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Münchnone−Alkene Cycloadditions: Deviations from the FMO Theory. Theoretical Studies in the Search of the Transition State

Martín Avalos, Reyes Babiano, Andrés Cabanillas, Pedro Cintas, José L. Jiménez,* and Juan C. Palacios

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain

Manuel A. Aguilar, José C. Corchado, and Joaquín Espinosa-García

Departamento de Química Física, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain

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The dipolar cycloaddition reactions of 3-methyl-2-(4-nitrophenyl)-4-phenyl-1,3-oxazolium-5-olate (**1**) and chiral nitroalkenes derived from D-*galacto*- and D-*manno*-hept-1-enitols **2** and **3** were found to proceed in a regiospecific manner to afford acyclic pyrrole *C*-nucleosides (**5** and **6**) in satisfactory yields. This protocol constitutes a novel and efficient route to such substances. Remarkably, the regiochemistry of this mesoionic-based cycloadditive process is *exactly opposite* that anticipated from the FMO view of 1,3-dipolar cycloadditions. A preliminary semiempirical PM3 study also reveals the inconsistencies of semiempirical studies with experimental data by applying the FMO approach to münchnone cycloadditions. The structural characteristics of the reagents, products, and transition states have been determined, and this calculation also evaluates the influence of steric and electronic factors involved. *Ab initio* MO calculations using a model system consisting of 1,3-oxazolium-5-olate with 2-(hydroxymethyl)nitroethylene were also performed. The *ab initio* study justifies, for the first time, the experimental results of 1,3-dipolar cycloadditions with münchnones. The process occurs through a concerted, slightly asynchronous transition state.

Introduction and Background

Cycloaddition reactions are far from exhausted in modern synthetic chemistry. Diels−Alder and dipolar cycloadditions illustrate well the enormous potential and practical applications of these simple processes.[1] Although numerous variations have been introduced to expand their versatility and accomplish transformations under milder conditions, the utilization of unusual substrates constitutes a current research topic of cycloaddition chemistry. In relation with the latter, mesoionic rings, that is, five-membered heterocycles that cannot be satisfactorily represented by Lewis formulas not involving charge separation, have emerged as attractive synthons and willing participants of dipolar cycloadditions owing to their behavior as masked 1,3-dipoles.[2]

Although mesoionic heterocycles themselves have been known for many years, it was not until Huisgen, Ollis, and co-workers developed convenient syntheses of such substances and outlined their general reactivity with common organics that mesoionic compounds became of general interest and importance to synthetic organic chemists.[3] Perhaps the most representative mesoionic heterocycles are münchnones, the common name of 1,3-oxazolium-5-olate systems, which can react with a wide variety of double- and triple-bond dipolarophiles. Thus, 1,3-dipolar cycloaddition with acetylenes containing either one or two electron-withdrawing substituents constitutes a general pyrrole synthesis.[4] In this process, the münchnone serves as an apparent cyclic azomethine ylide providing an initial cycloadduct that further releases carbon dioxide. Cycloadditions with olefins also lead to pyrrole or pyrroline derivatives depending on the starting alkene.[5] Furthermore, the existence of a ketene-type valence tautomer in equilibrium with the münchnone ring has been postulated. Support of this surmise comes

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[1] For complete accounts on cycloaddition reactions: (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (b) Trost, B. M., Fleming, I., Paquette, L. A., Eds. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 5. (c) Padwa, A., Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984; Vols. 1−2.

[2] (a) Potts, K. T. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 1−82. (b) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22−28. (c) Padwa, A.; Hornbukcle, S. *Chem. Rev.* **1991**, *91*, 263−309. (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385−5453. (e) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123−141. (f) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797−1815.

[3] For general reviews on mesoionic compounds: (a) Ohta, M.; Kato, H. In *Nonbenzenoid Aromatics*; Snyder, J. P., Ed.; Academic Press: New York, 1969; Vol. 1, pp 117−248. (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389−437. (c) Ollis, W. D.; Ramsden, C. A. *Adv. Heterocycl. Chem.* **1976**, *19*, 1−22. (d) Yashunskii, V. G.; Kholodov, L. E. *Russ. Chem. Rev. (Engl. Trans.)* **1980**, *49*, 28−45. (e) Newton, C. G.; Ramsden, C. A. *Tetrahedron* **1982**, *38*, 2965−3011. (f) Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239−2329. (g) Gingrich, H. L.; Baum, J. S. In *The Chemistry of Heterocyclic Compounds. Vol. 45: Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; pp 731−961.

[4] (a) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C. *Angew. Chem.* **1964**, *76*, 185−186. (b) Boyd, G. V. *Chem. Commun.* **1968**, 1410−1412. (c) Gotthardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.* **1970**, *92*, 4340−4344. (d) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C. *Chem. Ber.* **1970**, *103*, 2611−2624. (e) Bayer, H. O.; Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1970**, *103*, 2356−2367. (f) Potts, K. T.; Baum, J. *J. Chem. Soc., Chem. Commun.* **1973**, 833−834. (g) Hershenson, F. M. *J. Org. Chem.* **1975**, *40*, 1260−1264. (h) Anderson, W. K.; Corey, P. F. *J. Org. Chem.* **1977**, *42*, 559−561. (i) Pizzorno, M. T.; Albonico, S. M. *J. Org. Chem.* **1977**, *42*, 909−910. (j) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 909−913. (k) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786−791. (l) Padwa, A.; Lim, R.; MacDonald, J. G.; Gingrich, H. L.; Kellar, S. M. *J. Org. Chem.* **1985**, *50*, 3816−3823. (m) Hershenson, F. M.; Pavia, M. R. *Synthesis* **1988**, 999−1001. (n) Wilde, R. G. *Tetrahedron Lett.* **1988**, *29*, 2027−2030.

[5] (a) Gotthardt, H.; Huisgen, R.; Schaefer, F. C. *Tetrahedron Lett.* **1964**, 487−490. (b) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Chem. Ber.* **1970**, *103*, 2368−2387. (c) Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1970**, *103*, 2625−2638. (d) Benages, I. A.; Albonico, S. M. *J. Org. Chem.* **1978**, *43*, 4273−4276.

