m/e (relative intensity) 213 (M^+, base), 198 (15), 182 (39), 180 (31), 166 (61), 66 (18), 53 (19); CIMS (isobutane) m/e 214 ($M + H^+$, base); EIHRMS m/e 213.0635 ($C_9H_{11}NO_5$ requires 213.0637).

5-Hydroxy-4-methoxy-5-(methoxycarbonyl)-1-methyl-3-pyrrolin-2-one (10). A solution of **9** (64 mg, 0.30 mmol) in 3:1 acetonitrile–water (376 mL, 0.8 mM) was treated with rose bengal (2.4 mg, 8 mequiv) and the solution was irradiated in a Quartz immersion vessel with a Hanovia high-pressure mercury lamp (450 watts) through a uranium yellow glass filter (transmits >330 nm) with a steady stream of oxygen bubbled through the solution at 22 °C. After 1 h, the reaction mixture was extracted with CH_2Cl_2 (5 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford 74 mg of an orange oil. Chromatography (SiO_2, 2 cm × 15 cm, Et_2O) afforded **10** as a colorless oil (55 mg, 60 mg theoretical, 92%): ^1H NMR ($CDCl_3$, 300 MHz) δ 5.11 (s, 1 H, C-3 CH), 4.52 (s, 1 H, OH), 3.87 (s, 3 H, OMe), 3.84 (s, 3 H, CO_2Me), 2.74 (s, 3 H, N-Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.0 (e, CO_2Me), 170.8 (e, C=O), 169.8 (e, C-4), 94.2 (o, C-3), 87.1 (e, C-5), 58.7 (o, OMe), 54.2 (o, CO_2Me), 23.4 (o, N-Me); UV (EtOAc) λ_{max} 262 nm (ϵ 960); IR (neat) ν_{max} 3421, 3133, 2958, 1762, 1685, 1647, 1434, 1234, 1136, 1043 cm^{-1}; EIMS m/e (relative intensity) 201 (M^+, 2), 142 (base), 82 (16), 69 (16), 57 (11); CIMS (isobutane) m/e 202 ($M + H^+$, base); EIHRMS m/e 201.0639 ($C_8H_{11}NO_5$ requires 201.0637).

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Registry No. 1, 104006-84-0; 2, 78331-70-1; 3, 136629-78-2; 4, 136629-79-3; 5, 136629-80-6; 6, 136629-81-7; 7, 92144-13-3; 8, 136629-82-8; 9, 136629-83-9; 10, 136629-84-0; lithium hydroxide, 1310-65-2; oxygen, 7782-44-7; rose bengal, 11121-48-5.

Supplementary Material Available: ^1H NMR of 3–6, 8–10 is provided (7 pages). Ordering information is given on any current masthead page.

Peroxidation of Saccharide Phenylhydrazones: Novel Hydrazono-1,4-lactones

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It is known[1-5] that phenylhydrazones undergo autoxidation by free-radical mechanisms to afford phenylazo hydroperoxides. The reaction is usually carried out at room temperature by shaking a solution of the hydrazone in benzene with oxygen or air. It is also known[6] that saccharide phenylhydrazones kept in contact with oxygen in the presence of bases produce free radicals detectable by ESR. We have now isolated stable products produced from these free radicals and found them to be novel hydrazono-1,4-lactones (**4a–c**).

