A Diels–Alder Study of the Diene Reactivity of 2-Methyl-5-vinyl-3-furoate Esters

Michael G. B. Drew,[a] Archie Jahans,[a] Laurence M. Harwood,*[a] and Sophie A. B. H. Apoux[a]

Dedicated to Professor Marc Julia on the occasion of his 80th birthday

Keywords: High-pressure chemistry / Cycloaddition / Natural products

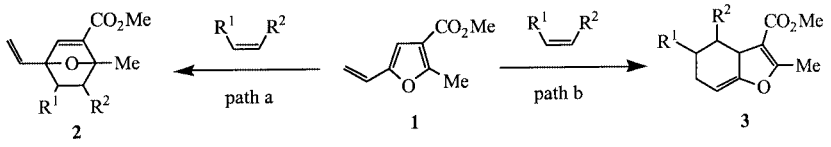
The reaction of a range of dienophiles with methyl 2-methyl-5-vinyl-3-furoate under thermal and high pressure conditions has been surveyed. Efficient cycloaddition onto the diene system involving the exocyclic alkene has been shown to occur without concommitant aromatisation. An intramolecular variant permits the synthesis of an analogue to the colletofragarone system.

Introduction

Although the furan nucleus has become an important diene in the synthesis of natural products, 2-vinyl-substituted furans have been less exploited since the first intermolecular cycloaddition between 2-vinylfuran and maleic anhydride was reported by Paul in 1939.[1a] Intermolecular Diels–Alder reactions with 2-vinylfuran substrates have been carried out under thermal conditions,[1a–1l] often by heating the reactants in a sealed tube,[1m–1p] but only once has high pressure been investigated briefly.[1q] Thermal intramolecular Diels–Alder reactions involving 2-vinylfuran substrates have been reported more recently and in all cases the dienophile is attached to C-2 of the vinyl substituent.[2a–2h]

In this paper we report the reactivity of methyl 2-methyl-5-vinyl-3-furoate (**1**) with a variety of dienophiles towards an intermolecular Diels–Alder reaction. The [4π+2π] cycloaddition between methyl 2-methyl-5-vinyl-3-furoate (**1**) and a dienophile can, in principle, occur over two distinct diene systems (Scheme 1), involving the furan diene to form adducts **2**, or involving the C4-C5 double bond of the furan and the extracyclic double bond to furnish adducts **3**.

Due to the electron-withdrawing effect of the ester group reducing the diene reactivity of the furan ring, we proposed that Diels–Alder reaction could be encouraged to involve the external double bond under conditions mild enough to avoid subsequent migration of the newly formed double bond of the cycloadduct to regenerate the furan nucleus.[1l,1o,1q,2] This outcome was desirable as such adducts were considered to present us with a means of constructing the tricyclic core of the colletofragarones. The colletofragarones **4** and **5** are members of a family of macro-lactone tricycles in which the rings possess a common carbon atom (Figure 1).[3] The retrosynthetic pathway is based upon constructing the tricyclic system **7** from a 2-vinylfuran



Scheme 1. Intra-annular cycloaddition (path a) and extra-annular cycloaddition (path b), with $R^1 = R^2$ or $R^1 \neq R^2$

Diels–Alder precursor **6** with the dienophile attached to the furan ring by a tether (Scheme 2). This is a very different situation to the few intramolecular Diels–Alder cycloadditions previously reported[2a–2h] in which the dienophile is tethered directly to the vinyl group, giving rise to linear tricycles.[2f,2g]

[a] Department of Organic Chemistry, University of Reading, P. O. Box 224 Whiteknights, Reading, Berkshire RG6 6AD, United Kingdom
Fax: (internat.) + 44-(0)118/3781-6121
E-mail: l.m.harwood@reading.ac.uk

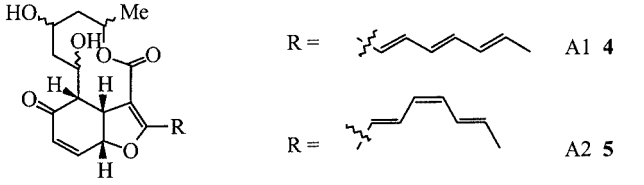
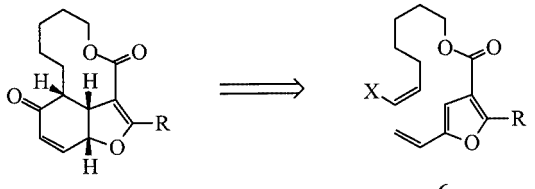


