The Synthesis and Properties of Two Stable Benzo[c]furans. An X-ray Crystallographic Structure Determination of the Geometry of 1-Cyano-5,6-(methylenedioxy)benzo[c]furan

Russell Rodrigo* and Susan M. Knabe

Department of Chemistry, Wilfrid Laurier University, Waterloo, Ontario, Canada N2L 3C5

Nicholas J. Taylor, Dayananda Rajapaksa, and Michael J. Chernishenko

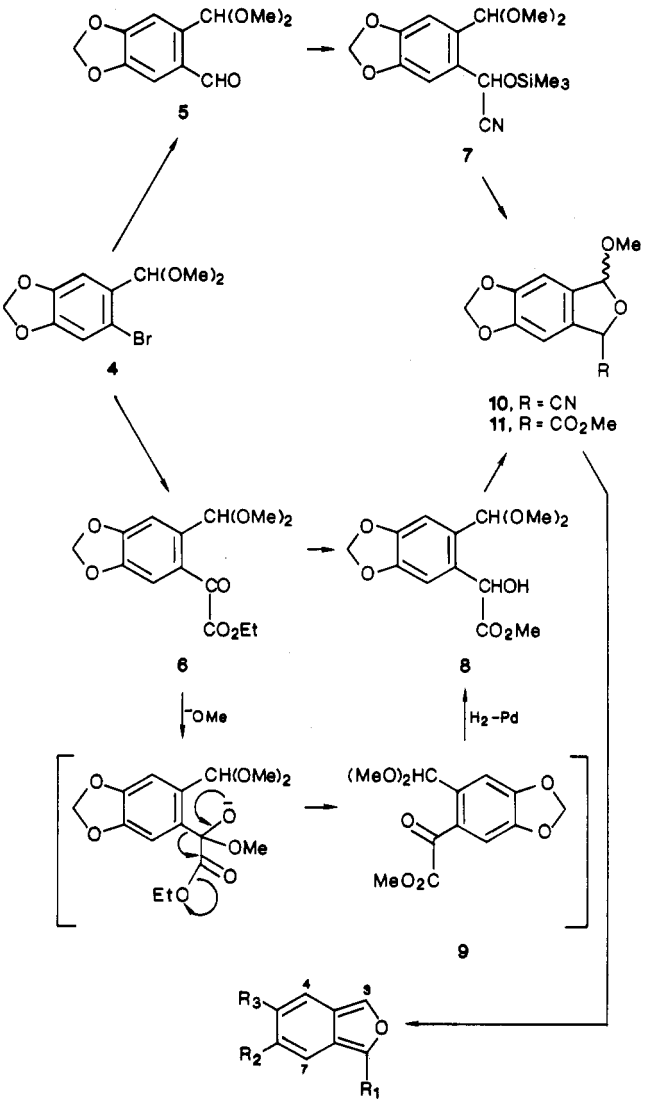
Guelph-Waterloo Centre for Graduate Work in Chemistry, Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Received May 6, 1986

Syntheses of crystalline benzo[c]furans **2** and **3** are described. ^{13}C NMR spectra of these compounds have been studied and chemical shifts assigned. The data appear to support a previously advanced structural representation of such *o*-quinonoidal heterocycles as a 6π-hetero-ring annelated at C-3 and C-4 to a noninteracting *cis*-butadiene fragment as in **14**. The first experimental determination of the geometry of a benzo[c]furan has been accomplished by an X-ray crystallographic study of **2**. The results show a planar molecule with carbon–carbon bonds alternating in length, in general agreement with several earlier calculations, but in even better agreement with the published geometry of furan. Diels–Alder reactions of **2** and **3** with common dienophiles provide good yields of "ortho" adducts as endo–exo mixtures.