Solutions of the phenylhydrazones of D-galactose (**1a**), 6-deoxy-D-galactose (D-fucose) (**1b**), and D-arabinose (**1c**) and their L enantiomers in aqueous ethanol containing enough KOH to bring the pH to 12–14 were stirred at room temperature in the presence of air. *Warning: Bubbling air or oxygen in such solutions leads to spontaneous explosion of dry peroxides formed on the reaction vessel walls.* In each case, analysis by HPLC showed a gradual decrease in the amount of starting hydrazone and the formation of a new product. Combustion analysis and EI–MS agreed with formulas having two hydrogen atoms less than the starting hydrazones. A 300-MHz proton NMR spectrum of derivative **4a** obtained from D-galactose phenylhydrazone in Me_2SO-d_6[7] showed an NH singlet, four OH protons, and a triplet and five multiplets due to aliphatic protons. The NH and OH protons were identified by ^2H_2O exchange, which altered the splitting pattern of all the C–H signals, except for a multiplet at δ 4.12. Proton decoupling also showed that this signal did not change when any of the OH protons was irradiated, denoting that its carbon was not linked to an OH group. Since the starting hydrazone possessed five hydroxyl groups, it was assumed that during the reaction one of the OH groups became involved in ring formation. Deuteration of the sample or irradiation of the lowest field OH doublet reduced a C–H triplet to a doublet, suggesting that it was generated by H-2. In order to identify the protons attached to C-3, C-4, and C-5, a COSY experiment was carried out on a deuterated sample, using the H-2 resonance to identify consecutively adjacent protons as shown in Table I. An ^1H-coupled ^{13}C NMR spectrum showed a low-field singlet (δ 150.0 ppm), which was assigned to a C=N group lacking hydrogen on the carbon and four doublets and a triplet, assigned by ^1H–^{13}C 2D NMR spectroscopy to C 2-6 as shown in Table I. To ascertain whether the product had retained its original galacto configuration or had undergone epimerization in the alkaline solution, the ^1H and ^{13}C NMR chemical shifts of the ring carbons and protons of **4a** were compared with those of D-galactono-1,4-lactone (**7d**) and of D-arabinonoimino-1,4-lactone[8] (**7e**), which has the same ring configuration as L-galactono-1,4-lactone. There was indeed a very close agreement (see Table I) in all the ^1H chemical shifts and in most of the ^{13}C resonances (one exception being C-1, which was significantly shifted to higher field upon replacement of the C=O and C=NH groups by C=NNHPh). To further confirm that product **4a** had not undergone epimerization, it was hydrolyzed with dilute acid to galactonic phenylhydrazide (**5a**). HPLC showed the absence of the enantiomeric talonic phenylhydrazide in the hydrolysate and the product was given an *N*-phenyl-D-galactonohydrazono-1,4-lactone (**4a**) structure.

The similarity between the newly prepared product **4a** and D-galactono-1,4-lactone (**7d**) is manifested by the tendency of both compounds to undergo elimination

Table I. ^1H and ^{13}C NMR Data (ppm)

^1H NMR							
compd	H-2	H-3	H-4	H-5		H-6	H-6′
7d	4.22	4.10	4.14	3.57		3.43	3.41
4a	4.35	4.05	4.12	3.61		3.56	3.51
4b	4.32	3.82	4.02	3.77		1.19 (Me)	
4c	4.34	3.98	4.19	3.73 (3.61, H-5′)			

^{13}C NMR						
compd	C-1	C-2	C-3	C-4	C-5	C-6
7d	176.1	74.5	73.7	80.9	69.8	62.9
7e	175.4	75.2	74.5	82.6	62.4	
4a	150.0	74.0	74.6	83.3	69.8	62.0[a]
4b	150.1	74.4	75.7	88.5	66.6	19.2
4c	150.6	74.3	74.8	86.3	60.8	

[a] Assignment by ^1H–^{13}C 2D NMR spectroscopy.

(1) Pausacker, K. H. *J. Chem. Soc.* **1950**, 3478–3481.
(2) Bellamy, A. J.; Guthrie, R. D. *Chem. Ind. (London)* **1964**, 1575–1579.
(3) Bellamy, A. J.; Guthrie, R. D. *J. Chem. Soc.* **1965**, 2788–2795.
(4) Hawkins, E. G. E. *J. Chem. Soc. C* **1971**, 1474–1477.
(5) Chaplin, A. F.; Hey, D. H.; Honeyman, J. *J. Chem. Soc.* **1959**, 3194–3202.
(6) Fatiadi, A. J. *Adv. Chem. Ser.* **1973**, *117*, 88–105.
(7) Perlin, A. S. *Can. J. Chem.* **1966**, *44*, 539–550.
(8) Serianni, A. S.; Nunez, H. A.; Barker, R. *J. Org. Chem.* **1980**, *45*, 3329–3341.

