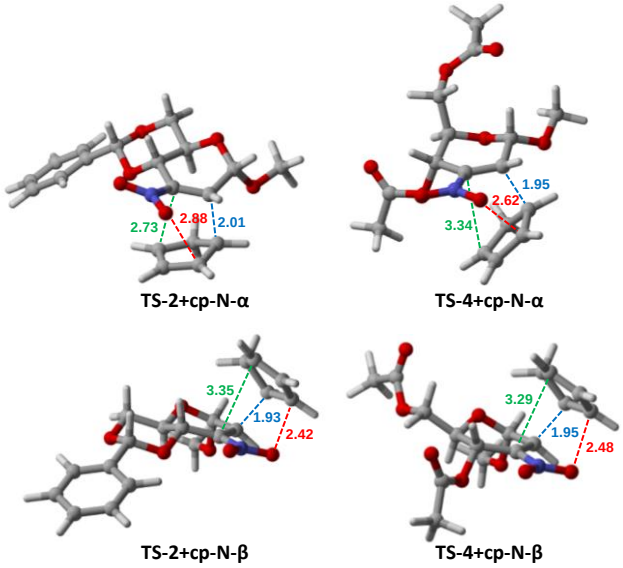


Figure 2. Transition state geometries (*endo* channels) for the reactions of **2** and **4** with cyclopentadiene. The selected bond distances (r_A in blue, r_B in green, r_C in red) are given in Å

Significantly, a higher Diels-Alder character was observed in the thermal reaction between nitroethylene and cyclopentadiene in the bis-perycyclic TS, with much shorter r_B values compared to r_B (2.56 vs. 3.13 Å, respectively). In fact, in that study the difference between r_C and r_B was only 0.12 Å for the $SnCl_4$-catalyzed transtormation, considerably shorter than the values discussed above (>0.7 Å). This suggests that these three transition states (TSs), while they could be considered bis-pericyclic,[20b,c] are significantly shifted to the canonical [2+4] process. IRC calculations clearly connect with the corresponding nitronates (**Int**), which are transformed to formal [4+2] Diels-Alder products through a Claisen rearrangement following a [3,3] sigmatropic shift transition structure (**TS2**). These transition structures exhibit bond lengths in the same direction (r_B 2.65-2.71 Å, r_C 2.41-2.59 Å) compared with the previous TSs, with small energy differences between them ($\Delta\Delta H^{\ddagger}$ between 0.3 and 1.2 kcal/mol), suggesting a flat hypersurface in that region of the potential energy surface (PES). On the other hand, the **TS-2+cp-N-α** shows a structure more consistent with a bis-pericyclic transition state, significantly lower in energy than its analog **TS-2+cp-N-β** ($\Delta\Delta H^{\pm}$ 2.6 kcal/mol), with a smaller difference between r_C and r_C (2.88 vs 2.73 Å, respectively). This transition structure is much similar to the one found for the thermal reaction betwen cyclopentadiene and nitroethylene,[20b] and connects with the [4+2] product via IRC. As **TS-2+cp-N-α** bypasses the nitronate intermediate, a mechanistic switch is observed depending on the nature of the protecting group used: pDA for compound **2** and [2+4] heterocycloaddition / Claisen tandem for compound **4**. According to our results, this could be due to a conformational change in the pyranose ring as consequence of releasing the restriction imposed by the benzylidene acetal group. In **TS-2+cp-N-α**, the pyranose ring can only exist in the ^5S_O conformation, characterized by a clear *trans*-diaxial relationship between H-4 and H-5 (Φ = 174.1º). In contrast, the di-acetylated counterpart has greater flexibility, allowing to adopt more convenient geometries. The pyranose ring adopts a $^OS_5$ shape in the global minima found for **TS-4+cp-N-α**, with H-4