The 10-π benzo[c]furan system **1** has been the subject of several theoretical studies.[1] A general consensus that the molecule does not possess the usual physical criteria of aromaticity (resonance energy and nonalternating bond lengths) is matched by the experimentally observed instability and well-known diene character, but is contradicted by the low-field H-1 resonance in the NMR spectrum which had been considered[2] indicative of a ring current. An interesting view of the system, developed from measurement of the $J_{4,5}/J_{5,6}$ ratios in ^1H NMR spectra of several *o*-quinonoidal heterocycles, regards[3] isobenzofuran as a six-electron furan annelated at the 3 and 4 positions to a noninteracting s-cis butandiene fragment so that aromaticity, if any, and diene character are traceable to the furan moiety as in the expression **14**. The geometry of the molecule has never been experimentally determined; standard geometry, assumed geometry, or iterative procedures have been used in the calculations. We therefore decided to attempt the synthesis of a simple stable, crystalline benzo[c]furan by application of general procedures developed earlier[4] in this laboratory. Although phenyl substituents are known to stabilize the system and 1,3-diphenylisobenzofuran is in fact commercially available, we preferred to avoid the large perturbation such groups impose and sought instead for a crystalline isobenzofuran just stable enough for X-ray and spectroscopic analysis. We now report the synthesis, ^{13}C NMR spectroscopic examination, and some Diels–Alder reactions of moderately stable, crystalline isobenzofurans **2** and **3** and the first crystal structure determination of the geometry of a benzo[c]furan, accomplished with a sample of **2**.

Syntheses of 2 and 3. The synthesis of both compounds began with 6-bromopiperonal dimethyl acetal (**4**) which was treated with *n*-butyllithium and quenched with dimethyl formamide[4] or excess diethyl oxalate to provide **5** (82%) and **6** (79%), respectively. The ortho-related hydroxy acetal structural unit required for the construction of the furan ring was generated in each case by trimethylsilyl cyanation of **5** with TMSCN to provide **7** (76%) and by reduction of **6** in a palladium-catalyzed hydrogenation in alkaline methanol to yield **8** (95%). It should be noted that a facile ester interchange also takes



1 ($R_1 = R_2 = R_3 = H$)
2 ($R_1 = CN$, $R_2 + R_3 = OCH_2O$
3 ($R_1 = CO_2Me$, $R_2 + R_3 = OCH_2O$

(1) For a comprehensive review, see: Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135. Also see: Wiersum, U. E. *Aldrichimica Acta* **1981**, *14*(3), 53.
(2) Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346.
(3) Chacko, E.; Bornstein, J.; Sardella, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 8248.
(4) Keay, B. A.; Plaumann, H. P.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 1987. Keay, B. A.; Lee, D. K. W.; Rodrigo, R. *Tetrahedron Lett.* **1980**, *21*, 3663.

0022-3263/86/1951-3973$01.50/0

Table I. ^{13}C NMR Chemical Shift Assignments (δ in ppm from Me_4Si) for 2 and 3 in $CDCl_3$

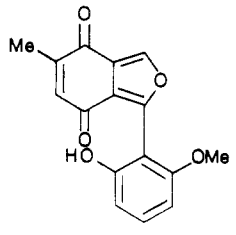
compd	carbon atoms											
	1	3	3a	7a	4	5	6	7	OCH_2O	CN	C=O	Me
2	117.6	139.5	121.9	130.9	91.2	148.7	151.5	93.1	101.8	112.5		
3	134.4	138.3	122.7	127.4	92.7	147.9	150.9	94.0	101.3		159.5	51.5
$\Delta\delta$(3 - 2)	16.8	-1.2	0.8	-3.5								
$\Delta\delta$(13 - 12)[a]	18.8	-1.6	0.3	-4.7								

[a] From ref 7 for corresponding carbon atoms in 12 and 13.

