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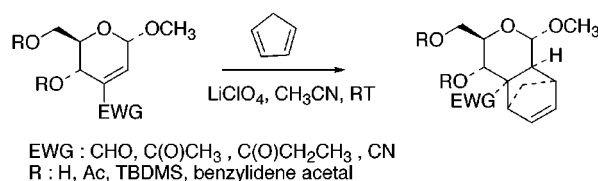
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ABSTRACT



A sugar-derived cyclic dienophile showed a high *exo* and face selectivity in the Diels–Alder reaction with cyclopentadiene. Structural modifications on the dienophile structure were made, and the outcomes of the cycloaddition reactions were investigated. These results and the spectroscopic data recorded within a series of analogues were used to analyze the factors affecting the reactivity and *exo* selectivity.

The Diels–Alder reaction has been widely applied to the syntheses of complex natural products. The reaction itself has become a valuable tool in the development of synthetic, mechanistic, and theoretical concepts, and this important role could be attributed to its remarkable regio- and stereoselectivities. It is generally accepted that the addition of cyclic dienes to cyclic dienophiles is the case in which the *endo* rule is most applicable; nevertheless, there are examples in the literature of Diels–Alder reactions that violate this rule.¹

The use of carbohydrates as a source of chirality has been thoroughly described in the literature,^{2,3} and they have also proved to be useful raw materials for the preparation of either diene or dienophiles⁴ as intermediates in the synthesis of

optically pure compounds. Despite a few exceptions,^{5,6} it has been established that cyclic sugar-derived dienophiles usually follow the Alder rule. Figure 1 shows a different possible

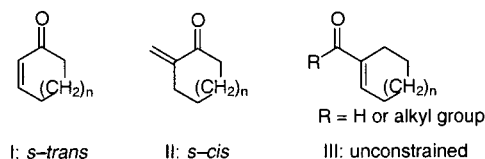


Figure 1. Types of cyclic dienophiles.

interpretation for the term cyclic dienophile in which *n* is a number that does not allow the system to adopt a different conformation.

(1) Fotiadu, F.; Archavlis, A.; Buono, G. *Tetrahedron Lett.* **1990**, 31, 4863.

(2) Collins, P.; Ferrier, R. *Monosaccharides*; John Wiley & Sons, Inc.: New York, 1995.

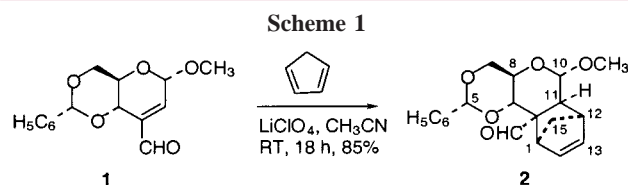
(3) Bols, M. *Carbohydrate Building Blocks*; John Wiley & Sons, Inc.: New York, 1996.

(4) *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M. Ed.; ACS Symposium Series 494; American Chemical Society: Washington, DC, 1992.

(5) Rehnberg, N.; Sundin, A.; Magnusson, G. *J. Org. Chem.* **1990**, 55, 5477.

(6) Kim, K. S.; Cho, I. H.; Joo, Y. H.; Yoo, I. Y.; Song, J. H.; Ko, J. H. *Tetrahedron Lett.* **1992**, 33, 4029.

In this context, we came across a cyclic dienophile system **1**⁷ that could be classified as unconstrained (Type III). This dienophile showed an exceptional *exo* and face selectivity when it was allowed to react with cyclopentadiene, affording adduct **2** as a single product (Scheme 1).⁸ The subsequent