10.1002/ejoc.202400650

RESEARCH ARTICLE

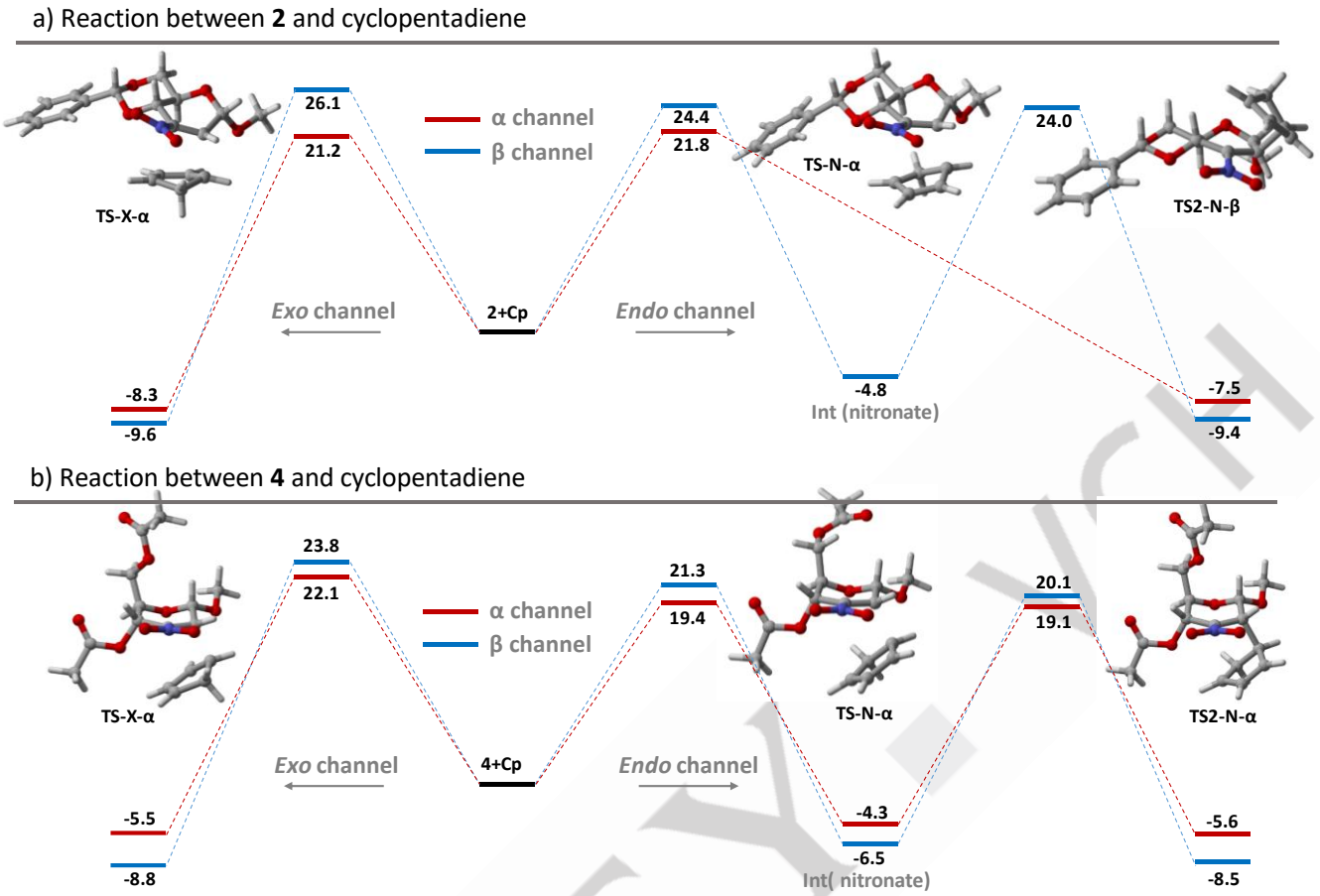


Figure 3. Reaction pathways computed for the reactions of **2** (top) and **4** (bottom) with cyclopentadiene. The relative enthalpies (H) are given in kcal/mol.