Figure 1. Structures of colletofragarones A1 **5** and A2 **6**



Scheme 2. Retrosynthetic analysis of tricyclic skeleton of the colletofragarones

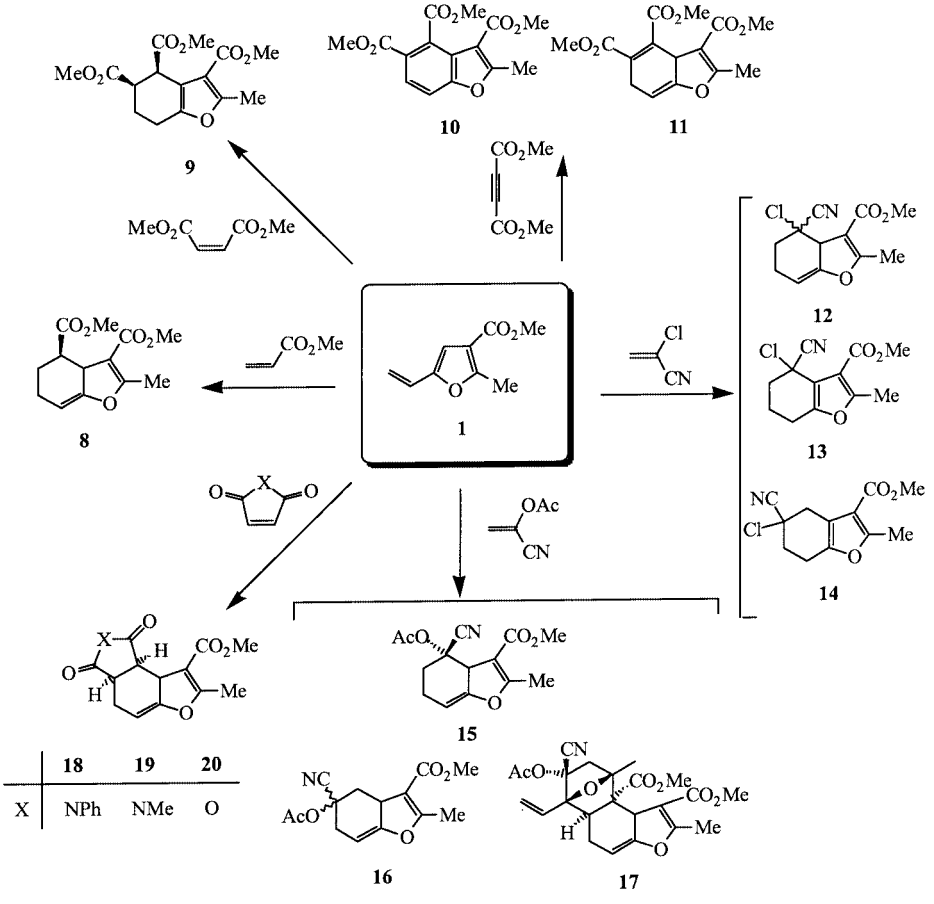
Results and Discussion

With methyl acrylate and dimethyl maleate, no adduct was detected under reflux in diethyl ether after seven days (higher temperatures resulted in extensive decomposition). However, after seven days at 1.1 Gpa[4] cycloadducts **8** and **9** were isolated in 23% and 51% yield respectively. In both cases, cycloaddition had occurred solely via the extra-annular cycloaddition mode; reformation of the furan ring in the case of **9** indicates the instability of the adducts to migration of the double bond.

Using dimethyl acetylenedicarboxylate (DMAD) as the dienophile, under thermal conditions in diethyl ether led to the isolation of the aromatised cycloadduct **10** in 61% yield (completion of the reaction required 19 days), whereas under high pressure conditions, cycloadducts **10** and **11** could be identified in the ^{1}H NMR spectrum of the crude mixture in a 1:6.5 ratio. However, extensive aromatisation occurred during attempted purification by column chromatography resulting in **10** being isolated in 49% yield and **11** in 24% yield (Scheme 3 and Table 1).

When 2-chloroacrylonitrile was used as the dienophile, after five days under reflux in diethyl ether an inseparable mixture of isomers **12** was isolated in 9% yield, whereas the same mixture was obtained in a yield of 70% under high pressure conditions. Leaving the reaction under high-pressure conditions for six days resulted in the formation of benzofuran regioisomers **13** and **14** (Table 1).

With 1-acetoxyacrylonitrile as the dienophile, after nine days under reflux in diethyl ether only one adduct **15** was isolated in 12% yield. Under high-pressure conditions, not only was adduct **15** isolated in 30% yield but also another isomer **16** and a by-product **17** were obtained in yields of



Scheme 3. Cycloaddition reactions with methyl 2-methyl-5-vinyl-3-furoate (**1**)

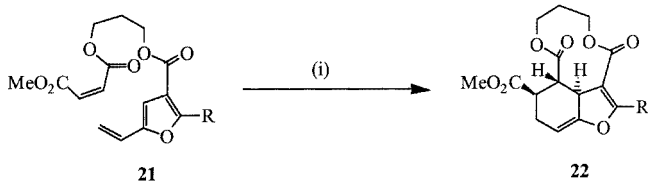
Table 1. Intermolecular cycloadditions with methyl 2-methyl-5-vinyl-3-furoate (**1**)

Dienophiles		Thermal conditions		High-pressure conditions	
		Time	Yields [%]	Conditions	Yields [%]
Methyl acrylate	**8**	7 d	–	7 d, 1.1 Gpa, 30 °C	23%
Dimethyl maleate	**9**	7 d	–	7 d, 1.1 Gpa, 30 °C	51%
Dimethyl	**10**	19 d	61%	1 d, 1.9 Gpa, 25 °C	49%
acetylenedicarboxylate	**11**		–		24%
2-Chloroacrylonitrile	**12**	5 d	9%	1 d, 1.9 Gpa, 25 °C	70% (**12**)
	13		–		
	14		–		
				6 d, 1.1 Gpa, 25 °C	23% (**12**), 9% (**13**), 10% (**14**)
1-Acetoxyacrylonitrile	**15**	9 d	12%	4 d, 1.9 Gpa, 25 °C	30%
	16		–		7%
	17		–		2%
N-Phenyl maleimide	**18**	8 d	90%	1 d, 1.9 Gpa, 25 °C	93%
N-Methyl maleimide	**19**	11 d	90%	1 d, 1.9 Gpa, 25 °C	92%
Maleic anhydride	**20**	2 d	87%	1 d, 1.9 Gpa, 25 °C	96%

7% and 2% respectively. The structures of **15** and **17** were confirmed by X-ray crystallographic analysis.[5,6]

Cyclic doubly activated dienophiles, such as *N*-phenyl maleimide, *N*-methyl maleimide or maleic anhydride, were also investigated. It was found that under both conditions investigated (either heating under reflux in diethyl ether or under high pressure conditions) only one product was isolated in each case, corresponding to the expected *endo* extra-annular cycloadducts **18**, **19** and **20** (Scheme 3). The structures were confirmed by X-ray crystallographic analysis.[5,6] Under either set of conditions, the yields were good but each substrate showed a modest improvement in yield under high pressure conditions and the reaction was completed within 24 hours as opposed to the seven days required for completion in the thermal processes.