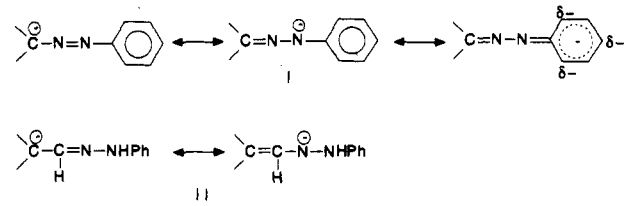
0022-3263/91/1956-6944$02.50/0

during benzoylation. Thus, treatment of D-galacto-1,4-lactone (**7d**) with benzoyl chloride in pyridine is known[9-11] to result in the elimination of two *O*-benzoyl groups and formation of compound 8. We found that benzoylation of compound **4a** resulted in a similar elimination, yielding an analogue of 8, namely *N*-benzoyl-*N*-phenyl-2,6-di-*O*-benzoyl-3,5-dideoxy-2,4-dienoaldohexonohydrazono-1,4-lactone (**9**). The fact that benzoylation of compound **4a** was accompanied by N-benzoylation of the hydrazone residue is not surprising, since benzoylation of saccharide phenylhydrazones with benzoyl chloride in pyridine is shown[12] to result in N-benzoylation. Furthermore, benzoylation of D-galactonic phenylhydrazide (**5a**) was found to result in di-N-benzoylation to afford di-*N,N'*-benzoyl-penta-*O*-benzoyl-*O*-benzoyl-D-galactonic phenylhydrazide (**6**).

The product obtained from L-galactose phenylhydrazone gave UV, IR, and MS as well as ^1H and ^{13}C NMR spectra identical with those of the D-isomer **4a**. Similarly, the products obtained from the phenyl hydrazones of D- and L-fucose and D- and L-arabinose gave UV, IR, and ^1H and ^{13}C NMR spectra that were quite similar to those of the galactose derivative. The NMR spectra differed only in the signals generated by the side chain (see Table I). The new products were accordingly given structures **4a–c** or enantiomeric ones.

A plausible mechanism for the free radical peroxidation of saccharide phenylhydrazones **1a–c** starts with an attack by oxygen on C-1 to give radicals, which rearrange to phenylazo hydroperoxides **2a–c**, similar to those isolated from phenylhydrazones of aldehydes and ketones.[1] These, or their tautomers, undergo nucleophilic substitution (addition of O-4 and elimination of a hydroperoxide ion) to form phenylazo furanosides **3a–c** or the isolated *N*-phenylaldonohydrazono-1,4-lactones **4a–c**. The ESR evidence reported in the literature[6] and the explosive nature of the intermediates observed in this work suggests that a significant part of the peroxidation proceeds via a free-radical mechanism.

From the above it would appear that aldoses and aldose phenylhydrazones behave differently in alkaline solutions. The first undergo epimerization and are degradatively oxidized with oxygen to lower aldonic acids and formic acid,[13] whereas the latter are not epimerized to any significant extent and are oxidized without degradation to hydrazono-1,4-lactones. The reason for the difference may lie in the ease of enolization of aldoses to give enediols and the resistance of aldose phenylhydrazones to enolization because of the lower acidity of their α hydrogen. In basic media, the hydrazone ion (I) is stabilized more by resonance than is the enehydrazine ion (II), and the partial negative charge on its carbon facilitates elimination of leaving groups to form azoalkenes.[13]



I

II

Experimental Section

General Methods. Infrared spectra were measured with a BIO RAD FTS-7 FTIR spectrophotometer and ultraviolet spectra with a Hewlett-Packard 8452A spectrophotometer. Optical rotations were measured for ethanol solutions on a Perkin-Elmer 141 polarimeter and mass spectra on a Hewlett-Packard 5995A EI-GC/MS. ^1H NMR and ^{13}C NMR were recorded at 300 MHz with a Bruker 300-MHz instrument. HPLC analyses were performed using a Waters carbohydrate analysis P/N84038 (28 cm) column eluted with CH_3CN/H_2O (5:1) pumped at a flow rate of 1.0 mL/min by a Waters 501 HPLC system. The reactants and products were estimated with a Lamda Max Model 481 LC spectrophotometer detector set at λ 270 nm and connected to a Hewlett-Packard HP 3396A Integrator.

Synthesis of the Different Aldonohydrazono-1,4-lactones. Solutions of phenylhydrazones **1a–c** (5.0 g) in 95% EtOH (500 mL) and 1.0 M KOH (20 mL) were stirred in the presence of air (see warning above) and the pH adjusted daily to 12–14 by adding base. Analysis by HPLC indicated that after 4–5 days the starting hydrazone was totally consumed and a different product was left in solution. The solution was concentrated under reduced pressure to about 40 mL and the crystalline product that separated filtered. Alternatively, the concentrate was subjected to constant ether extraction and the ether evaporated to deposit crystalline products (extraction with ether is not hazardous at this time since all the peroxides have decomposed in the alkali).