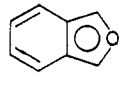
place during the latter reaction either directly or possibly by means of a benzilic acid type of rearrangement, through an intermediate 9 which is hydrogenated to the product 8. Methoxyphthalans 10 and 11 are easily obtained from 7 and 8, respectively, by treatment with acid. Both compounds are formed as approximately 1:1 mixtures of cis and trans diastereomers, and in each case the trans isomer crystallized from the mixture and was recognized by its $^4J_{1,3}$ coupling[4] of ca. 2.5 Hz. The isobenzofurans 2 and 3 are prepared by further acid treatment of the phthalans but the formation of 2 required more vigorous conditions than 3. In both cases column chromatography gave relatively pure crystalline products but crystals suitable for X-ray analysis could only be obtained by the high vacuum (10^{-5} torr) sublimation of 2 at 60 °C. The cyanoisobenzofuran 2 could also be prepared in one step by treating aldehyde acetal 5 with potassium cyanide in acetic acid under reflux for extended periods. This adaptation of a method previously employed[5] to produce 1-cyano-3-phenylisobenzofuran was rapid but rather irreproducible and varying yields of 2 were obtained together with large amounts of decomposition products.

^1H and ^{13}C NMR Spectra of 2 and 3. The proton spectra (in deuteriochloroform) are unexceptional. The furanoid proton H-3 is the farthest downfield at 7.85 and 7.88 ppm, respectively, in 2 and 3 compared with 7.98 ppm in 1.[6] Signals due to protons at H-4 and H-7 are coincident at 6.69 in 2 but well separated at 6.65 and 7.15 ppm in 3 presumably due to the anisotropic deshielding of H-7 by the C-1 carbomethoxy group in the latter compound.

Since no record of ^{13}C NMR spectra of any isobenzofuran exists in the literature, a study and assignment of the ^{13}C resonances of 2 and 3 were undertaken. Existing data, gathered[7] for several furans, in particular the 2-cyano- (12) and 2-carbomethoxyfurans (13) were of considerable value in this task. Broad band decoupled spectra and fully coupled spectra of 2 and 3 enabled firm assignments for OCH_2O, CN, and CO_2Me carbons in 2 and 3. The protonated furanoid carbon atom C-3 in both compounds was distinguished by its characteristically large ^1J(C–H) coupling of >200 Hz while the nonprotonated furanoid carbon C-1 produced a signal of characteristically low intensity which was a doublet in both compounds ($^3J(C_1–H_3)$ = 7.6 Hz in 2) at 117.6 in 2 and 134.4 ppm in 3. The signals at 130.9 in 2 and 127.4 ppm in 3, both triplets, are assigned to C-7a coupled almost equally ($^3J \approx 6$ Hz) to H-3 and H-4. The corresponding signal due to C-3 in 12 and 13 shows ^3J couplings ($C_3–H_5$) of 5.8 and 6.0, respectively. The last furanoid carbon atom C-3a produces signals at 121.9 and 122.7 ppm in 2 and 3 and in both cases these signals are quartets due to the characteristically[7] large ^2J coupling ($C_{3a}–H_3$) of 13.4 Hz and a normal ^3J coupling ($C_{3a}–H_7$) of 5.7 Hz. Differential substitution parameters $\Delta\delta$ (CO_2Me–CN) for the 3 and 2, 13 and 12 pairs obtained by subtraction show, by their close similarity, that each furanoid carbon is equally affected by these substituents whether the system is furan or benzo[c]furan. This not only provides support for the foregoing assignments but also implies that the furanoid moiety in 2 and 3 is much like furan in its ^{13}C behavior. The remaining carbon atoms belong to the cyclohexadiene ($C_4–C_7$) moiety and can be considered as two pairs (C_4,C_7 and C_5,C_6) which appear as such in the spectra of 2 and 3. The C_4,C_7 pair of protonated carbons are found at high field (91–93 ppm) while the oxygenated pair (C_5 and C_6) are in the 148–152-ppm region. In the ester 3 where the signals of H-4 and H-7 are separate in the ^1H spectrum, C-4 and C-7 are easily distinguished by selective ^1H decoupling of H-4 (at δ 6.65). This results in the collapse of the doublet at 92.7 ppm which is therefore assigned to H-4, and the doublet at 94 ppm is attributed to H-7. The assignments of these carbons in 2 are based on analogy with 3: the low-field doublet at 93.1 to H-7 and the high field doublet at 91.2 ppm to H-4. Assignments of C-5 and C-6 are arbitrary and may be interchanged. The data and assignments are summarized in Tables I and II.