Having studying a range of dienophiles for the intermolecular Diels−Alder reaction, attention was then directed towards the intramolecular Diels−Alder cycloaddition to see if it would permit large ring construction and present a possible means of access to the colletofragarone skeleton. In light of the enhanced reactivity of doubly activated dienophiles, model precursor **21** was synthesised with a maleate dienophile. The cycloaddition under thermal or high pressure conditions furnished a single tricyclic adduct **22** (Scheme 4), resulting from the desired extra-annular cycloaddition, as confirmed by X-ray crystallographic analysis[5,6] (Figure 2), without subsequent double bond migration, with a higher yield of 75% being observed under high pressure conditions than under thermal conditions (28%). It should be noted that the adduct **22** has the ester units in a *trans* relationship, whereas the starting material possesses a *cis*-configured dienophilic moiety. As such an isomerism is not observed in the equivalent intermolecular example furnishing **9**, we conclude that this epimerisation step occurs subsequent to cycloaddition.



(i) 1.1 Gpa, DCM, 25 °C, 24 h, 75%; or atm. pressure, benzene, 80 °C, 24 h, 28%.

Scheme 4. Intramolecular cycloaddition with precursor **21**

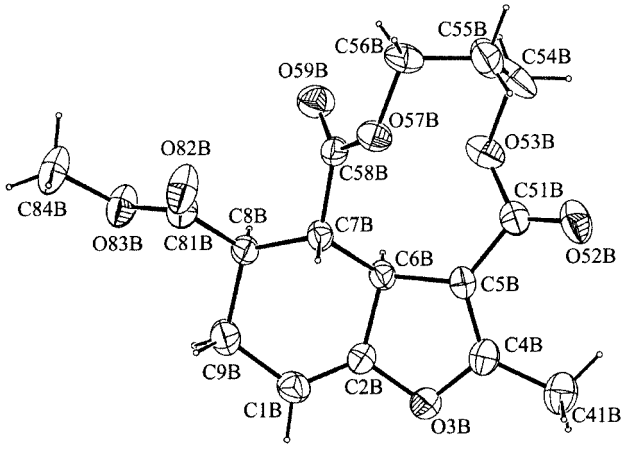


Figure 2. ORTEP representation of **22** (ellipsoids drawn at 30% probability)

Conclusion

We have shown that methyl 2-methyl-5-vinyl-3-furoate (**1**) acts as a diene, reacting solely by extra-annular cycloaddition under high-pressure-mediated conditions, whereas under thermal conditions, reaction is less efficient or does not occur. With dimethyl maleate, the product isolated resulted from the migration of the double bond to reform the furan ring, and with dimethyl acetylenedicarboxylate the cycloadduct was prone to aromatisation. 2-Chloroacrylonitrile formed a mixture of stereoisomers in high yield under high-pressure conditions but only in low yield under thermal

conditions. Doubly activated dienophiles such as *N*-phenyl maleimide, *N*-methyl maleimide and maleic anhydride underwent high yield extra-annular cycloaddition under both sets of conditions, although slightly improved yields and shortened reaction times were observed under high pressure. The intramolecular study showed that the use of a 2-vinylfuran substrate with the dienophile connected by a tether chain at C-4 of the furan nucleus, formed a single tricyclic adduct with a similar skeleton to that the colletofragarones. In this instance, the mildness of the high-pressure conditions permits the cycloadducts to be isolated without subsequent isomerisation of the double bond to reform the furan, and in greatly superior yields to the thermal conditions.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra (δ) were recorded in $CDCl_3$ using a Bruker Avance DPX 250 (250 MHz), a JEOL JNM-EX 400 (400 MHz) or a Bruker AMX 400 (400 MHz) spectrometers. Spectra were referenced to tetramethylsilane (TMS) as the internal standard defined as δ = 0 ppm. Chemical shifts are quoted in ppm. The coupling constants (*J*) are given in Hertz. Assignment of the fully decoupled ^{13}C spectra was assisted by the application of DEPT experiments acquired using the above instruments operating at 62.8 and 100.6 MHz respectively.

Mass spectra and high resolution mass measurements (HRMS) were recorded under conditions of chemical ionisation (CI) with ammonia as the ionising source. The instrument used was a Fisons VG Autospec mass spectrometer. Peaks are quoted in the form *m*/*z* (relatively intensity).

Infra-red spectra ($\tilde{\nu}_{max}$) were recorded either as a thin film between two sodium chloride plates or as a potassium bromide disk. Instruments used were a Perkin−Elmer Paragon 1000 FT-IR spectrometer and a Perkin−Elmer 1720 FT-IR spectrometer. All absorptions are quoted in cm^{-1} with broad signals indicated by the suffix br.

Elemental analyses were performed at Medac Ltd., Brunel Science Centre in Egham.

Melting points were recorded using a Reichert Kofler heated-stage microscope in Celsius (C) and are uncorrected.

Flash column chromatography was performed according to the procedure developed by Still et al.[7] using Merck 60 silica gel (particle size: 0.040−0.063 nm, 230−400 mesh ASTM) with head pressure produced by hand bellows. Dry flash column chromatography refers to column chromatography on Merk 60 silica gel using a water aspirator by following the method according to Harwood.[8]

Thin layer chromatography was performed on Merck aluminium plates coated with 0.2 mm silica 60 F_{254}. Products spots were visualised either by UV light at 254 nm or by staining with a solution of 2% aqueous potassium permanganate.

Reagents were obtained from Acros, Aldrich, BDH, Fisons or Lancaster Fine Chemicals and used directly as supplied or following purification according to the procedures described by Perrin and Armarego.[9] Diethyl ether and tetrahydrofuran were dried by distillation from sodium-benzophenone ketyl under nitrogen. Methanol and dichloromethane were dried by distillation from magnesium hydride under inert atmosphere. Light petroleum refers to the fraction boiling in the range 30−40 °C and was purified by fractional distillation through a 36 cm Vigreux column before use. Diisopropylamine was distilled over potassium hydroxide and stored over 3 Å molecular sieves under nitrogen.