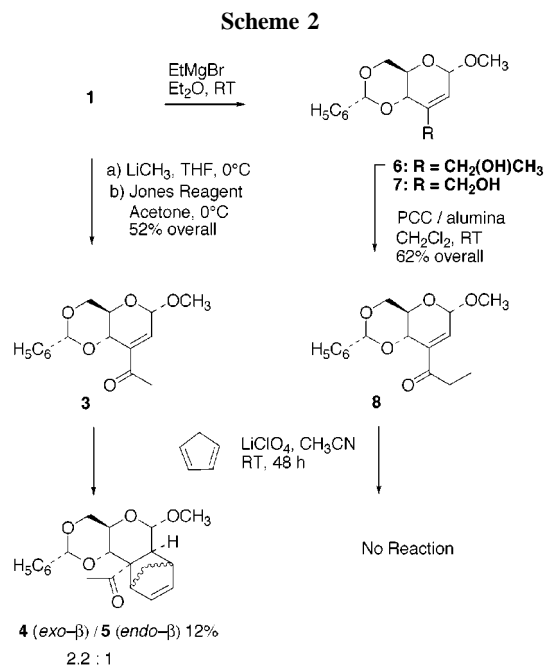


cleavage of the cycloadduct double bond unveiled a highly functionalized cyclopentane ring, which was proposed as a versatile building block for several different natural products.⁹ More recently, we proved the feasibility of its transformation into the angularly fused quinane skeleton of the antibiotic pentalenolactone.¹⁰

The high *exo* selectivity observed with **1** is an interesting example of an abnormal addition mode. Unfortunately, the factors that determine the outcome of a cycloaddition process can hardly ever be established. Even though in previous studies Rousch¹¹ and Takeda¹² attributed the predominant *exo* selectivity of some conformationally rigid cyclic *s-cis* dienophiles to dipolar effects, in our case we could not disregard the influence of steric or stereoelectronic effects in their multiple forms. We hence decided to study the factors affecting the stereoselectivity of this reaction by making structural modifications on the original dienophile system and comparing the outcome of the resulting cycloaddition.

Our first attempt involved the elongation of the exocyclic hydrocarbon side chain by synthesizing the corresponding methyl and ethyl ketones (**3** and **8**). This change should increase the steric hindrance of the side chain and reveal whether it has any influence on the *exo* selectivity. The syntheses of ketones **3** and **8** from aldehyde **1** are outlined

in Scheme 2.¹³ It is noteworthy to mention that the reaction of **1** with ethylmagnesium bromide also afforded the primary



alcohol **7** as a byproduct. The reduction of the carbonyl group is known to compete with the addition process when the carbonyl group is sterically hindered. Furthermore, in the ¹H NMR spectrum of ethyl ketone **8**, the signal for the methylene group α to the carbonyl appeared as four quartets. This coupling pattern can only be explained if the methylene group has a restricted rotation around the single bond so both protons are nonequivalent, which confirmed the steric congestion around the carbonyl group.

The Diels–Alder reaction of the methyl ketone **2** afforded only 12% yield of a mixture of *exo*-β/*endo*-β cycloadducts (**4** and **5**)¹⁴ in a 2.2:1 ratio, even after 48 h. Under the same experimental conditions the ethyl ketone **8** did not react.

A different structural modification was envisaged with the purpose of gaining conformational flexibility. It implied the cleavage of the benzylidene acetal ring and the subsequent protection of the free hydroxyl groups as *tert*-butyl dimethyl silyl ethers. Scheme 3 outlines the synthetic sequence followed to obtain this derivative from known nitrile **9**.⁷

In this case, the reaction of the dienophile **12** with cyclopentadiene afforded a mixture of three different isomeric products in 87% yield (Scheme 4). The *exo*-β cycloadduct was again the main product, with a minor proportion of the *endo*-β isomer and traces of a third adduct that could not be purified from the mixture. The structure of the latter one could not be unequivocally assigned, but as a result of the

(7) Spanevello, R. A.; Pellegrinet, S. C. *Synth. Comm.* **1995**, 25, 3663.
 (8) In a typical procedure, the dienophile **1** (3.750 g, 13.59 mmol) was dissolved in dry acetonitrile (136 mL) and stirred during 30 min with anhydrous LiClO₄ (7.2345 g, 67.95 mmol). Freshly cracked cyclopentadiene (9.125 mL, 135.90 mmol) was added under an inert atmosphere at room temperature. The reaction was completed after 18 h. The mixture was diluted with ethyl ether and washed with water. The organic layer was dried over Na₂SO₄ and concentrated under vacuum. Flash chromatography to remove the excess of bicyclopentadiene afforded compound **2** (4.0480 g, 11.84 mmol) in 85% yield. The same results were obtained when the reaction was catalyzed by BF₃·OEt₂ in methylene chloride at –78 °C or run under thermal conditions in xylene at 80 °C, although in the later case the yield was 51%. The ¹H and ¹³C NMR signals of **2** were unequivocally assigned by using homo- and heteronuclear 2D NMR techniques. The NOE observed between C₁₀–H and C₁₃–H and between C₁₂–H and C₁₀–H (IUPAC numbering) suggested the β approach. Further corroboration was obtained from irradiation of C₁₁–H and the carbonyl proton, which enhanced the C₈–H signal. The NOE observed between C₁₁–H and one of the C₁₅–H showed the *exo* character of the addition.