and H-5 being almost perpendicular (Φ = 88.3º) and the –CH_2OAc group taking a *pseudo*-axial position. This allows the oxygen atoms attached to nitrogen (O_a) and C-4 to separate further (3.03 vs 3.11 Å), positioning the nitro group more coplanar with the C=C (3.2 vs 13.5º), and thus facilitating a better approach of O_b with the C-2' of the cyclopentadiene (2.62 Å *vs* 2.88 Å). These results are consistent with our original calculations, where we observed that Coulombic repulsion played a significant role in destabilizing competitive transition states.[8]

The energy calculations exhibited an excellent alignment with the experimental observations conducted (Figure 3). In the case of the reaction between **2** and cyclopentadiene, a high α selectivity is predicted, with **TS-2+cp-N-α** and **TS-2+cp-X-α** being more stable (2.6 kcal/mol and 4.9 kcal/mol, respectively) than the corresponding transition structures resulting from the attack of the diene to the β face, **TS-2+cp-N-β** and **TS-2+cp-N-β**. Notably, there is a significant change in the energy profile when transitioning to **4**, as both *endo* channels are more stable than the corresponding *exo* approaches (~2.6 kcal/mol), coherent to the high *endo* selectivity observed in this reaction. Furthermore, unlike the reaction employing **2**, in this case, the rate-limiting step is the sigmatropic rearrangement, which explains the identification and isolation of the nitronate intermediate when using **4** as the starting material. While the calculations support the formation of both nitronates, the higher barrier calculated for the Claisen reaction of **int-β** (26.6 kcal/mol *vs* 23.4 kcal/mol) justifies the selectively experimental observed isolation. This gap (3.2 kcal/mol) showed a very good fit with the energy values recalculated at other levels of theory, such as PCM/M06-2X/6-311+G**//B3LYP/6-311+G** (2.8 kcal/mol), and PCM/B3LYP-D3/6-311+G**//B3LYP/6-311+G** (2.9 kcal/mol) using acetonitrile as solvent, eliminating the possibility of any energy bias associated with the level employed. It has been shown that the reactions between nitroalkenes and cyclopentadiene take place through a highly asynchronous bis-pericyclic transition state to give both Diels-Alder and hetero Diels-Alder cycloadducts, in which the position of the Claisen TS relative to the bis-pericyclic TS dictates the PES landscape and branching ratio of the bifurcating pathway.[20b,c] The impossibility to locate the formal [4+2] transition structure in the reactions involving **4** reinforces with that hypothesis, but our experimental results are more consistent with the [2+4]//[4+2] tandem. This is based on the fact that the kinetic study shown in Table 2 demonstrates the exclusive formation of the [2+4] adduct at early stages of the reaction, whose proportion decreases over time with the concomitant generation of the [4+2] adduct. One way to reconcile both approaches is to propose the possibility of a bifurcated system, where the branching favors the formation of the [2+4] adduct, which subsequently transforms into the thermodynamically more stable [4+2] product.

Conclusion

Nitroalkenes could act as dienophiles or as heterodienes, or both, in DA reaction. This change in the periselectivity of the cycloaddition mainly depends on whether the reaction is conducted under thermal or Lewis acid catalysis. Only a few examples were found where the molecular structure of the nitroalkene gave preferentially the cyclic nitronate under thermal conditions.

The cycloaddition of structurally related nitroalkene derives from carbohydrates with **Cp** afforded different periselectivity depending on the protected group present. Conformationally rigid nitroalkene **2** produces two nitronorbornene derivatives as result of the normal DA reaction. Interestingly, non-rigid nitroalkenes **3**, **4** and **5** reacted as heterodienes with **Cp** affording a cyclic nitronic ester in a stereospecific way. The formation of nitronate seemed to be related to the presence of a free hydroxyl group on the adyacent carbon atom of the nitroalkene functionality. This observation was supported by X-ray crystallography study of **8**. Cyclic nitronates, purified through standard chromatographic methods, are stable heterocyclic system at room temperature. Under heating in acetonitrile, these ones underwent the [3,3]-Claisen sigmatropic rearrangement, leading quantitatively to the formation of the corresponding β-*endo* cycloadduct. DFT calculations were carried out to shed light in the mechanistic landscape, matching nicely with the experimental observations.