High pressure reactions were carried out with PSIKA high pressure equipment allowing pressures of up to 2.0 Gpa with temperature control between ambient temperature and 150 C. Samples were dissolved in dichloromethane and were placed in Teflon® vessels.

General Procedure for Thermal Reactions: A solution of methyl 2-methyl-5-vinyl-3-furoate **1** (70 mg, 0.42 mmol, 1.0 equiv.) and the dienophile (0.42 mmol, 1.0 equiv.) in diethyl ether (5 mL) was heated under reflux until TLC analysis indicated disappearance of the starting material (usually 7 days). The solution was concentrated under reduced pressure and the cycloadduct was recrystallised from diethyl ether and collected as colourless crystals.

General Procedure for High Pressure Reactions: A solution of methyl 2-methyl-5-vinyl-3-furoate (**1**) (52 mg, 0.31 mmol, 1.0 equiv.) and the dienophile (0.31 mmol, 1.0 equiv.) in anhydrous dichloromethane (3 mL) was subjected to high pressure (1.1−1.9 Gpa) for 24 hours at room temperature. On depressurisation, the solution was filtered through a plug of cotton wool and the solvent removed in vacuo to afford the crude product. Purification by column chromatography on silica, eluting with ethyl acetate/light petroleum (1:3), furnished the cycloadducts as colourless crystals.

Methyl Acrylate Cycloadduct 8: (1.1 Gpa, 23%) colourless oil. IR (film): $\tilde{\nu}_{max}$ = 1720, 1605 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.65−1.99 (m, 4 H, 2 × CH_2), 2.53 (s, 3 H, CH_3), 2.55−2.58 (m, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.77−3.82 (m, 1 H, CH) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 14.3, 20.9, 23.0, 27.5, 39.9, 51.3, 52.3, 112.7, 115.1, 151.0, 158.5, 165.1, 175.6 ppm. MS (CI): *m*/*z* (%) = 253.1067 (32) $[MH]^+$ ($C_{13}H_{17}O_5$ requires 253.1076), 221 (18) $[MH - 32]^+$, 192 (100) $[MH - 61]^+$, 161 (16) $[MH - 92]^+$.

Dimethyl Maleate Cycloadduct 9: (1.1 Gpa, 51%) colourless flakes, m.p. 98−101 °C. $C_{15}H_{18}O_7$: calcd. C, 58.06, H 5.85; found C 58.06, H 5.88. IR (KBr): $\tilde{\nu}_{max}$ = 1715, 1595 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.15−2.22 (m, 2 H, CH_2), 2.53 (s, 3 H, CH_3), 2.57−2.74 (m, 2 H, CH_2), 2.79−2.90 (m, 1 H, CH), 3.66 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.28 (dd, J_{H-H} = 1.5, J_{H-H} = 5.7 Hz, 1 H, CH) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 14.2, 21.4, 22.3, 41.5, 43.4, 51.4, 52.3, 52.5, 112.6, 115.0, 150.3, 158.9, 164.8, 172.5, 173.8 ppm. MS (CI): *m*/*z* (%) = 311.1124 (27) $[MH]^+$ ($C_{15}H_{19}O_7$ requires 311.1131), 279 (35) $[MH - 32]^+$, 250 (100) $[MH - 61]^+$, 219 (32) $[MH - 92]^+$, 191 (57) $[MH - 120]^+$, 159 (20) $[MH - 152]^+$.

Aromatised Dimethyl Acetylenedicarboxylate Cycloadduct 10: (atm. pressure, 61%; 1.9 Gpa, 49%) white powder; m.p. 133−136 C. $C_{15}H_{14}O_7$: calcd. C 58.8, H 4.6; found C 59.0, H 4.6%. IR (film): $\tilde{\nu}_{max}$ = 1726, 1594 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.77 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 7.50 (d, J_{H-H} = 8.7 Hz, 1 H, H), 8.00 (d, J_{H-H} = 8.7 Hz, 1 H, H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 13.8, 50.8, 51.5, 51.6, 108.6, 110.8, 121.8, 123.0, 125.8, 128.6, 154.7, 162.3, 163.8, 165.2, 167.1 ppm. MS (CI): *m*/*z* (%) = 306.0741 (11) $[M]^+$ ($C_{15}H_{14}O_7$ requires 306.0739), 275 (100) $[M - 31]^+$.

Dimethyl Acetylenedicarboxylate Cycloadduct 11: (1.9 Gpa, 24%) white powder. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.30 (d, J_{H-H} =

1.8 Hz, 3 H, CH_3), 2.54 (s, 1 H, H), 3.18−3.28 (m, 1 H, H), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.36−4.48 (1 H, 2 × m, H), 5.38−5.41 (m, 1 H, H) ppm.

Chloroacrylonitrile Cycloadduct Mixture 12: (atm. Pressure, 9%; 1.9 Gpa, 1 d, 70%) colourless powder. IR (film): $\tilde{\nu}_{max}$ = 2219, 1720 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.28 (d, J_{H-H} = 1.7 Hz, 3 H, CH_3), 2.31 (d, J_{H-H} = 1.7 Hz, 3 H, CH_3), 2.33−2.60 (m, 8 H, 4 × CH_2), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.26−4.31 (m, 1 H, H), 4.32−4.34 (m, 1 H, H), 5.27−5.30 (m, 1 H, H), 5.34−5.40 (m, 1 H, H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 14.3, 14.6, 19.8, 21.8, 36.6, 38.6, 50.9, 51.2, 51.5, 54.7, 55.0, 56.9, 100.0, 100.9, 104.1, 116.4, 149.5, 150.8, 164.7, 164.9, 169.8, 170.0 ppm. MS (CI): *m/z* (%) = 254.0587 (75) $[MH]^+$ ($C_{12}H_{13}ClNO_3$ requires 254.0584), 218 (30) $[MH - HCl]^+$, 166 (100) $[MH - 88]^+$, 151 (15) $[MH - 103]^+$.

