

Table 1. Preparation of 4-Methoxydienamides **2**.^a

No.	R ¹	R ²	yield ^b (%)	R _f ^c
2a		(CH ₂) ₄	85	0.15
2b		(CH ₂) ₅	93	0.45
2c	H	Bu ⁱ	86	0.42
2d	H	(<i>S</i>)-PhCHCH ₃	89	0.27 ^c

^a All compounds gave satisfactory spectroscopic data (¹H and ¹³C NMR, IR and MS) ^b Crude yield (>90% pure by 300 MHz ¹H NMR). ^c Hexane/AcOEt 1:1. ^c [α]_D²² = -54.4 (c, 1.6; CHCl₃).

The [4+2] cycloaddition reaction between compounds **2** and different dienophiles was carried out under thermal conditions to give the corresponding cycloadducts **3** and are summarized in Table 2. The reaction with *N*-phenylmaleimide and dimethyl fumarate took place with *endo* selectivity affording mainly *cis*-adducts **3aa**, **3ba**, and **3bb** (Table 2, entries 1, 2, and 4). In the case of compound **3ba**, when the reaction was carried out under toluene reflux for 6d, a *ca.* 1:1 *endo/exo* mixture was obtained⁹ (Table 2, entry 3).

Intermolecular Diels-Alder reaction of **2** with electron-rich dienophiles such as enamines or vinyl ethers failed. Several attempts with dienophiles bearing one or two electron-releasing groups at the same olefinic carbon such as acrylic systems (methyl vinyl ketone, 1-chloroacrylonitrile and 1-bromoacrolein) also failed, probably due to the low reactivity of the dienophile or to steric reasons in the case of disubstituted olefins. The use of different Lewis acids [AlCl₃, Et₂AlCl, BF₃·Et₂O, ZnCl₂, Eu(tfd)₃] produced mainly hydrolysis of the vinyl methyl ether moiety to the corresponding (*E*)-2-oxo-2-pentenamides. In the case of the reaction of monoalkylated amide **2c** with *N*-phenylmaleimide, only complex mixtures of adducts were obtained. When chiral diene **2d**, derived from (*S*)-phenylethylamine, was allowed to react with 4-phenyl-1,2,4-triazoline-3,5-dione as dienophile for **1d** and at 50°C in a sealed tube the process showed a lack of diastereoselectivity with the isolation of a mixture of diastereomeric cycloadducts **3da** in a *ca.* 1:1 molar ratio (Table 2, entry 7).

According to calculations using the AM1 semi-empirical method¹⁰⁻¹³ for **2b**, the energy for the all *s-cis* conformation is -48.77 kcal/mol and for the *s-trans* is -48.33 kcal/mol (Scheme 1), and the energies corresponding to the frontier orbitals are typical for electron-rich dienes (*E*_{HOMO} = -9.49466 eV, *E*_{LUMO} = -0.30949 eV). Moreover, calculations on the model reaction between (*2E*)-4-methoxy-2,4-pentadienamide and maleimide were used to locate the *endo/exo* transition structures (Figure 1), showing that the *exo* transition state (ΔH_f = -61.0 kcal/mol) should be slightly favored over the *endo* (ΔH_f = -60.3 kcal/mol).

This value is subjected to the usual uncertainties in AM1 predictions as is shown in earlier Diels-Alder reaction analyses,¹⁴ where AM1 underestimates the relative stability of the sterically most crowded transition state by 1.4-3.4 kcal/mol when compared to the available experimental data and *ab initio* calculations. Assuming similar errors for the currently studied reaction, we would estimate the *endo* transition state to be

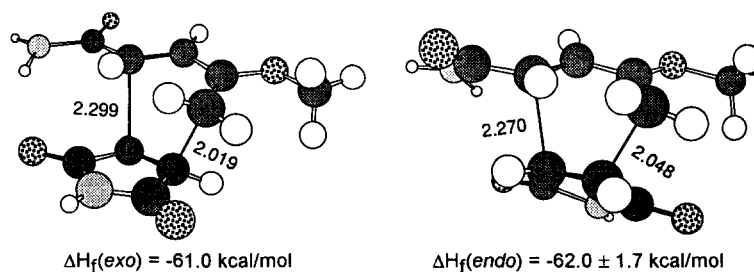
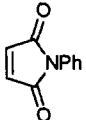
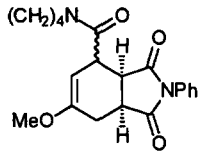
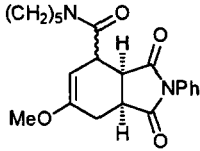
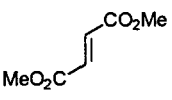
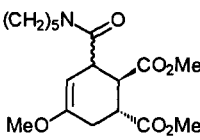
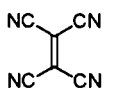
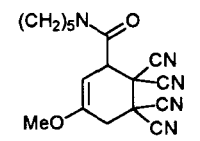
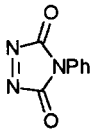
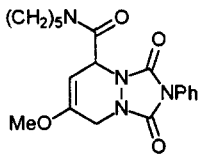
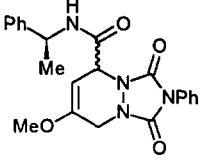


Figure 1. Computer plot of the AM1 transition states (lengths in Å) for the *exo* and *endo* cycloaddition of (*2E*)-4-methoxy-2,4-pentadienamide and maleimide.