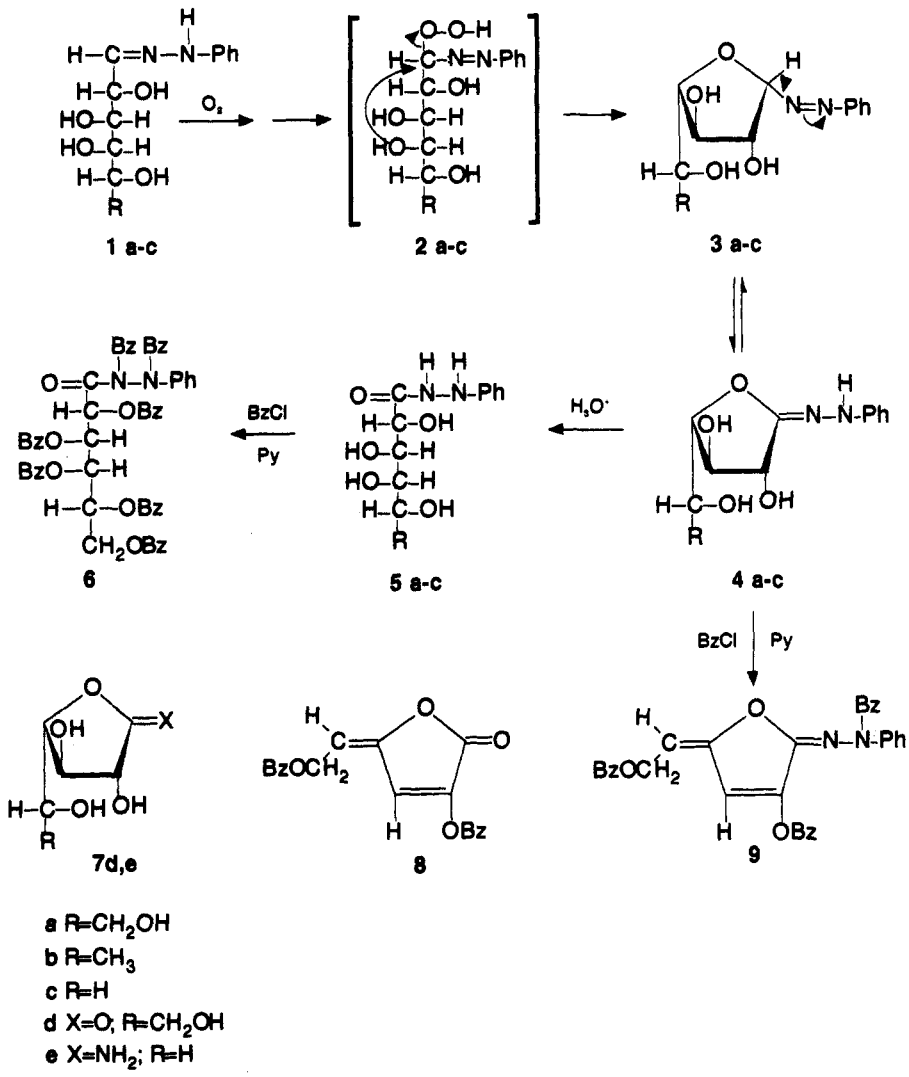
***N*-Phenyl-D-galactonohydrazono-1,4-lactone (4a) and Its L Enantiomer.** The crystals obtained from D- or L-galactose phenylhydrazone by concentrating the reaction mixture were recrystallized from ethanol–water (yield 2.5g, 49%) in needles mp 143–145 °C. Product **4a** had $[\alpha]_D$ −75.2° and its L isomer, $[\alpha]_D$ +75.2° (*c*, 0.1, EtOH): λ_{max} 270 nm (EtOH); ν (KBr) 1686 (OC=N) and 1601 (C=C); EI–GC/MS *m/z* 268 (M^+); ^1H NMR (Me_2SO-d_6) δ 8.3 (s, 1 H, NH), phenyl ring protons, meta, 7.15 (t), ortho 7.0 (d), para 6.63 (t); hydroxyl protons, δ 5.75 (d, 1 H, OH-2), 5.65 (d, 1 H, OH-3), 5.1 (d, 1 H, OH-5), 4.78 (t, 1 H, OH-6); CH protons H-2 (t 1 H), δ 4.35 ($J_{2,3}$ = 6.2 Hz); H-4, 4.12 (dd, 1 H, $J_{4,3}$ = 6.3 Hz, $J_{4,5}$ = 3.0 Hz); H-3, 4.05 (m 1 H, $J_{3,4}$ = 6.3 Hz), 3.61 (m, 1 H, H-5), 3.54 (m, 2 H, H-6,6'); ^{13}C NMR data (Me_2SO-d_6) δ 150.0 (C=N), phenyl ring, δ 146.5 (C-1'), 128.5 (C-2'), 117.5 (C-3'), 112.0 (C-4'); other ring carbons, 83.3 (C-4), 74.6 (C-3), 74.0 (C-2); side chain carbons, 69.8 (C-5), 62.0 (C-6). Anal. Calcd for $C_{12}H_{16}N_2O_5 \cdot H_2O$: C, 50.35; H, 6.29; N, 9.79. Found: C, 50.47; H, 6.03; N, 9.84.