Double-Bond Migrated Chloroacrylonitrile Cycloadduct 13: (1.1 Gpa, 6 d, 9%) colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.03−2.13 (m, 2 H, CH_2), 2.57 (s, 3 H, CH_3), 2.54−2.70 (m, 4 H, 2 × CH_2), 3.92 (s, 3 H, OCH_3) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 14.2, 18.8, 22.8, 40.8, 51.5, 52.1, 108.1, 115.7, 119.2), 152.5, 160.4, 163.5 ppm. MS (CI): *m/z* (%) = 271.0852 (46) $[M + H_2O]^+$ ($C_{12}H_{14}ClNO_4$ requires 271.0611), 217 (100) [M − 54], 166 (100) $[MH - 88]^+$, 151 (15) $[MH - 103]^+$.

Double-Bond Migrated Chloroacrylonitrile Cycloadduct 14: (1.1 Gpa, 6 d, 10%) colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.91 (s, 3 H, CH_3), 2.13−2.20 (m, 2 H, CH_2), 2.57−2.63 (m, 2 H, CH_2), 2.67−2.73 (m, 2 H, CH_2), 3.69 (s, 3 H, OCH_3) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 20.0, 22.5, 29.1, 38.2, 52.5, 96.6, 117.0, 130.3, 144.6, 171.4, 176.2, 195.9 ppm.

Acetoxyacrylonitrile Cycloadduct 15: (atm. Pressure, 12%; 1.9 Gpa, 30%) colourless rhombs; m.p. 111−115 °C. $C_{14}H_{15}NO_5$: calcd. C 60.64, H 5.45, N 5.05; found C 60.38, H 5.46, N 4.98. IR (KBr): $\tilde{\nu}_{max}$ = 3020, 2250, 1752 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.12−2.16 (m, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 2.27 (d, J_{H-H} = 1.7 Hz, 3 H, CH_3), 2.42−2.67 (m, 2 H, CH_2), 3.75 (s, 3 H, OCH_3), 4.40−4.46 (m, 1 H, H), 5.30−5.35 (m, 1 H, H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 14.8, 21.0, 21.8, 31.5, 50.9, 51.7, 74.8, 100.4, 104.5, 115.4, 150.2, 165.1, 169.4, 169.8 ppm. MS (CI): *m/z* (%) = 278.1019 (82) $[MH]^+$ ($C_{14}H_{16}NO_5$ requires 278.1028), 236 (57) $[MH - 42]^+$, 217 (100) $[MH - 61]^+$, 185 (20) $[MH - 93]^+$, 166 (32) $[MH - 112]^+$, 79 (88) $[MH - 199]^+$.

Acetoxyacrylonitrile Cycloadduct 16: (1.9 Gpa, 7%) colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.93−2.06 (m, 4 H, 2 × CH_2), 3.74 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.94−3.97 (m, 1 H, H), 5.08−5.13 (m, 1 H, H) ppm.

Bis(cycloadduct) 17: (1.9 Gpa, 2%) colourless filaments, m.p. 161−164 °C. IR (film): $\tilde{\nu}_{max}$ = 3100, 2250, 1728, 1647 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.72 (s, 3 H, CH_3), 2.10 (d, J_{H-H} = 1.5 Hz, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.21 (d, J_{H-H} = 15.4 Hz, 1 H, H), 2.44−2.32 (ddd, J_{H-H} = 6.0, J_{H-H} = 8.5, J_{H-H} = 14.5 Hz, 2 H, CH-CH_2-CH), 2.61 (d, J_{H-H} = 15.4 Hz, 1 H, H), 3.04−3.11 (dd, J_{H-H} = 6.0, J_{H-H} = 12.0 Hz, 1 H, H), 3.57 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.86 (br. s, 1 H, H), 5.36−5.43 (quint, J_{H-H} = 3.9, J_{H-H} = 8.5 Hz, 1 H, H), 5.53 (dd, J_{H-H} = 1.4, J_{H-H} = 11.0 Hz, 1 H, H), 5.58 (dd, J_{H-H} = 1.4, J_{H-H} = 17.2 Hz, 1 H, H), 5.99 (dd, J_{H-H} = 11.0, J_{H-H} = 17.2 Hz, 1 H, H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 13.9, 20.5, 21.1, 26.1, 45.8, 46.8, 51.1, 51.7, 52.2, 70.6, 79.2, 87.8, 91.5, 94.4, 108.2, 119.7, 130.1, 155.1, 163.3, 166.5, 164.9, 172.7 ppm. MS (CI): *m/z* (%) = 444.1647 (31) $[MH]^+$ ($C_{23}H_{26}NO_8$ requires 444.1658), 412 (21) $[MH - 12]^+$, 251 (27) $[MH - 193]^+$, 167 (100) $[MH - 277]^+$.