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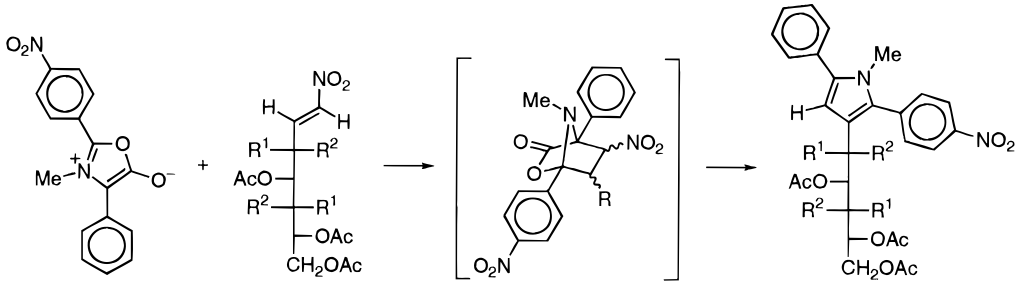
Scheme 1. Synthesis of *C*-Pyrrole Nucleosides by Münchnone Cycloaddition



1

2 $R^1 = H, R^2 = OAc$
3 $R^1 = OAc, R^2 = H$

4 R = Sugar chain

5 $R^1 = H, R^2 = OAc$
6 $R^1 = OAc, R^2 = H$

from reactions of münchnones with imines leading to β-lactams, which would arise from a formal [2 + 2] cycloaddition instead of a dipolar reaction.[6]

For the last several years we have been interested in asymmetric transformations with mesoionic heterocycles, especially carbohydrate-based cycloadditions, as a synthetic route to certain optically active heterocycles and other substances of biological significance like nucleosides.[7] In light of our experience with münchnones and encouraged by the aforementioned results for dipolar cycloadditions with olefins, we did envisage a novel and concise synthesis of pyrrole *C*-nucleosides from carbohydrate dipolarophiles. In the present paper, we report such an application as well as other mechanistic and theoretical insights into the cycloadditions of münchnones, which have elicited considerable controversy concerning their regiochemical outcome.

Results and Discussion

Cycloaddition Reactions. As far as we know, the reactions of münchnones with nitroalkenes have not yet been synthetically exploited. 3-Methyl-2-(4-nitrophenyl)-4-phenyl-1,3-oxazolium-5-olate (**1**) was prepared according to the previously reported procedure[8] and was added to sugar nitroalkenes **2** and **3** having carbon side chains of D-*galacto* and D-*manno* configuration, respectively.[9] Reactions proceeded smoothly in acetic anhydride at room temperature for several days to give the corresponding pyrrole derivatives **5** and **6**, in good yield (69 and 65%, respectively), through the elimination of carbon dioxide and nitrous acid[10] from the initial cycloadducts (**4**) that were not isolated (Scheme 1). Inspection of crude reaction mixtures by ^{1}H NMR gave no evidence of regioisomers other than compounds **5** or **6**.

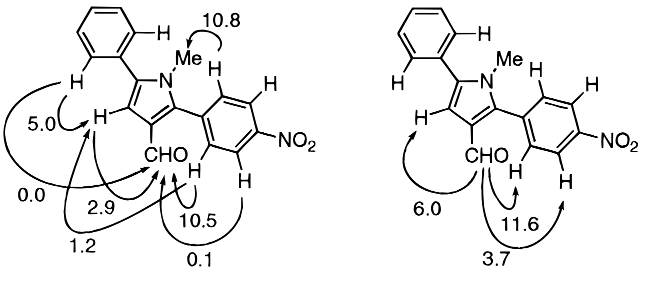


Figure 1. NOEs observed upon irradiation of protons in compound **9**.

The products **5** and **6** were characterized spectroscopically. The UV electronic spectra revealed absorptions at ~270 and ~380 nm, which are typical of the pyrrole nucleus and the 4-nitrophenyl group, respectively. ^{1}H NMR spectra showed resonances at ~6.3 ppm (H-4, pyrrole ring) and ~3.4 ppm (*N*-methyl group), both consistent with the presence of the heterocyclic ring.

Deacylation of compounds **5** and **6** with NaOMe/MeOH afforded the unprotected acyclic nucleosides **7** (66%) and **8** (73%), respectively. This protocol offers an advantageous alternative to the synthesis of acyclic pyrrole *C*-nucleosides, which have been hitherto prepared by the classical reaction of amino sugars with β-dicarbonyl compounds.[11,12]

To ascertain the exact regiochemistry of the heterocyclic moiety, the pentahydroxyalkyl chains of compounds **7** and **8** were subjected to oxidative degradation with $NaIO_4$ to give exclusively the 3-formyl derivative **9**, whose structure was established from analytical and spectroscopic data. Nuclear Overhauser interactions depicted in Figure 1 agree with the structure attributed to **9** and confirm the regiochemistry assigned to cycloadducts **5**–**8**. Thus, irradiation of *ortho* protons of the phenyl group of **9** caused enhancements of the signal for H-4 (5%) and not for the aldehyde proton (0%), whereas irradiation of those protons of the 4-nitrophenyl ring induced NOEs at the signals of H-4 (1%) and formyl proton (10%). Similarly, irradiation of the latter proton influenced the signal of H-4 (6%), indicating the relative position of the sugar chain linked to the heterocycle. These results rule out the alternative regioisomeric structure **10** and, consequently, those of its precursors **11** and **12**, which were not isolated or detected in the reaction mixtures.

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(6) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–632. (b) Huisgen, R.; Funke, E; Schaefer, F. C.; Knorr, R. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 367–368. (c) Funke, E.; Huisgen, R. *Chem. Ber.* **1971**, *104*, 3222–3228.

(7) (a) Avalos, M.; Babiano, R.; Bautista, I.; Fernández, J. I.; Jiménez, J. L.; Palacios, J. C.; Plumet, J.; Rebolledo, F. *Carbohydr. Res.* **1989**, *186*, C7–C8. (b) Areces, P.; Avalos, M.; Babiano, R.; González, L.; Jiménez, J. L.; Palacios, J. C.; Pilo, M. D. *Carbohydr. Res.* **1991**, *222*, 99–112. (c) Areces, P.; Avalos, M.; Babiano, R.; González, L.; Jiménez, J. L.; Méndez, M. M.; Palacios, J. C. *Tetrahedron Lett.* **1993**, *34*, 2999–3002. (d) Avalos, M; Babiano, R.; Cabanillas, C.; Cintas, P.; Diánez, M. J.; Estrada, M. D.; Jiménez, J. L.; López-Castro, A.; Palacios, J. C.; Pérez-Garrido, S. *J. Chem. Soc., Chem. Commun.* **1995**, 2213–2214.