***N*-Phenyl-D-fuconohydrazono-1,4-lactone (4b) and Its L Enantiomer.** Evaporation of the ether extract obtained from D- or L-Fucose phenylhydrazone afforded long buff-colored crystals (yield 21%) which were recrystallized from ethanol in needles, mp 158–160 °C. Product **4b** had $[\alpha]_D$ −50.4° and its L isomer, $[\alpha]_D$ +51.3° (*c*, 0.1, EtOH); λ_{max} 270 nm (EtOH); ν (KBr) 1666 (OC=N) and 1599 (C=C); EI–GC/MS *m/z* 252 (M^+); ^1H NMR data δ 8.36 (s, 1 H, NH), five monosubstituted phenyl ring protons (meta, 7.10, t; ortho, 6.98, para, 6.63 t); four OH protons, 5.76 (d, OH-2), 5.65 (d, OH-3), 4.91 (d, OH-5), ring protons 4.32 (t, 1 H, H-2), 3.82 (dd, 1 H, H-3), 4.02 (dd, 1 H, H-4), 3.77 (m, 1 H, H-5), 1.19 (d, 3 H, CH_3); ^{13}C NMR data (Me_2SO-d_6) δ 150.1 (CN), aromatic 146.8 (C-1'), 129.2 (C-2'), 116.2 (C-3'), 112.4 (C-4'), 88.5 (C-4), 75.7 (C-3), 74.4 (C-2), 66.6 (C-5), 19.2 (CH_3). Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.10; H, 6.32; N, 11.12. Anal. Calcd for $C_{12}H_{16}N_2O_4 \cdot H_2O$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.45; H, 6.63; N, 10.26.

***N*-Phenyl-D-arabinonohydrazono-1,4-lactone (4c) and Its L Enantiomer.** The ether extract obtained from the reaction of D- or L-arabinose phenylhydrazone was evaporated and an off-white crystalline product was isolated (0.3g, 6.0%), which was recrystallized from 95% EtOH in needles, mp 75–76 °C, $[\alpha]_D$ +84.7° for the D isomer and −83.9° for the L isomer (*c*, 0.1 in EtOH): λ_{max} 270 nm (EtOH; ν (KBr) 1671 (OC=N) and 1600 (C=C) cm^{-1}, EI–GC/MS *m/z* 238 (M^+). The ^1H NMR data are as follows (solvent Me_2SO-d_6): δ 8.40 (s, 1 H, NH), five monosubstituted phenyl ring protons (meta, 7.14, t; ortho, 7.03, d; para, 6.68, t), 5.84 (d, 1 H, OH-2), 5.69 (d, 1 H, OH-3), 5.13 (t, 1 H, OH-5), 4.34 (t, 1 H, H-2), 4.19 (dd, 1 H, H-4), 3.98 (dd, 1 H, H-3),

(9) De Lederkremer, R. M.; Litter, M. I. *Carbohyd. Res.* **1971**, *20*, 442–444.
(10) Jeroncic, L. O.; Varela, O. J.; Fernandez Cirelli, A.; De Lederkremer, R. M. *Tetrahedron* **1984**, 40(8), 1425–1430.
(11) Varela, O. J.; Fernandez Cirelli, A.; De Lederkremer, R. M. *Carbohyd. Res.* **1982**, *100*, 424–430.
(12) El Khadem, H. *J. Org. Chem.* **1964**, *29*, 2073.
(13) Isbell, H. S. *J. Res. Nat. Bur. Stand.* **1942**, *29*, 227. Hardegger, E.; Kreis, K.; El Khadem, H. *Helv. Chim. Acta* **1952**, *35*, 618.
(14) Wolfrom, M. L.; Thompson, A.; Lineback, D. R. *J. Org. Chem.* **1962**, *27*, 2563–2567.