***N*-Phenyl Maleimide Cycloadduct 18:** (atm. pressure, 90%; 1.9 Gpa, 93%) colourless flakes; m.p. 130−133 °C. $C_{19}H_{17}NO_5$: calcd. C 67.2, H 5.0, N 4.1; found C 67.3, H 5.1, N 4.1). IR (KBr): $\tilde{\nu}_{max}$ = 3086, 1720, 1711, 1599, 1634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.19 (ddt, J_{H-H} = 15.3, J_{H-H} = 7.8, J_{H-H} = 3.3 Hz, 1 H, H), 2.31 (d, J_{H-H} = 1.6 Hz, 3 H, CH_3), 3.06 (ddd, J_{H-H} = 15.3, J_{H-H} = 7.8, J_{H-H} = 1.6 Hz, 1 H, H), 3.26 (ddd, J_{H-H} = 7.8, J_{H-H} = 7.8, J_{H-H} = 1.6 Hz, 1 H, H), 3.82 (s, 3 H, OCH_3), 3.83−3.87 (m, 1 H, H), 3.98 (dd, J_{H-H} = 9, J_{H-H} = 7.8 Hz, 1 H, H), 5.32 (dt, J_{H-H} = 7.8, J_{H-H} = 3.5 Hz, 1 H, J_{H-H} = 3.3, H), 7.15−7.47 (m, 5 H, phenyl); NOE: irradiated at δ = 3.26 ppm H → H (1.90%), → H (6.20%), → H (15.00%); irradiated at δ = 3.98 ppm H → H (13.40%); irradiated at δ = 5.32 ppm H → H (4.60%), → H (2.20%). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.4, 24.9, 38.8, 42.5, 42.7, 51.8, 94.3, 107.3, 126.8, 129.0, 129.5, 132.1, 156.2, 165.4, 166.4, 175.3, 178.7 ppm. MS (CI): *m/z* (%) = 340.1185 (68) $[MH]^+$ ($C_{19}H_{18}NO_5$ requires 340.1185), 308 (43) $[MH - 32]^+$, 166 (100) $[MH - 174]^+$.

***N*-Methyl Maleimide Cycloadduct 19:** (atm. pressure, 90%; 1.9 Gpa 92%) colourless solid; m.p. 113−116 °C. $C_{14}H_{15}NO_5$: calcd. C 60.6, H 5.4, N 5.0; found C 60.3, H 5.2, N 4.8. IR (KBr): $\tilde{\nu}_{max}$ = 3050, 1720, 1700, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.04−2.17 (m, 1 H, H), 2.32 (d, J_{H-H} = 1.6 Hz, 3 H, CH_3), 2.89 (s, 3 H, CH_3), 2.92−3.01 (m, 1 H, H), 3.04−3.13 (m, 1 H, H), 3.75−3.81 (m, 2 H, 2 × H), 3.84 (s, 3 H, OMe), 5.21 (dt, J_{H-H} = 3.40, J_{H-H} = 7.90 Hz, 1 H, H); NOE: irradiated at δ = 2.10 ppm H → H (8.50%), → H (8.19%),→ H and/or CH_3 (32.51%); irradiated at δ = 2.96 ppm H → H (8.37%), → H (1.41%), → H (14.18%), irradiated at δ = 3.08 ppm H → H (16.81%), → H (3.77%); irradiated at δ = 3.79 or 3.77 ppm H → H (8.53%), → H (1.67%); irradiated at δ = 5.21 ppm H → H (1.30%), → H (4.21%). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 24.3, 25.4, 38.6, 42.3, 42.4, 51.7, 94.4, 107.3, 155.9, 165.4, 166.2, 176.3, 179.7 ppm. MS (CI): *m/z* (%) = 278.1033 (100) $[MH]^+$ ($C_{14}H_{16}NO_5$ requires 278.1028), 246 (38) $[MH - 32]^+$, 166 (56) $[MH - 112]^+$.

Maleic Anhydride Cycloadduct 20: (atm. pressure, 87%; 1.9 Gpa, 96%) colourless rhombs; m.p. 126−130 °C ($C_{13}H_{12}O_6$: calcd. C 59.1, H 4.6; found C 59.2, H 4.6). IR (KBr): $\tilde{\nu}_{max}$ = 3045, 1779, 1708, 1645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.17 (ddt, J_{H-H} = 15.4, J_{H-H} = 6.7, J_{H-H} = 3.5 Hz, 1 H, J_{H-H} = 3.3, H), 2.33 (d, J_{H-H} = 1.8 Hz, 3 H, CH_3), 2.98 (ddd, J_{H-H} = 15.4, J_{H-H} = 7.9, J_{H-H} = 1.7 Hz, 1 H, H), 3.41 (ddd, J_{H-H} = 6.7, J_{H-H} = 9.7, J_{H-H} = 1.7 Hz, 1 H, H), 3.78 (m, 1 H, H), 3.83 (s, 3 H, OCH_3), 4.08 (dd, J_{H-H} = 7.9, J_{H-H} = 9.7 Hz, 1 H, H), 5.34 (dt, J_{H-H} = 7.9, J_{H-H} = 3.5 Hz, 1 H, J_{H-H} = 3.5, H); NOE: irradiated at δ = 2.17 ppm H → H (4.35%), → OCH_3 and H (22.96%), → H (3.45%), → CH_3 (16.01%); irradiated at δ = 2.98 ppm H → H (1.65%), → OCH_3 and H (11.22%), → CH_3 (10.05%); irradiated at δ = 3.41 ppm H → OCH_3 and H (5.76%), → CH_3 (6.86%); irradiated at δ = 3.78 ppm H → H (1.38%), → CH_3 (4.54%), → H (1.46%); irradiated at δ = 4.08 ppm H → H (2.00%), → CH_3 (6.62%), → H (2.31%). ^{13}C NMR (100.6 MHz, $CDCl_3$,): δ = 13.9, 24.5, 38.9, 41.9, 43.0, 51.5, 94.6, 106.0, 155.8, 164.6, 167.1, 169.6, 173.7 ppm. MS (CI): *m/z* (%) = 265.0700 (22) $[MH]^+$ ($C_{13}H_{13}O_6$ requires 265.0712), 250 (8) $[MH - 15]^+$, 233 (18) $[MH - 32]^+$, 167 (100) $[MH - 98]^+$, 150 (17) $[MH - 115]^+$.