These nitronates are stereochemically pure, chemically stable compounds and they are not only important from a mechanistic point of view, but also represent an interesting heterocarbon structures for obtaining more complex molecular substrates.

Crystallographic data:

Deposition Number(s) <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/ejoc.202400650">2308519</url> contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

Experimental Section

General considerations:

Melting points were taken on a Leitz Wetzlar Microscope Heating Stage, Model 350 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-300 spectrometer with Me_4Si as the internal standard and dimethysulfoxide-d_6 or chloroform-*d* as solvents. Abbreviations: s =singlet, d = doublet, t = triplet, and m = multiplet expected but not resolved. High resolution mass spectra of the dendrimers were analyzed by electrospray ionization (ESI) using a Bruker micrOTOF-Q II instrument, positive ion polarity. Reactions were monitored by TLC on 0.25 mm E. Merck Silica Gel Plates (60F254), using UV light (254 nm) and anysaldehyde as developing agent. Flash column chromatographies using E. Merck silica gel 60H were performed by gradient elution of mixture of n-hexane and increasing volumes of ethyl acetate. Reactions were run under an argon atmosphere with freshly anhydrous distilled solvents, unless otherwise noted. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated.

General procedure for the synthesis of the DA and HDA cycloadducts were described, the synthetic protocols for the preparation of dienophyles **3**, **4**, **5** and cycloadducts **6**, **7**, **8**, **9**, **10,** **13**, **14**, **15**, **16**, **17** and **18** and intermediates are described in the Supporting Information

General procedure for Diels-Alder reaction with **Cp**: Nitroalkene (1 equiv.) was dissolved in anhydrous acetonitrile (0.05 M) under an argon atmosphere at room temperature in a Hach vessel. To this solution freshly cracked cyclopentadiene (15-20 equiv.) was added, and the mixture was heated at 70–80 °C for 16 h in a closed system. The organic solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography.

General procedure for Diels-Alder reaction with **2,3-dimethyl-1,3-butadiene**: Nitroalkenes **3**, **4** and **5** (1 equiv.) were dissolved in anhydrous acetonitrile (0.05 M) under an argon atmosphere at room temperature in a Hach vessel. To this solution, commercial 2,3-dimethyl-1,3-butadiene (15-20 equiv.) was added. The mixtures were heated at 50 °C for 16 h and at 70 °C for another 16 h in a closed system. The progress of the reactions was monitored by TLC, which showed very little progress at these temperatures. Consequently, they were heated for another 16 h at 100°C, resulting in almost complete consumption of nitroalkenes **3** and **5** and the formation of a less polar product. The organic solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography. In the case of **4**, with the days of heating and increasing temperature, decomposition of the nitroalkene was observed, no cycloadduct was obtained.

Computational details

Conformational searches of the reactants, the transition structures (TSs) and the products were run to locate the global minima employing the B3LYP functional, coupled with the 6-311+G** basis set. Initially, different structures were generated using the conformational search module of Hyperchem with the MM+ force field.[29] The selected structures were then optimized at the B3LYP/6-311+G level of theory, using Gaussian 09.[30] The reported thermochemical properties include zero-point energies (ZPEs) without scaling and were calculated at 1 atm, and 298 K. Normal mode analysis was used to confirm the nature of the stationary points and to evaluate the thermochemical properties. All transition structures were confirmed to have only one imaginary frequency corresponding to the formation of the expected bonds.

Supporting Information

The authors have cited additional references within the Supporting Information. [24, 28]

Acknowledgements

We thank Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET - Argentina), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT - Argentina) and Universidad Nacional de Rosario (UNR). M.I.M., R.A.S and A.M.S. are scientific members of CONICET. D.V. thanks CONICET for the award of his fellowship. We are grateful for the collaboration of B.Sc. Gustavo Terrestre for the Single Crystal X-Ray structure determination performed in X-Ray Diffractometer laboratory, CCT-Rosario-CONICET and his valuable contributions.