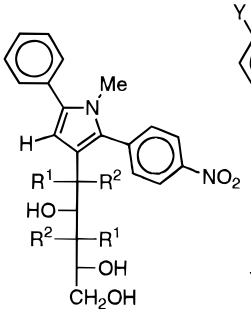
(8) Bayer, H. O.; Huisgen, R.; Knorr, R.; Schaefer, F. C. *Chem. Ber.* **1970**, *103*, 2581–2597.

(9) (a) Sowden, J. C.; Schaffer, R. *J. Am. Chem. Soc.* **1951**, *73*, 4662–4664. (b) Sowden, J. C.; Strobach, D. R. *J. Am. Chem. Soc.* **1960**, *82*, 954–955.

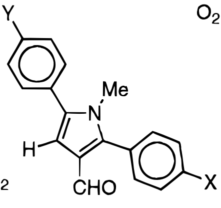
(10) Parham, W. E.; Bleasdale, J. L. *J. Am. Chem. Soc.* **1950**, *72*, 3843–3846.

(11) García González, F.; Gómez Sánchez, A. *Adv. Carbohydr. Chem.* **1965**, *20*, 303–355.

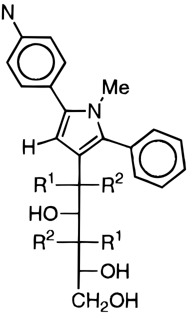
(12) Galbis, J. A.; Palacios, J. C.; Jiménez, J. L.; Avalos, M. *Carbohydr. Res.* **1984**, *132*, 153–161.



7 R^1 = H, R^2 = OH
8 R^1 = OH, R^2 = H



9 X = NO$_2$, Y = H
10 X = H, Y = NO$_2$



11 R^1 = H, R^2 = OH
12 R^1 = OH, R^2 = H

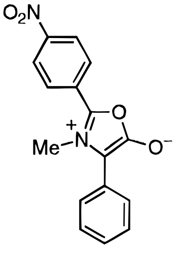
Toward the Rationalization of Münchnone Cycloadditions. From a practical viewpoint, the synthetic utility of certain 1,3-dipolar cycloadditions has been seriously hampered by their low regioselectivities and often their unpredictable outcome.[1a,c] With the exception of reactions in which chelate effects and noncovalent interactions likely play a crucial role on the geometry of transition states,[13] and therefore controlling the facial selectivity, most 1,3-dipolar cycloadditions may be rationalized on the basis of the PMO (perturbation molecular orbital) theory[14] and considering the simpler HOMO/LUMO approach only.[15] However, as noted by Houk,[15c] our understanding of these reactions is restricted by the lack of information on their transition states. In fact, electronic and steric effects appear to be sometimes contradictory and, though it is generally agreed that 1,3-dipolar cycloadditions are concerted,[16,17] several stepwise pathways involving diradical[18] or zwitterionic intermediates[19] have been proposed to account for experimental results.

While the reactivity and regiochemistry of other useful mesoionics, such as thioisomünchnones,[2] can be satisfactorily explained by the frontier molecular orbital (FMO) theory,[20] münchnone−alkene cycloadditions usually exhibit opposite or low regioselectivities to those that are predicted by the FMO theory. Semiempirical calculations have by far suggested different levels of asynchronization for the transition structures.[21−23] What factors account for this lack of consistency between experimental and theoretical results and thus determine the regiochemistry of the process? Coppola, Trost, and co-workers, who have reviewed numerous münchnone cycloadditions, have recently suggested a transition state with a Michael-like character for these reactions[23] and point out that the simplified FMO theory is inadequate for explaining the addition regiochemistry.

Table 1. HOMO and LUMO Energies and Coefficients of Compounds 1 and 13 by PM3 Calculations

			1		13	
compd	OM	energy	c_2	c_4	c_1	c_2
1	HO	−8.43	−0.49	0.63		
	LU	−1.79	0.14	0.14		
13	HO	−11.53			0.55	0.43
	LU	−1.06			−0.50	0.67

Semiempirical PM3 Calculations.[24,25] We proceeded to locate the PM3 transition structure for the cycloaddition of münchnone **1** with the nitroalkene **13**. This model system is very close to the real reaction of Scheme 1, the differences being the lack of the chiral skeleton of nitroalkene, albeit **13** maintains the *E* disposition around the double bond and the same configuration at the first stereogenic carbon.



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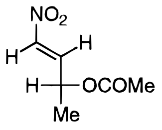

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The cycloadditive process of **1** and **13** does generate eight possible diastereomers (**14**−**21**). Considering that **13** approaches to only one face (*e.g.*, the *re*(C2), *re*(C4) face) of münchnone **1**, geometrical parameters, formal charge distributions, enthalpies of formation at 298 K, and the ionization potentials were calculated for reactants **1** and **13**, cycloadducts **14**−**17**, and saddle points (see the supporting information). The formal charge distributions of +0.145 at the mesoionic ring and −0.344 at the exocyclic oxygen clearly reflects the polar character of **1**, thus warranting the model approach.

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(13) (a) Sustmann, R.; Sicking, W. *Chem. Ber.* **1987**, *120*, 1653−1658. (b) Huisgen, R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 1−32. (c) Curran, D. P.; Jeong, K.-S.; Heffner, T. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 9238−9240. (d) Curran, D. P.; Choi, S.-M.; Gothe, S. A.; Lin, F. *J. Org. Chem.* **1990**, *55*, 3710−3712. (e) Kanemasa, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 3633−3636. (f) DeShong, P.; Li, W.; Kennington, J. W., Jr.; Ammon, H. L.; Leginus, J. M. *J. Org. Chem.* **1991**, *56*, 1364−1373. (g) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817−5820. (h) Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056−7066. (i) Akiyama, T.; Okada, K.; Ozaki, S. *Tetrahedron Lett.* **1992**, *33*, 5763−5766. (j) Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87−90. (k) Vedejs, E.; Piotrowski, D. W. *J. Org. Chem.* **1993**, *58*, 1341−1348.