3-{[(*Z*)-2-(Methoxycarbonyl)-1-ethenyl]carbonyloxy}propyl 2-Methyl-5-vinyl-3-furoate (21): A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (983 mg, 5.0 mmol, 4.0 equiv.) in

dichloromethane (40 mL) was added dropwise at 0 °C to a solution of 2-methyl-5-vinyl-3-furoic acid (191 mg, 1.25 mmol. 1.0 equiv.), 1-(3-hydroxypropyl)-4-methyl-(*Z*)-2-butenedioate (236 mg, 1.25 mmol, 1.0 equiv.) and dimethylaminopyridine (77 mg, 0.63 mmol, 0.5 equiv.) in dichloromethane (40 mL) under argon. The solution was allowed to warm to room temperature and was stirred for 1 hour. The mixture was quenched by addition of water (10 mL) and diethyl ether (10 mL), followed by extraction with diethyl ether (30 mL). The aqueous phase was further extracted with diethyl ether (2 × 30 mL) and the combined extracts washed with brine (30 mL) and water (30 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography on silica, eluting with light petroleum/ethyl acetate (6:1), furnished the title compound **21** (198 mg, 50%) as a colourless oil. IR (film): $\tilde{\nu}_{max}$ = 3040, 1721, 1602 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.13 (quint, $J_{H\text{-}H}$ = 6.2, $J_{H\text{-}H}$ = 6.3 Hz, 2 H, O-CH_2-CH_2-CH_2-O), 2.59 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.34 (dt, $J_{H\text{-}H}$ = 6.2, $J_{H\text{-}H}$ = 6.3 Hz, 4 H, 2 × OCH_2), 5.18 (dd, $J_{H\text{-}H}$ = 11.3, $J_{H\text{-}H}$ = 1.1 Hz, 1 H, H), 5.65 (dd, $J_{H\text{-}H}$ = 17.5, $J_{H\text{-}H}$ = 1.1 Hz, 1 H, H), 6.41 (q, $J_{H\text{-}H}$ = 17.5 Hz, 1 H, $J_{H\text{-}H}$ = 11.3, H), 6.46 (s, 1 H, CH), 6.87 (s, 2 H, 2 × CH) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 12.9, 27.0, 51.34, 59.6, 61.1, 107.3, 111.9, 113.5, 123.3, 132.4, 132.5, 150.0, 158.1, 162.7, 163.8, 164.3 ppm. MS (CI): *m/z* (%) = 323.1120 (100) $[MH]^+$ ($C_{16}H_{19}O_7$ requires 323.1131), 193 (65) $[MH - 130]^+$, 171 (40) $[MH - 152]^+$, 135 (63) $[MH - 188]^+$.

Intramolecular Cycloadduct 22: (atm. Pressure, 28%; 1.1 Gpa, 75%) lustrous colourless needles, m.p. 95−98 °C. IR (film): $\tilde{\nu}_{max}$ = 3040, 1739, 1644 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.95−1.05 (m, 1 H, H), 1.70−1.82 (m, 1 H, H), 1.86−1.96 (tdd, $J_{H\text{-}H}$ = 4.4, $J_{H\text{-}H}$ = 10.5, $J_{H\text{-}H}$ = 17.6 Hz, 1 H, H), 2.05 (d, $J_{H\text{-}H}$ = 1.8 Hz, 3 H, Me), 2.28 (d quint, $J_{H\text{-}H}$ = 3.9, $J_{H\text{-}H}$ = 17.6 Hz, 1 H, H), 2.77 (dd, $J_{H\text{-}H}$ = 10.6, $J_{H\text{-}H}$ = 11.3 Hz, 1 H, H), 3.21 (dt, $J_{H\text{-}H}$ = 7.5, $J_{H\text{-}H}$ = 10.5 Hz, 1 H, H), 3.28 (s, 3 H, OCH_3), 3.33 (dddd, $J_{H\text{-}H}$ = 1.2, $J_{H\text{-}H}$ = 3.2, $J_{H\text{-}H}$ = 5.1, $J_{H\text{-}H}$ = 11.5 Hz, 1 H, H), 3.44 (dt, $J_{H\text{-}H}$ = 2.7, $J_{H\text{-}H}$ = 10.9 Hz, 1 H, H), 3.74−3.82 (m, 1 H, H), 4.69 (ddt, $J_{H\text{-}H}$ = 1.3, $J_{H\text{-}H}$ = 11.2, $J_{H\text{-}H}$ = 3.9 Hz, 1 H, H), 4.81 (dt, $J_{H\text{-}H}$ = 3.3, $J_{H\text{-}H}$ = 4.4 Hz, 1 H, H), 5.00 (ddd, $J_{H\text{-}H}$ = 2.2, $J_{H\text{-}H}$ = 9.7, $J_{H\text{-}H}$ = 11.9 Hz, 1 H, H) ppm. ^{13}C NMR (100.6 MHz, C_6D_6): δ = 13.0, 25.9, 26.4, 42.0, 45.4, 47.4, 51.5, 63.1, 63.7, 97.4, 106.7, 154.6, 164.3, 168.2, 173.8, 174.3 ppm. MS (CI): *m/z* (%) = 323.1119 (100) $[MH]^+$ ($C_{16}H_{19}O_7$ requires 323.1131), 295 (26) $[MH - 28]^+$, 262(19) $[MH - 33]^+$, 159 (36) $[MH - 103]^+$.

Acknowledgments

S. A. B. H. A. thanks the University of Reading for financial support. We thank EPSRC and the University of Reading for funds for the Image Plate system.