Keywords: Nitroalkene • Hetero Diels-Alder reaction • Nitronic ester • DFT calculations • Sigmatropic rearrangement

[1] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

[2] a) F. Fringuelli, A. Taticchi in *The Diels–Alder Reaction. Selected Practical Methods*, John Wiley & Sons: New York, **2002**. b) I. Fleming in *Pericyclic Reactions*; Oxford University Press: New York, **1999**. c) J-A. Funel, S. Abele, *Angew. Chem. Int. Ed*. **2013**, *52*, 3822. d) M. Juhl, D. Tanner, *Chem. Soc. Rev*. **2009**, *38*, 2983. e) K. C. Nicolau, S. A. Snyder, T. Montagnon,G. Vassilikogiannakis, *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

[3] a) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, D. A. Efremov, in *Nitroalkenes: Conjugated Nitroalkenes*, Wiley, New York, **1994**. b) N. Ono in *The Nitro Group in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**.

[4] S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137.

[5] A. Łapczuk-Krygier, A. Kącka-Zych, K. Kula, *Curr. Chem. Lett.* **2019**, *8*, 13.

[6] R. Jasiński, *Symmetry* **2021**, *13*, 1911.

[7] a) R. Jasiński, M. Kwiatkowska, A. A. Barański, *J. Mol. Struct.: THEOCHEM* **2009**, *910*, 80. b) R. Jasiński, M. Rzyman, A. Barański, *Collect. Czech. Chem. Commun*. **2010**, *75*, 919.

[8] M. I. Mangione, A. M. Sarotti, A. G. Suárez, R. A. Spanevello, *Carbohyd. Res.* **2011**, *346*, 460.

[9] M. I. Mangione, A. G. Suárez, R. A. Spanevello, *Carbohydr. Res.* **2005**, *340*, 149.

[10] A. Seta, K. Tokuda, M. Kaiwa, T. Sakakibara, *Carbohydr. Res.* **1996**, *281*, 129.

[11] H. H. Baer, F. Kienzle, F. Rajabale, *Can. J. Chem.* **1968**, *46*, 80.

[12] S. K. Chaudhary, O. Hernandez, *Tetrahedron Lett*. **1979**, *20*, 95.

[13] C. F. Tormena. V. Lacerda Jr., K. T. de Oliveira, *J. Braz., Chem. Soc.* **2010**, *21*, 112.

[14] a) S. C. Pellegrinet, M. T. Baumgartner, R. A. Spanevello, A. B. Pierini, *Tetrahedron* **2000**, *56*, 5311. b) . C. Pellegrinet, R. A. Spanevello, *Org. Lett.* **2000**, *2*, 1073. c) R. M. Giuliano in *Cycloaddition Reactions in Carbohydrate Chemistry: An Overview*. *ACS Symposium Series* **1992**, *494*, 1-23.

[15] a) P. A. Wade, J. K. Murray Jr., S. Shah-Patel, H. T. Le, *Chem. Commun*. **2002**, 1090. b) S. E. Denmark, B. S. Kesler, Y-C. Moon, *J. Org. Chem.* **1992**, *57*, 4912.

[16] P. A. Wade, A. Pipic, M. Zeller, P. Tsetsakos, *Beilstein J. Org. Chem.* **2013**, *9*, 2137.

[17] Deposition Number(s) <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/ejoc.202400650">2308519</url> contain the supplementary crystallographic data for **8**. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[18] a) E. Wadaa, M. A. Yoshinaga, *Tetrahedron Lett.* **2004**, *45*, 2197. b) R-S. Malykhin, A. O. Kokuev, V. S. Dorokhov, Y. V. Nelyubina, V. A. Tartakovsky, A. A. Tabolin, S. L: Ioffe, A. Y. Sukhorukov, *J. Org. Chem*. **2019**, *84*, 13794. c) L. R. Domingo, M. Arnó, J. Andrés, *J. Org. Chem*. **1999**, *64*, 5867. d) H. Waldmann, *Synthesis* **1994**, 535. e) P. Biswas, J. Ghosh, S. Maiti, S. Banerjee, C. Bandyopadhyay, *Tetrahedron Lett.* **2013**, *54*, 3466.