(14) (a) Dewar, M. J. S. *Molecular Orbital Theory for Organic Chemists*; McGraw-Hill: New York, 1969. (b) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Plenum Press: New York, 1975.

(15) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976. (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−176. (c) Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 407−450.

(16) (a) Houk, K. N.; Firestone, R. A.; Munchausen, L. L.; Mueller, P. H.; Arison, B. H.; García, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227−7228. (b) Sustmann, R.; Sicking, W. *Tetrahedron* **1988**, *44*, 379−387. (c) Sustmann, R.; Sicking, W.; Lamy-Schelkens, H.; Ghosez, L. *Tetrahedron Lett.* **1991**, *32*, 1401−1404. (d) Dewar, M. J. S.; Hwang, J. C.; Kuhn, D. R. *J. Am. Chem. Soc.* **1991**, *113*, 735−741.

(17) For an excellent and recent account on pericyclic reactions: Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81−90.

(18) Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603−4607.

(19) (a) Huisgen, R.; Langhals, E. *J. Org. Chem.* **1990**, *55*, 1412−1414. (b) Huisgen, R.; Mloston, G. *Heterocycles* **1990**, *30*, 737−740. (c) Quast, H.; Regnat, D.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 695−697.

(20) (a) Avalos, M.; Babiano, R.; Diánez, M. J.; Espinosa, J.; Estrada, M. D.; Jiménez, J. L.; López-Castro, A.; Méndez, M. M.; Palacios, J. C. *Tetrahedron* **1992**, *48*, 4193−4208. (b) Cabanillas, A. Ph.D. Thesis, University of Extremadura, Badajoz, 1995.

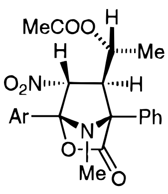
(21) Yebdri, O.; Henri-Rousseau, O.; Texier, F. *Tetrahedron Lett.* **1983**, *24*, 369−372.

(22) Maryanoff, C. A.; Turchi, I. J. *Heterocycles* **1993**, *35*, 649−657.

(23) Coppola, B. P.; Noe, M. C.; Schwartz, D. J.; Abdon, R. L. H.; Trost, B. M. *Tetrahedron* **1994**, *50*, 93−116.

(24) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220. (b) For additional references to semiempirical Hamiltonians, see: *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: Weinheim, Germany, 1990; Vol. 1, Chapter 2; 1991; Vol. 2, Chapter 8.

(25) Sustmann, R.; Sicking, W.; Felderhoff, M. *Tetrahedron* **1990**, *46*, 783−792.



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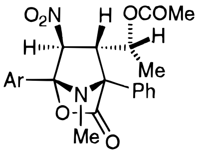

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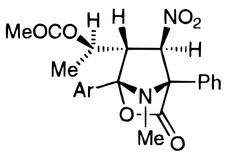

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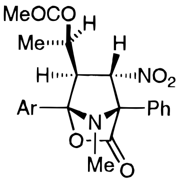

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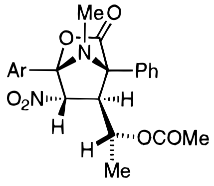

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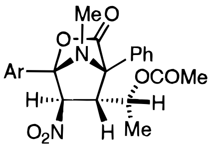

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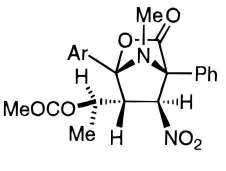

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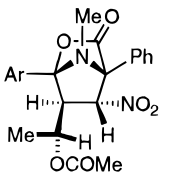

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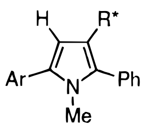
The energetic balance of a particular process when the orbitals of one reactant overlap with those of another can be determined by the well-known perturbation theory equation,[14,15a] in which the HOMO/LUMO interaction usually makes the largest contribution to the third term of equation (the second-order perturbation term). Energy values for HOMOs/LUMOs of **1** and **13** lead to consider the $\mathrm{HOMO_{dipole}}-\mathrm{LUMO_{dipolarophile}}$ interaction as prevalent ($\Delta E = -7.37$ eV versus -9.74 eV for the second HOMO/LUMO pair) (Table 1). Münchnones may be considered as allyl-type dipoles, being from a formal standpoint cyclic equivalents of azomethine ylides. As in these dipoles, many cycloaddition reactions of münchnones fall into the Sustmann type-I dipoles ($\mathrm{HOMO_{dipole}}-\mathrm{LUMO_{dipolarophile}}$ control), which have relatively high-lying HOMOs and LUMOs and are generally referred to as HOMO-controlled or nucleophilic 1,3-dipoles.[26]

(a) Regiochemistry. After it is identified which HOMO/LUMO pair is closer in energy, the relative sizes of the coefficients of the atomic orbitals do predict the regioselectivity. In all cases C2 and C4 atoms of the 1,3-oxazolium-5-olate system interact with the C1−C2 bond of the nitroalkene. Orbital interactions in which HOMO and LUMO face the coefficients with larger sizes give rise four cycloadducts (Figure 2) that, after extrusion of carbon dioxide and nitrous acid, provide exclusively the pyrrole **22**. This result contrasts with the experimental one that accounts for the alternative pyrrole **23** solely.



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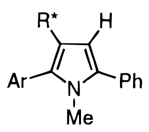

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(b) Energetics. Figure 3 summarizes the energy changes for the four reaction approaches illustrating the corresponding activation and reaction energies. The PM3 data indicate that **15** is kinetically favored, whereas the formation of **16** is enthalpy favored. The cycloadduct **15** is expected to be initially formed as most pericyclic reactions proceed under kinetic control. Our experimental results as well as those of other münchnone cycloadditions[23] are only compatible with the formation of compounds **16** or **17**, in which the approach may be either *exo* or *endo* respect to the nitro group, and both of them would afford pyrrole derivatives like **9** or **23**.