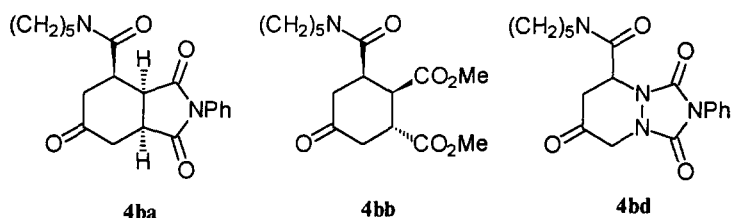
Table 2. Cycloaddition Reaction of 4-Methoxydienamides **2** with Dienophiles.

Entry	diene no.	dienophile	conditions	product ^a			
				structure	no.	endo/exo ratio ^b	yield ^c (%)
1	2a		THF reflux, 3d		3aa	1.5:1	31
2	2b		THF reflux, 1d		3ba	10:1	56
3	2b		PhCH ₃ reflux, 6d		3ba	0.86:1	90
4	2b		PhCH ₃ reflux, 3d		3bb	4:1	40
5	2b		THF r.t., 7d		3bc	-	51
6	2b		THF 50°C, 2d ^d		3bd	-	80
7	2d		THF 50°C, 1d ^d		3da	- ^e	60

^a All compounds gave satisfactory spectroscopic data (¹H and ¹³C NMR, IR and MS)^b. Determined by ¹H NMR (300 MHz). ^c Isolated yield after column chromatography: Neutral alumina (entries 1, 2, and 4), deactivated silica gel (entry 5) or florisil® (entries 3, 6, and 7). ^d In a sealed tube. ^e Diastereomeric mixture *ca.* 1:1.

more stable than the *exo* one with a heat of formation of -62.0 ± 1.7 kcal/mol. The calculated values for the forming C-C bonds are in agreement with a one-step reaction occurring through a concerted pathway that is asynchronous, but with partial formation of both bonds. Lastly, AM1 predicts the *exo* cycloadduct ($\Delta H_f = -136.2$ kcal/mol) to be 1.4 kcal/mol more stable than the *endo* ($\Delta H_f = -134.8$ kcal/mol). The obtained results are in concordance with the experimental findings: the initial formation of the *endo* adduct through the less energetic transition state and the following equilibrium to the most stable *exo* adduct.

Final hydrolysis of the obtained cycloadducts furnished stereoselectively cyclohexanone derivatives **4**. In the case of adduct **3ba** obtained as a 0.86:1 *endo:exo* ratio (Table 1, entry 3), after treatment with 10% H_2SO_4 in THF for 4d, only *cis*-**4ba** was obtained in 67% isolated yield referred to **3ba**. The fumarate *cis/trans*-adduct **3bb** (Table 2, entry 4) gave only *cis*-**4bb** in 85% isolated yield after hydrolysis on alumina. Compound **3bd**, was hydrolyzed with conc. HCl in CH_2Cl_2 for 1d to provide **4bd** in 55% isolated yield, whereas in the case of adduct derived from tetracyanoethylene **3bc**, only extensive decomposition was observed after hydrolysis under different conditions.



In summary, (2*E*)-4-methoxy-2,4-pentadienamides are appropriate dienes in Diels-Alder reactions with normal-electron demand dienophiles for the synthesis of highly functionalized adducts which can be useful synthetic intermediates.¹⁵ Further studies about the use of these new dienes are now under way.

In a *typical procedure* for the synthesis of dienes **2**, a solution of **1**⁴ (0.3 mmol) in 1M methanolic KOH (5 mL) was stirred for 3 h at rt. The resulting solution was evaporated (15 Torr) and the residue was dissolved in water (10 mL) and extracted with EtOAc (3x10 mL). The organic phase was dried (Na_2SO_4) and evaporated (15 Torr) to yield compounds **2** (see Table 1) which were pure enough for subsequent use.¹⁷

REFERENCES AND NOTES

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2. For reviews see for instance: (a) Oppolzer, W. In *Comprehensive Organic Synthesis*, Paquette, L. A.; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5; pp 315-399. (b) Roush, W. In *Comprehensive Organic Synthesis*, Paquette, L. A.; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5; pp 513-550. (c) Carruthers, W. *Cycloadditions Reactions in Organic Synthesis*; Pergamon: New York, 1990.
3. Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley & Sons: New York, 1990.
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5. Prepared by iodosulfonylation of the corresponding (2*E*)-pentadienamides.⁴
6. Spectral NMR data for compound **2b**: δ_{H} (300 MHz) 1.54-1.68 (m, 6H), 3.53-3.65 (m, 4H), 3.66 (s, 3H), 4.41, 4.43 (2d, $J=2.1$ Hz, 2H), 6.71 and 7.04 (2d, $J=15.0$ Hz, 2H); δ_{C} (75 MHz) 24.5, 25.5, 26.6, 43.1, 46.8, 54.8, 91.7, 117.8, 137.8, 157.9 and 165.1.
7. Similar behaviour has been observed in the case of the (*E*)-*N*-isopropyl-3-tosylacrylamide to give *N*-isopropyl-2-methoxyacrylamide.⁸
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9. The stereochemistry of compounds **3** could be deduced by one- and two-dimensional ^1H NMR studies, and NOE experiments.
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15. Cycloaddition adducts of *N*-arylmaleimides and 2-methoxy-1,3-butadiene^{16a} or 2-(trimethylsilylmethyl)-1,3-butadiene have been used as starting products in the synthesis of Gracilins B and C.^{16b}
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17. We thank DGICYT (Project PB94-1515) from the Spanish Ministerio de Educación y Ciencia (MEC) and the Universidad de La Rioja (Project 95PYB23MRB) for financial support. R. C. thanks the Universidad de Alicante for a grant.

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