[19] a) L. Wang, Y. Zhou, Z. Su, F. Zhang, W. Cao, X. Liu, X. Feng *Angew. Chem. Int. Ed.* **2022**, *61*, e202211785; *Angew. Chem.* **2022**, *134*, e202211785. b) Y. Liu, X. Liu, X. Feng *Chem. Sci.* **2022**, *13*, 12290. c) X Liu, H. Zheng, Y. Xia, L. Lin, X. Feng *Acc Chem Res*. **2017**, *50*, 2621. d) Y. Zhou, L. Lin, X. Liu, X. Hu, Y. Lu, X. Zhang, X. Feng, *Angew. Chem. Int. Ed.* **2018**, *57*, 9113. e) M. Xie, L. Lin, X. Feng *Chem Rec*. **2017**, *17*, 1184. f) Y. Zhu, X. Chen, M. Xie, S. Dong, Z. Qiao, L. Lin, X. Liu, X. Feng *Chem. Eur. J.* **2010**, *16*, 11963. g) T. Zhan, L. Zhou, Y. Zhou, B. Yang, X. Feng, X. Liu *Chem Sci.* **2024**, *15*, 4797.

[20] a) R. S. Paton, J. L. Mackey, W. H. Kim, J. H. Lee, S. J. Danishefsky, K. N. Houk, *J. Am. Chem. Soc*. **2010**, *132*, 9335. b) N. Çelebi-Ölçum, D. H. Ess, V. Aviyente, K. N. Houk, *J. Org. Chem*. **2008**, *73*, 7472. c) N. Çelebi-Ölçüm, D. H. Ess, V. Aviyente, K. N. Houk *J. Am. Chem. Soc.* **2007**, *129*, 4528.

[21] M. V. Gómez, A. I. Aranda, A. Moreno, F. P. Cossío, A. de Cózar, A. Díaz-Ortiz, A. de la Hoz, P. Prieto, *Tetrahedron* **2009**, *65*, 5328.

[22] a) P. A. Wade, J. K. Murray Jr, S. Shah-Patel, H. T. Le, *Chem. Commun*. **2002**, 1090. b) P. A. Wade, A. Pipic, M. Santhanaraman, H. T. Le, *Chem. Commun*. **2009**, 3531. c) P. Arroyo, M. T. Picher, L. R. Domingo, F. Terrier, *Tetrahedron* **2005**, *61*, 7359.

[23] M. O. Marcarino, L. Passaglia, M. M. Zanardi, A. M. Sarotti, *Chem. Eur. J.* **2023**, *29*, e202300420.

[24] Bruker **2022** APEX4 v2022.10-1, Bruker AXS Inc., Madison, Wisconsin, USA.

[25] Bruker **2019** SAINT V8.40B, Bruker AXS Inc., Madison, Wisconsin, USA.

[26] G. M. Sheldrick, *Acta Cryst.* **2015**, *A71*, 3.

[27] G. M. Sheldrick, *Acta Cryst.* **2015**, *C71*, 3.

[28] C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler, P. A. Wood, *J. Appl. Cryst.* **2020**. *53*, 226.

[29] Hyperchem Professional Release 7.52, Hypercube, Inc., 2005.

[30] M. J. Frisch, et al., Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford, CT, 2009.

10.1002/ejoc.202400650

WILEY VCH

RESEARCH ARTICLE

Entry for the Table of Contents

This research explores the synthesis of cyclic nitronates from sugar-derived nitroalkenes through a hetero-Diels-Alder/[3,3]-sigmatropic rearrangement. The method enables efficient access to diverse chemically stable and structurally interesting nitronic esters, pivotal in organic synthesis. DFT computational calculations are in satisfactory agreement with experimental data. These structures offering potential applications in medicinal chemistry and natural product development.

Institute and/or researcher @IQUIR_CONICET; @Marine007007