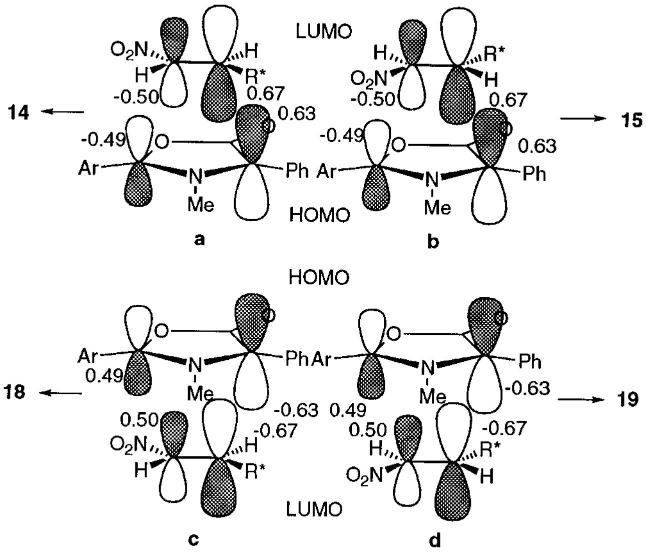

Figure 2.

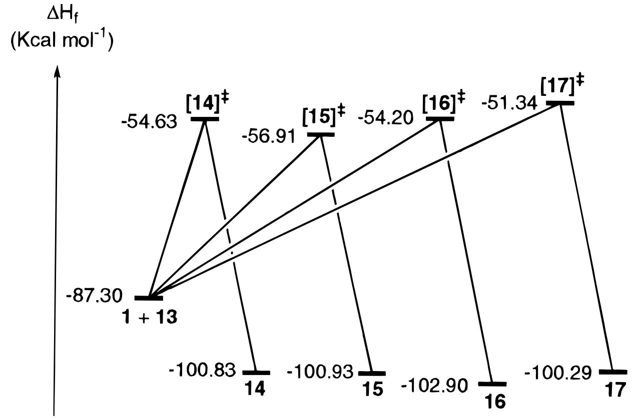

Figure 3. Energetic profile for the cycloaddition of **1** and **13**.

Furthermore, Figure 3 does show a somewhat later TS for the four reactions. The reaction energies for the dipolar cycloaddition involving münchnones range from -13.0 to -15.6 kcal mol^{-1}, which disagree with estimated values for typical dipolar cycloadditions (-30 to -50 kcal mol^{-1}).[15] For these less exothermic reactions the Hammond postulate claims a later TS, and it is known that we can expect that frontier orbital effects will be particularly strong in exothermic reactions,[15a] for which TSs are reactant-like. The origin of the inconsistencies for münchnone cycloadditions could tentatively be ascribed to other changes or factors that are not included in the FMO approach. However, we have observed that 1,3-dipolar cycloadditions of thioisomünchnones, which are otherwise compatible with the FMO predictions, are even less exothermic (about -5 kcal mol^{-1}).[20]

The theoretical information provided above *clearly reveals that FMO theory fails in münchnone cycloaddi-*

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(26) (a) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717−2720. (b) Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838−840. (c) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569−593. (d) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403−419.

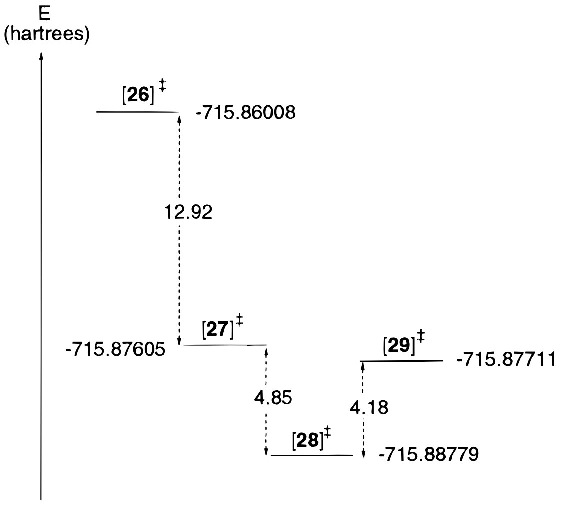
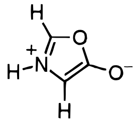


Figure 4.

tions, which are just one notable exception. By applying the FMO approach, we are not accounting for all the other orbital interactions, which are generally less energetically profitable, and notably other factors being ignored or at least underestimated such as entropy or solvent effects. We have analyzed the Coulombic contribution of the PMO equation,[14,15a] given the dipolar character of the mesoionic heterocycle, as well as entropy and solvent effects. Likewise, rate constants at different temperatures, inferred from the free activation energy $\Delta G^{\ddagger}$, were calculated using the transition state theory (TST)[27] with the MORATE program.[28] The AMSOL program allowed us to calculate the dipole moments and solvation energies by using a cavity adopted to the molecular shape and used a monopole-distributed expansion of the solute charge distribution.[29] Although this model is parametrized for water ($\epsilon = 78.5$) whereas our experiment was performed in acetic anhydride ($\epsilon = 20$), one can expect small differences ($<10\%$) as the reaction field factors do not vary significantly with ϵ for high dielectric constants. Still, it was not possible to explain the regioselectivity of this reaction by considering the aforementioned factors. Moreover, one realizes that the full system can only be treated semiempirically, but these procedures, which are parametrized for minima along the reaction pathway but not for saddle points, often give erroneous results. In particular, PM3 seems to overestimate long-range repulsive effects, and a rationalization of the experiment presuming one regioisomer is not possible. *It is therefore quite surprising that previous studies on münchone cycloadditions have stressed the energy of the frontier orbitals and the application of semiempirical methods*.[21−23] Our study demonstrates that this methodology does not seem to be very reasonable.

Further Calculation Level: *Ab Initio* MP2 Computation. In order to infer the particular reactivity of münchnone cycloadditions, *ab initio* MO calculations were done on the aforementioned reaction. However, this forced us to reduce the size of the model by considering the reaction of mesoionic compound **24** with nitroalkene **25**.



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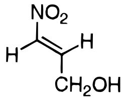

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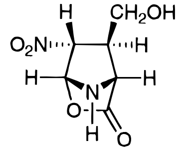
Still, this model system is close to the real situation depicted in Scheme 1, the differences now being the complete lack of the chiral fragment of the nitroalkene as well as the aromatic and methyl substituents in the münchnone substrate. From these reagents four hypothetical 1:1 cycloadducts (**26**−**29**) could be obtained.