(9) Pellegrinet, S. C.; Spanevello, R. A. *Tetrahedron: Asymmetry* **1997**, 8, 1983.

(10) Pellegrinet, S. C.; Spanevello, R. A. *Tetrahedron Lett.* **1997**, 38, 8623.

(11) Rousch, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, 57, 3380.

(12) Takeda, K.; Imaoka, I.; Yoshii, E. *Tetrahedron* **1994**, 50, 10839.

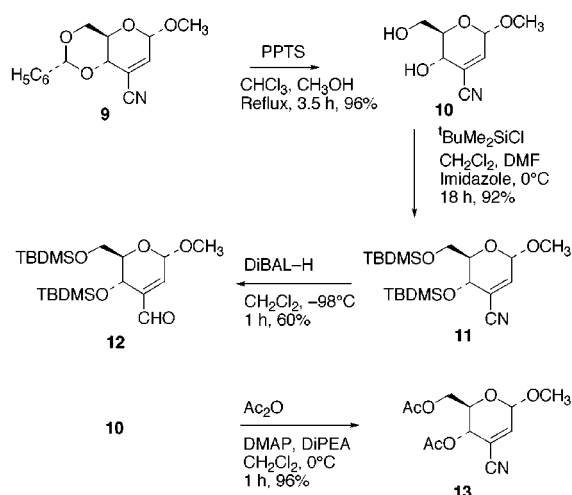
(13) All attempts to obtain these ketones directly from the aldehyde precursor, the nitrile **9** (Scheme 3) through a nucleophilic addition were fruitless.

(14) The structure of the cycloadducts were assigned on the basis of the NOE experiments as described in ref 8 for cycloadduct **2**.

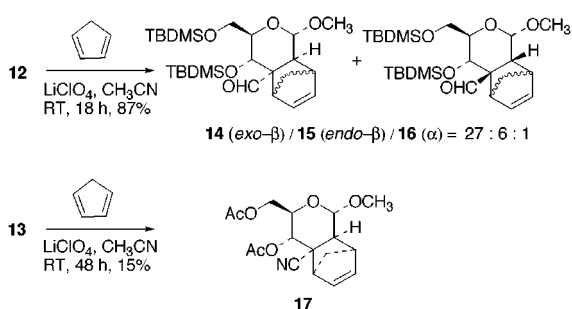
Table 1. Cycloaddition Reactions: Experimental Results and Spectroscopic Data

entry	dienophile	adducts [ratio]	yield [%]	¹ H NMR chemical shift vinyl proton [ppm]	¹³ C NMR chemical shift C-2/C-3 [ppm]	IR absorbance obsd (theoretical) [cm ⁻¹]
1	1	<i>exo</i> -β	85	6.59	138.9/139.6	1690 (1695–1660)
2	12	<i>exo</i> -β/ <i>endo</i> -β/α [27:6:1]	87	6.57	140.2/143.3	1700 (1695–1660)
3	3	<i>exo</i> -β/ <i>endo</i> -β [2.2:1]	12	6.43	132.1/140.9	1696 (1675)
4	8	no reaction		6.38	131.0/140.7	1702 (1675)
5	9	no reaction		6.49	140.6/113.7	2227 (2240–2215)
6	10	no reaction		6.51	139.8/120.2	2236 (2240–2215)
7	13	<i>exo</i> -β	15	6.59	141.2/114.2	2230 (2240–2215)

difference in the coupling constant of the anomeric proton in the ¹H NMR spectrum, we assumed it was one of the two possible isomers produced by the addition from the α face of the molecule.