Scheme I



3.73 (m, 1 H, H-5), 3.61 (m, 1 H, H-5'); ^{13}C NMR data (Me_2SO-d_6) δ 150.6 (CN), aromatic 146.4 (C-1'), 129.2 (C-2'), 118.1 (C-3'), 112.4 (C-4'), 86.3 (C-4), 74.8 (C-3), 74.3 (C-2), 60.8 (C-5). Anal. Calcd for $C_{11}H_{14}N_2O_4 \cdot H_2O$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.40; H, 6.54; N, 10.71.

Hydrolysis of Hydrazono-1,4-lactones 4a-c to Aldonic Phenylhydrazides (5a-c). Suspensions of aldonohydrazono-1,4-lactones **4a-c** and their enantiomers (1.0 g) in water (50.0 mL) containing a drop of concentrated HCl were warmed to 70 °C for 5 h and concentrated to a volume of 5 mL. The products that separated were recrystallized from 95% EtOH in needles, mp 203 °C for **5a**, 108 °C for **5b**, and 215 °C for **5c** and their enantiomers, alone or mixed with authentic samples of the corresponding aldonic phenylhydrazides. HPLC of the mother liquor revealed one product (**5a**, **5b** and **5c** or their enantiomers) and the absence of any epimer.

***N*-Benzoyl-*N*-phenyl-2,6-di-*O*-benzoyl-3,5-dideoxy-2,4-dienoaldohexohydrazono-1,4-lactone (9).** To a cold suspension of *N*-phenyl-D-galactonohydrazono-1,4-lactone (**4a**; 2.0 g) in pyridine (20.0 mL) was added dropwise ice-cold benzoyl chloride (6.0 mL) and kept at room temperature overnight. The brown solution was poured on ice, taken in ether, and washed successively with saturated $NaHCO_3$, 1 M HCl, and water. The residue was triturated with ether and the product (0.4 g) recrystallized from 95% EtOH, in needles, mp 143-144 °C *m/z* 544 (M^+). ^1H NMR data (Me_2SO-d_6): δ 8.02-7.30 (m, 20 H), 7.20 (s, 1 H, H-3), 5.40 (t, 1 H, *J* = 7.61 Hz, H-5), 4.57 (d, 2 H, *J* = 7.63 Hz, H6, 6'). Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 72.79; H, 4.44; N, 5.14. Found: C, 72.65; H, 4.35; N, 4.99.

***N*,*N'*-Dibenzoylpenta-*O*-benzoyl-D-galactonic Phenylhydrazide (6d).** To a cold solution of D-galactonic phenylhydrazide (**5a**; 3.0 g) in pyridine (60.0 mL) was added ice-cold benzoyl chloride (20.0 mL). After standing overnight at room temperature, the solution was poured onto ice and the oil that separated treated with 95% EtOH. The benzoate (2.0 g) crystallized from 95% EtOH in needles, mp 151-152 °C; ν (KBr) 1726 (O=CO), 1658 (O=CN), 1601 (C=C). Anal. Calcd for $C_{61}H_{46}N_2H_{13}$: C, 72.18; H, 4.57; N, 2.76. Found: C, 72.26; H, 4.65; N, 2.69.

Registry No. D-**1a**, 18841-76-4; L-**1a**, 136981-92-5; D-**1b**, 6035-58-1; L-**1b**, 6055-85-2; D-**1c**, 28767-74-0; L-**1c**, 622-12-8; D-**4a**, 136863-60-0; L-**4a**, 136863-66-6; D-**4b**, 136863-61-1; L-**4b**, 136863-67-7; D-**4c**, 136863-62-2; L-**4c**, 51532-88-8; D-**5a**, 29617-77-4; L-**5a**, 136981-91-4; D-**5b**, 136863-63-3; L-**5b**, 136863-68-8; D-**5c**, 66663-89-6; L-**5c**, 5346-84-9; **6d**, 136863-64-4; **9**, 136863-65-5.

High-Pressure Induced 1,3-Dipolar Cycloadditions of Azides with Electron-Deficient Olefins

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1,3-Dipolar cycloadditions of aryl and alkyl azides with a variety of olefins have been studied in some detail.[1] The