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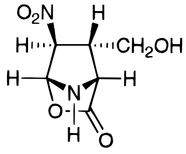

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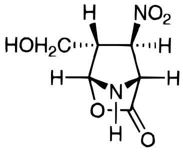

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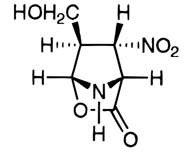

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The MP2/6-31G calculation[30] allows the determination of total energies and energy differences for all the species involved: reactants, products, and saddle points. Figure 4 depicts the total energies (hartrees) and energy changes (kcal mol^{-1}) for saddle points leading to **26**−**29**. Even at this moderate *ab initio* level, the computational study does require a basis set of 133 functions.

Assuming that the full optimization of the geometries has been already performed at the PM3 level, the data of Figure 4 have to be taken in a relative sense. The potential energy differences for compounds **26**−**29** are −45.7, −45.4, −47.1, and −45.3 kcal mol^{-1}, respectively. Notwithstanding the limited computational facilities, the trends are now clear and the approach leading to cycloadduct **28** is both kinetic and thermodynamically favored. There is no electrostatic repulsion between the O1−C5−O fragment of münchnone **24** with the nitro group of **25**, which could account for the instability of the approaches leading to **26** and **29**. Therefore, this process represents a borderline reaction wherein a simpler approach does not work while a better level of calculation works as well as experiment does.

Electronic Reorganization. The last issue we address here is whether the TSs are synchronous or not. We located only one TS for each reaction and confirmed that it was a true TS (a saddle point) on the basis of frequency analysis. However, a concerted reaction needs not be synchronous since bonds do not have to form or break to the same extent in the TS of a concerted process. In order to ascertain whether these reactions are syn-

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(27) (a) Gladstone, S.; Laidler, K. J.; Eyring, H. *Theory of Rate Processes*; McGraw-Hill: New York, 1941. (b) Johnston, H. S. *Gas Phase Reaction Rate Theory*; Ronald Press: New York, 1966. (c) Laidler, K. J. *Theories of Chemical Kinetics*; McGraw-Hill: New York, 1969.

(28) Hu, W.-P.; Lynch, G. C.; Liu, Y.-P.; Truong, T. N.; Rossi, I.; Stewart, J. J. P.; Steckler, R.; Garrett, B. C.; Isaacson, A. D.; González-Lafont, A.; Lu, D.-H; Melisas, V.; Rai, S. N.; Hancock, G. C.; Joseph, T.; Truhlar, D. G. MORATE, version 6.2, University of Minnesota, Minneapolis, 1994.

(29) Cramer, C. J.; Truhlar, D. G. *J. Comput. Chem.* **1992**, *13*, 1089−1097.

(30) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213−222.

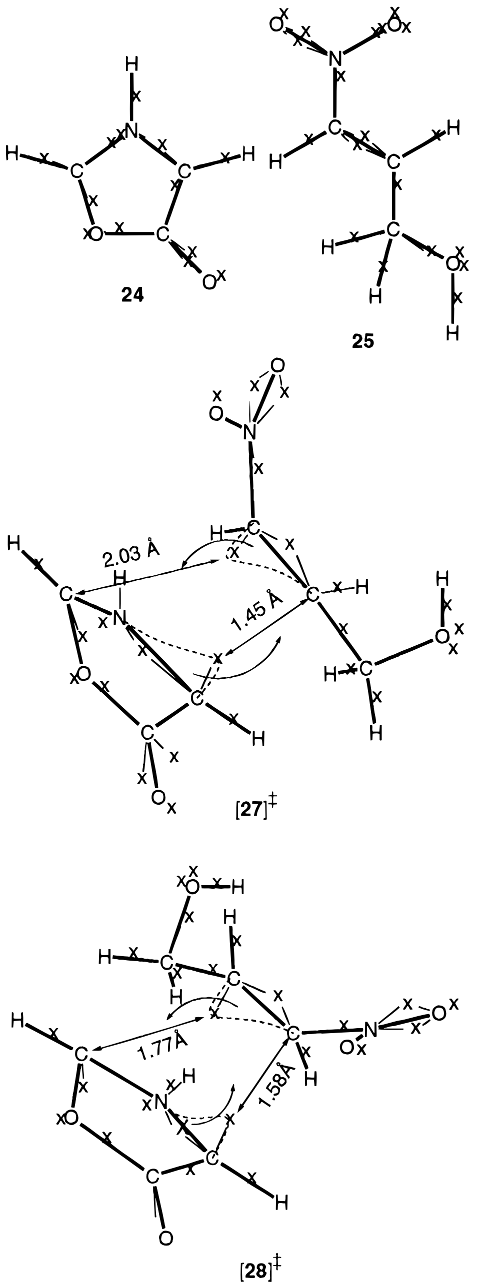

Figure 5.

chronous, we have followed the electronic reorganization that takes place along the cycloaddition by computing the charge centroids for localized molecular orbitals according to the method described by Boys.[31] Figure 5 shows the charge centroids calculated for several points along the reaction pathway (reactants and saddle points), focusing the attention on the approaches leading to **27** and **28**, which exhibit the larger discrepancies in our previous analysis. The solid lines connect a centroid with the nearest atom or pair of atoms, whereas the dashed lines show the migration of a particular centroid from its previous position. The evolution of such centroids at the saddle point is still weak, as the approach leading to **28** is more synchronous than the formation of **27**. The electronic reorganization starts near the saddle point region. The π electrons of the N1−C4 and C1−C2 bonds of **24** and **25**, respectively, move toward the zone of the future C2−C1′ and C4-C2′ bonds of **23** and C2−C2′ and C4−C1′ bonds of **28** in following a cyclic counterclockwise movement. This outcome of electronic migrations appears to be fixed by the net charge of the terminal atoms (C2 and C4) of the dipole **24**. The displacement of centroids starts at the end of dipole, as this is a more negative atom, and this fact accounts for the asynchronicity of the process. The forming single bonds at the saddle point leading to **28** of 1.58 and 1.77 Å reveal that the münchnone−nitroalkene cycloaddition outlined is a concerted, slightly asynchronous process, whereas a nonconcertedness (1.45 and 2.03 Å for the forming bond) should practically be assumed for the approach affording **27**.