[1] [1a] R. Paul, *Compt. Rend.* **1939**, *208*, 1028−1030. [1b] R. Paul, *Bull. Soc. Chim. Fr.* **1943**, 163−168. [1c] W. Herz, *J. Am. Chem. Soc.* **1946**, *68*, 2732. [1d] W. J. Davidson, J. A. Elix, *Aust. J. Chem.* **1973**, *26*, 1059−1075. [1e] G. Jones, P. Rafferty, *Tetrahedron* **1979**, *35*, 2027−2033. [1f] W. E. Noland, C. K. Lee, S. K. Bae, B. Chung, C. S. Hahn, K. J. Kim, *J. Org. Chem.* **1983**, *48*, 2488−2491. [1g] T. Sasaki, Y. Ishibashi, M. Ohno, *Heterocycles* **1983**, *20*, 1933−1936. [1h] H. Ohmura, S. Motoki, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1131−1137. [1i] J-M. Keil, T. Kämpchen, G. Sietz, *Tetrahedron Lett.* **1990**, *31*, 4581−4584. [1j] J. Ancerewicz, P. Vogel, *Heterocycles* **1993**, *36*, 537−552. [1k] J-M. Keil, W. Massa, R. Riedel, G. Seitz, S. Wocadlo, *Tetrahedron Lett.* **1994**, *35*, 7923−7926. [1l] L. S. Avalos, A. Benítez, J. M. Muchowski, M. Romero, F. X. Talamás, *Heterocycles* **1997**, *45*, 1795−1804. [1m] G. Freslon, Y. Lepage, *Bull. Soc. Chim. Fr.* **1974**, 2105−2110. [1n] T. Sasaki, T. Ishibashi, M. Ohno, *J. Chem. Res.(S)* **1984**, 218. [1o] R. S. Kusurkar, D. K. Bhosale, *Synth. Commun.* **1990**, *20*, 101−109. [1p] C. K. Lee, Y. S. Park, I-S. H. Lee, *Bull. Korean Chem. Soc.* **1991**, *12*, 121−130. [1q] H. Kotsuki, A. Kondo, H. Nishizawa, M. Ochi, K. Matsuoka, *J. Org. Chem.* **1981**, *46*, 5454−5455.

[2] [2a] H. Kotsuki, A. Kawamura, M. Ochi, *Chem. Lett.* **1981**, 917−920. [2b] K. Hayakawa, M. Yodo, S. Ohsuki, K. Kanematsu, *J. Am. Chem. Soc.* **1984**, *106*, 6735−6740. [2c] C. P. Dell, E. H. Smith, D. Warburton, *J. Chem. Soc., Perkin Trans. 1* **1985**, 747−756. [2d] K. Fischer, S. Hünig, *Chem. Ber.* **1987**, *120*, 325−329. [2e] K. Hayakawa, F. Nagatsugi, K. Kanematsu, *J. Org. Chem.* **1988**, *53*, 860−863. [2f] J. A. Cooper, P. Cornwall, C. P. Dell, D. W. Knight, *Tetrahedron Lett.* **1988**, *29*, 2107−2110. [2g] P. Cornwall, C. P. Dell, D. W. Knight, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2395−2405. [2h] W. V. Murray, S. Sun, I. J. Turchi, F. K. Brown, A. D. Gautier, *J. Org. Chem.* **1999**, *64*, 5930−5941.

[3] [3a] M. Inoue, H. Takenaka, T. Tsurushima, H. Miyagawa, T. Uneo, *Tetrahedron Lett.* **1996**, *37*, 5731−5734. [3b] M. Inoue, H. Takenaka, T. Tsurushima, H. Miyagawa, T. Uneo, *Tetrahedron Lett.* **1996**, *37*, 8823.

[4] [4a] W. G. Dauben, A. P. Kozikowski, *J. Am. Chem. Soc.* **1974**, *96*, 3664−3666. [4b] W. G. Dauben, H. O. Krablenhoft, *J. Am. Chem. Soc.* **1976**, *98*, 1992−1993. [4c] H. Kotsuki, H. Nishizawa, S. Kitagawa, M. Ochi, N. Yamasaki, K. Matsuoka, T. Tokoroyama, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 544−548. [4d] K. Matsumoto, A. Sera, T. Uchida, *Synthesis* **1985**, 1−26. [4e] K. Matsumoto, A. Sera, *Synthesis* **1985**, 999−1027. [4f] J. Jurczak, B. Baranowski, *High Pressure*, Elsevier, Oxford, **1989**.[4g] *Organic Synthesis at High Pressures* (Eds.: K. Matsumoto, R. M. Acheson), Wiley Interscience, **1991**.[4h] W. B. Holzapfel, N. S. Isaacs, *High Pressure Techniques in Chemistry and Physics*, Oxford University Press, **1997**.

[5] Data for all six crystals were collected with Mo-K_α radiation using the MAResearch Image Plate System. The crystals were positioned at 70 mm from the Image Plate. 95 frames were measured at 2° intervals with a counting time of 2 minutes. Data analysis was carried out with the XDS program. The structures were determined by direct methods using the SHELX86 program. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2-times those of the atom to which they are attached. The structures were then refined by full-matrix least-squares on F^2 using the SHELXL program. X-ray crystallographic data for **22**: $C_{16}H_{18}O_2$, monoclinic, $P2_1/c$ a = 8.423 Å, b = 25.47 Å, c = 14.984 Å, β = 105.184°, V =3103 Å^3, Z = 8, D_c = 1.380 g cm^{-3}, F(000) = 1360, θ range for data collection 2.13°−26.03°, 5669 independent reflections $I > 2\sigma(I)$ were used in the analysis. Final R = 1.21, weighted R = 3.80. CCDC-192622−192627 contain the supplementary crystallographic data for **15, 17, 18, 19, 20** and **22**, respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

[6] [6a] W. Kabsch, *J. Appl. Crystallogr.* **1988**, *21*, 67−71. [6b] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467−473. [6c] G. M. Sheldrick, SHELXL, *Program for Crystal Structure Refinement*, University of Göttingen, **1993**.

[7] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923−2925.

[8] L. M. Harwood, *Aldrichimica Acta* **1985**, *18*, 25−40.

[9] D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, Oxford, **1988**.

Received August 30, 2002
[O02488]