Scheme 3

A third type of modification was made on the electron-withdrawing group. Replacement of the carbonyl group by a cyano, which has a linear geometry, would avoid any speculation on the dienophile *s-cis* or *s-trans* conformation. However, the bicyclic nitrile **9** (Scheme 3) proved to be

Scheme 4

completely unreactive with cyclopentadiene under several different conditions.¹⁵ Since it is known that a cyano group has a withdrawing effect less strong than that of an aldehyde,¹⁶ we removed the electron-rich benzylidene acetal group and tested the nitrile **10**, but it was also unreactive. An alternative to increase the reactivity of the α,β-unsaturated nitrile system was the protection of the free hydroxyl groups with protecting groups that could have some electron-withdrawing effect on the double bond. We found the acetate group could partially fulfill our expectation. The ¹H NMR spectrum of the diacetate **13** revealed a higher polarization effect on the olefin. The vinyl proton signal was shifted downfield, from 6.49 ppm in the bicyclic nitrile **9** to 6.58 ppm in the acetate derivative.

We further verified this effect experimentally by the outcome of the reaction between nitrile **13** with cyclopentadiene. The reaction afforded the *exo*-β isomer, as a single product in 15% yield, plus recovered starting material. Table 1 summarizes the observed results.¹⁷

A comparative analysis of the spectroscopic data shows a correlation with the observed results. The value of the chemical shift of the vinyl proton in the ¹H NMR spectra gives a qualitative idea of the degree of polarization of the double bond (hence, the activation for undergoing a cycloaddition process). A similar matter happens with the values of the β olefinic carbon in the ¹³C NMR spectra. Usually the β carbon of α,β-unsaturated systems suffers a deprotection effect due to this conjugation. Even though there is a good correlation among the chemical shifts of protons and carbons in both series of compounds, we consider it more appropriate to compare the absolute value of the chemical shift only within each series. Otherwise we could draw a wrong conclusion by omitting to take into consideration other effects.

The IR data confirmed the decrease or lack of conjugation of the α,β-unsaturated ketones, especially in the case of the ethyl ketone **8**. However, IR spectra of the nitrile series show an absorbance peak (for the carbon–nitrogen stretching

(15) We tested the same conditions described for aldehyde **1** in ref 8 and also other Lewis acid catalysts: AlCl₃, MgBr₂·OEt₂, and TiCl₄ in methylene chloride at -78 °C.

(16) Sauer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* **1964**, *97*, 3183.

(17) The spectroscopic and physical properties of all new compounds reported herein are in complete agreement with the assigned structures.

vibrations) within the range for conjugated nitrile groups, as was expected for a group with linear geometry.

In view of the experimental evidences we could infer that the observed stereoselectivity in the cycloaddition reaction of aldehyde **1** is mainly caused by steric effects. When the dienophile system becomes more flexible (entry 2 in Table 1) the selectivity decreases. This assumption is in agreement with the steric hindrance effect caused by the methylene group of the cyclopentadiene mentioned by Sauer.¹⁸ The steric interaction between this methylene and the axial hydrogen attached to C-4 and C-6 of the dienophile **1** are probably responsible for the high *exo* selectivity. Although the lower or lack of reactivity of the ketone derivatives (entries 3 and 4) was attributed to a low degree of polarization of the double bond, it is caused by a steric interaction that does not allow the carbonyl group to adopt the adequate conformation to attain a good conjugation with the double bond. Entry 3 also showed the influence of the carbonyl side chain on the *exo* selectivity.

(18) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779 and references cited therein.

In the case of the α,β -unsaturated nitrile series, it is known that the activation effect of the cyano group is lower than that of an aldehyde, and this could be responsible for the lack of reactivity observed in entries 5 and 6. Only when an additional electron-withdrawing group is present in the allylic position (entry 7), is it possible to observe an increase in the reaction rate. Moreover, since this reactivity is still very low, it provokes a higher *exo* selectivity than in entry 2.

Acknowledgment. Financial support from the International Foundation for Science (IFS), Third World Academy of Sciences (TWAS), Universidad Nacional de Rosario, Agencia Nacional de Promoción Científica y Tecnológica, and CONICET is gratefully acknowledged. The authors thank Prof. E. A. Rúveda for helpful suggestions, and S.C.P. thanks CONICET for the award of a fellowship.

Supporting Information Available: Characterization data for compounds **1–5** and **8–17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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