Conclusions

(a) 1,3-Dipolar cycloadditions of münchnones with appropriately functionalized carbohydrate alkenes constitute a simple and straightforward route for the preparation of pyrrole *C*-nucleosides such as **5**−**8**, which are potential therapeutic agents. (b) The process is regiospecific, and one regioisomer was exclusively obtained. (c) Unlike other mesoionic systems, the regioselectivity observed is opposite to that anticipated by the FMO theory. (d) Münchnone cycloadditions constitute a limiting case of dipolar cycloadditions for which the FMO approach cannot be applied at all in combination with a semiempirical method. (e) An *ab initio* refinement is able to provide satisfactory conclusions with regard to the nature and energetics of TSs. The observed selectivity is predicted from such an study from which the cycloadduct **28** is formed under kinetic and thermodynamic controls. (f) Unlike previous studies based on FMO assumptions suggesting asynchronous, even nonconcerted pathways, our findings show that the 1,3-dipolar cycloaddition of münchnone with an unsymmetrically substituted dipolarophile proceeds through a concerted, slightly asynchronous TS.

Experimental Section

Materials and Apparatus. Solvents and reagents were purchased from Aldrich and used without further purification. Silica gel (230−400 mesh ASTM, Merck) was used for flash chromatography.[32] Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 18 ± 2 °C. Electronic absorption spectra were recorded in ethanolic solutions unless otherwise specified. IR spectra were recorded with a FT-IR spectrophotometer using KBr pellets unless otherwise specified. NMR experiments were conducted at 400 and 100 MHz for ^{1}H and ^{13}C nuclei, respectively. Chemical shifts are reported in δ relative to TMS, and apparent coupling constants are given in Hz. Combustion analyses were determined at Servicio de Microanálisis, CSIC, Barcelona, Spain.

Computational Methods. Semiempirical molecular orbital calculations on reactants, transition structures, and reaction products were performed by using the PM3[24] method of the MOPAC program[33] implemented on the CONVEX 210 computer. All stationary points were located on the potential energy surfaces, and the corresponding geometries were subsequently refined by minimizing the energy (for minimums) or the norm of the gradient[34] (for saddle points)[35] with full optimization of all geometric variables (bond lengths, bond

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(31) Boys, S. F. *Rev. Mod. Phys.* **1960**, *32*, 296−299.

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(33) Stewart, J. J. P. MOPAC 6.0. QCPE Program 455.

(34) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625−2633.

angles, and dihedral angles). Stationary points on the potential energy surfaces were characterized according to the number of negative vibrational frequencies.[34] With the optimized geometries at the PM3 level, the energy determination was made using a single point restricted second-order Møller-Plesset (RMP2) perturbation calculation with frozen core (FC) approximation using the 6-31G basis set of Pople.[30] The *ab initio* calculations were performed using the GAUSSIAN 92 system of programs.[36]

3-(Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1-methyl-2-(4-nitrophenyl)-5-phenylpyrrole (5). Procedure A. A suspension of **1** (1.18 g, 4.0 mmol) and **2** (0.87 g, 2.0 mmol) in toluene (50 mL) was refluxed for 3 h. The solvent was evaporated under reduced pressure to give an oily residue that crystallized from ethanol (0.89 g, 69%): mp 150−152 °C; $[\alpha]_D$ −78° (*c* 0.5, $CHCl_3$); λ_{max} (96% EtOH) 227, 269, 382 nm (ϵ_{mM} 10.2, 14.1, 8.1); ν_{max} 1740 (C=O), 1590, 1510 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.36 (d, 2H, 4-nitrophenyl), 7.60 (d, 2H, 4-nitrophenyl), 7.39 (m, 5H, phenyl), 6.31 (s, 1H, H-4), 5.91 (d, 1H, $J_{1',2'} = 4.2$ Hz, H-1′), 5.39 (dd, 1H, $J_{3',4'} = 3.0$ Hz, H-3′), 5.19 (dd, 1H, $J_{2',3'} = 8.2$ Hz, H-2′), 5.10 (m, 1H, $J_{4',5'} = 4.5$ Hz, $J_{4',5''} = 7.0$ Hz, H-4′), 4.20 (dd, 1H, $J_{5',5''} = 11.8$ Hz, H-5′), 3.85 (dd, 1H, H-5″), 3.43 (s, 3H, NCH_3), 2.09, 1.99, 1.88 (s, 15H, CH_3CO); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.3, 170.2, 169.5 (CH_3*CO*), 147.1, 138.4, 137.5, 132.4, 131.2, 128.9, 128.6, 127.7, 123.8, 117.6 (aryl), 108.2 (C-4), 71.0 (C-2′), 68.7 (C-3′), 68.0 (C-4′), 67.5 (C-1′), 62.1 (C-5′), 21.0, 20.8, 20.7, 20.6, 20.3 (*C*H_3CO). Anal. Calcd for $C_{32}H_{34}N_2O_{12}$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.06; H, 5.39; N, 4.12.

Procedure B. A suspension of **1** (1.36 g, 4.6 mmol) and **2** (1.00 g, 2.3 mmol) in acetic anhydride (15 mL) was stirred at room temperature for 7 days. The reaction mixture was poured into ice−water, and the resulting oil was extracted with dichloromethane (10 mL), washed successively with sodium hydrogencarbonate saturated solution (3 × 5 mL) and water (3 × 5 mL), and dried. The solvent was evaporated and the residue crystallized from ethanol (1.02 g, 69%).

3-(Penta-*O*-acetyl-D-*manno*-pentitol-1-yl)-1-methyl-2-(4-nitrophenyl)-5-phenylpyrrole (6). A suspension of **1** (1.36 g, 4.6 mmol) and **3** (1.00 g, 2.3 mmol) in acetic anhydride (15 mL) was stirred at room temperature for 7 days. Then, the reaction mixture was poured into ice−water to give a yellow solid. The product was purified by flash chromatography (benzene−hexane−ethyl acetate, 4:4:1) and crystallized from ethanol (0.96 g, 65 %): mp 84−86 °C; $[\alpha]_D$ +53° (*c* 0.5, $CHCl_3$); λ_{max} (96% EtOH) 227, 270, 383 nm (ϵ_{mM} 5.8, 8.4, 5.1); ν_{max} 1740 (C=O), 1590, 1510 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34 (d, 2H, 4-nitrophenyl), 7.69 (d, 2H, 4-nitrophenyl), 7.39 (m, 5H, phenyl), 6.41 (s, 1H, H-4), 5.69 (d, 1H, $J_{1',2'} = 9.0$ Hz, H-1′), 5.56 (dd, 1H, $J_{2',3'} = 2.0$ Hz, H-2′), 5.53 (dd, 1H, $J_{3',4'} = 9.0$ Hz, H-3′), 5.08 (m, 1H, $J_{4',5'} = 3.5$ Hz, $J_{4',5''} = 5.0$ Hz, H-4′), 4.23 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5′), 4.02 (dd, 1H, H-5″), 3.43 (s, 3H, N-CH_3), 2.03, 2.00, 1.98, 1.96, 1.88 (s, 15H, CH_3CO); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.8, 169.7, 169.4, 168.9 (CH_3*CO*), 146.9, 138.4, 137.4, 133.0, 132.3, 130.9, 128.8, 128.4, 127.4, 123.6, 118.0 (aryl), 108.7 (C-4), 70.3 (C-2′), 67.9 (C-4′), 67.6 (C-3′), 66.3 (C-1′), 61.8 (C-5′), 33.9 (NCH_3) 20.9, 20.8, 20.5 (*C*H_3CO). Anal. Calcd for $C_{32}H_{34}N_2O_{12}$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.26; H, 5.34; N, 4.69.

1-Methyl-2-(4-nitrophenyl)-3-(D-*galacto*-pentitol-1-yl)-5-phenylpyrrole (7). A solution of **5** (1.5 g, 2.35 mmol) in methanol (30 mL) was treated with 1 M sodium methoxide solution (15 mL). After 15 min at room temperature, water (50 mL) and Amberlite IR-120 were added until neutral pH. The Amberlite was filtered off and washed with additional portions of methanol, which was evaporated under reduced pressure, and the aqueous solution was extracted with 1:1 ethyl acetate−diethyl ether (3 × 50 mL). The organic extracts were dried and evaporated to give a residue that crystallized from ethyl acetate (0.35 g, 66%): mp 168−170 °C; $[\alpha]_D$ −67° (*c* 0.5, C_5H_5N); λ_{max} (96% EtOH) 276, 397 nm (ϵ_{mM} 15.3, 10.9); ν_{max} 3360 (OH), 1590, 1510 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6/D_2O) δ 8.31 (d, 2H, 4-nitrophenyl), 7.80 (d, 2H, 4-nitrophenyl), 7.51 (m, 5H, phenyl), 6.67 (s, 1H, H-4), 4.76 (s, 1H, $J_{1',2'} = 0$ Hz, H-1′), 3.77−3.41 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-5″), 3.50 (s, 3H, NCH_3): ^{13}C NMR (DMSO-d_6/D_2O) δ 145.6, 138.7, 136.4, 132.7, 131.1, 130.8, 128.6, 128.2, 127.0, 132.4 (aryl), 109.6 (C-4), 73.9 (C-2′), 70.1 (C-4′), 69.8 (C-3′), 64.5 (C-1′), 63.1 (C-5′), 34.1 (NCH_3). Anal. Calcd for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.50; H, 5.72; N, 6.29.

1-Methyl-2-(4-nitrophenyl)-3-(D-*manno*-pentitol-1-yl)-5-phenylpyrrole (8). A solution of **6** (0.45 g, 0.7 mmol) in methanol (5 mL) was treated with 1 M sodium methoxide solution (2 mL). After 15 min at room temperature, water (5 mL) and Amberlite IR-120 were added until neutral pH. The Amberlite was filtered off and washed with methanol. The solution was evaporated to dryness and the resulting oil crystallized from diethyl ether (0.22 g, 73%): mp 98−100 °C dec; $[\alpha]_D$ −53° (*c* 0.5, C_5H_5N); λ_{max} (96% EtOH) 232, 278, 399 nm (ϵ_{mM} 11.4, 15.0, 11.2); ν_{max} 3360 (OH), 1595, 1510 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6/D_2O) δ 8.30 (d, 2H, 4-nitrophenyl), 7.88 (d, 2H, 4-nitrophenyl), 7.45 (m, 5H, phenyl), 6.42 (s, 1H, H-4), 4.84 (s, 1H, $J_{1',2'} = 5.3$ Hz, H-1′), 3.91−3.31 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-5″), 3.40 (s, 3H, NCH_3); ^{13}C NMR (DMSO-d_6/D_2O) δ 145.6, 138.8, 136.6, 132.7, 132.3, 130.9, 128.6, 128.2, 127.6, 127.0, 123.2 (aryl), 108.0 (C-4), 72.2 (C-2′), 71.6 (C-4′), 69.8 (C-3′), 64.3 (C-1′), 63.8 (C-5′), 34.1 (NCH_3). Anal. Calcd for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.73; H, 5.47; N, 6.43.

3-Formyl-1-methyl-2-(4-nitrophenyl)-5-phenylpyrrole (9). To a suspension of **7** (0.1 g, 0.23 mmol) in water (10 mL) was added a solution of sodium metaperiodate (0.43 g, 2.0 mmol) in water (2 mL), and the reaction mixture was stirred vigorously at room temperature. Within a few minutes, the title compound crystallized as a yellow solid (0.07 g, 99%): mp 148−149 °C; λ_{max} ($CHCl_3$) 264, 370 nm (ϵ_{mM} 22.3, 8.9); ν_{max} 1660 (C=O), 1595, 1510 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.62 (s, 1H, CHO), 8.38 (d, 2H, 4-nitrophenyl), 7.68 (d, 2H, 4-nitrophenyl), 7.46 (m, 5H, phenyl), 6.81 (s, 1H, H-4), 3.53 (s, 3H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 185.6 (CHO), 147.8, 140.5, 138.3, 138.1, 131.6, 131.3, 129.1, 128.7, 128.3, 128.2, 124.2, 123.7 (aryl), 108.0 (C-4), 33.8 (NCH_3). Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.21; H, 4.60; N, 8.87.

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Supporting Information Available: Geometrical parameters, formal charge distributions, enthalpies of formation, and the ionization potentials for reactants, cycloadducts, and saddle points, as well as calculation of Coulombic contributions and MP2 energies and coefficients (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[35] According to the nonconventional theories of the transition state, a saddle point may not be coincidental with the transition state since the former concept constitutes a more precise refinement over the conventional approach. In the context of this work, however, the readership should consider the concepts of saddle point and transition state as equivalents.

[36] Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; González, C.; DeFrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. GAUSSIAN 92, Gaussian, Inc., Pittsburgh, 1992.