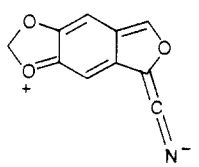


15

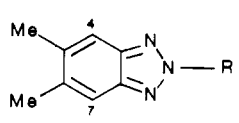


14

12 (R = CN)
13 (R = CO_2Me)



17



16
(R = a 3,4 diacetoxy erythropyranoside)

X-ray Crystallographic Results for 2. Atomic coordinates and isotropic thermal parameters are given in Table S1 and bond lengths and angles in Table S2 (supplemental material). An ORTEP view of the two molecules of the asymmetric unit is shown in Figure 1. The results indicate that 2 is an essentially planar molecule; only the carbon atom of the methylenedioxy group is slightly out of plane. The bond lengths compare reasonably well with previously calculated values,[8,9] but remarkably good agreement is found for the bond lengths of the furanoid moiety of 2 with experimental values for both furan itself[10,11] and for 15, a 1-substituted isobenzofuran-4,7-

(5) Petracek, F. J.; Sugisaka, N.; Klohs, M. W.; Parker, R. G.; Bordner, J.; Roberts, J. D. *Tetrahedron Lett.* **1970**, 707.
(6) Palmer, M. H.; Kennedy, S. M. F. *J. Chem. Soc., Perkin Trans. 2* **1976**, 81.
(7) Gronowitz, S.; Johnson, I.; Hörnfeldt, A.-B. *Chem. Scr.* **1975**, *7*, 211.
(8) Dewar, M. J. S. Harget, A. J.; Trinajstic, N.; Worley, S. D. *Tetrahedron* **1970**, *26*, 4505.
(9) Results of an MNDO calculation carried out by Prof. W. Friedrichsen. Personal communication from the author.
(10) Fourme, R. *Acta Crystallogr., Sect. B* **1972**, *28*, 2984.

Table II. Comparison of Coupling Constants (Hz) for 2, 3, 12, and 13

	^1J					^2J	^3J			
compd	C_3–H_3	C_4–H_4	C_7–H_7	OCH_2O	CH_3	C_{3a}–H_3	C_{3a}–H_7	C_1–H_3	C_{7a}–H_3	C_{7a}–H_4
2	208	170	169	175		13.4	5.7	7.6	6.3	5.7
3	206	169	172	175	147.3	13.4	5.7	*b*	5.7	5.7
12[a]	207					13.3		*b*	6.0	
13[a]	205					13.5		*b*	5.8	

[a] From ref 7 for corresponding carbon and hydrogen atoms. [b] Not measurable.

Table III. Comparison of Bond Lengths (Å) for Furans and Benzo[c]furans

	calculated		experimental			
bond	Dewar[8] (1)	Friedrichsen[9] (2)	**2**[a]	furan[11]	**16**[14]	**15**[12]
1–2	1.378	1.371	1.374	1.362		1.384
2–3	1.378	1.355	1.355	1.362		1.364
3–3a	1.355	1.400	1.356	1.361		1.353
3a–7a	1.459	1.470	1.436	1.430	1.405	1.429
1–7a	1.355	1.406	1.372	1.361		1.371
3a–4	1.462	1.447	1.431		1.407	
4–5	1.353	1.368	1.330		1.372	
5–6	1.454	1.478	1.422		1.446	
6–7	1.353	1.370	1.348		1.358	
7–7a	1.462	1.448	1.419		1.420	

[a] Mean values for the AB pair from Table S2.

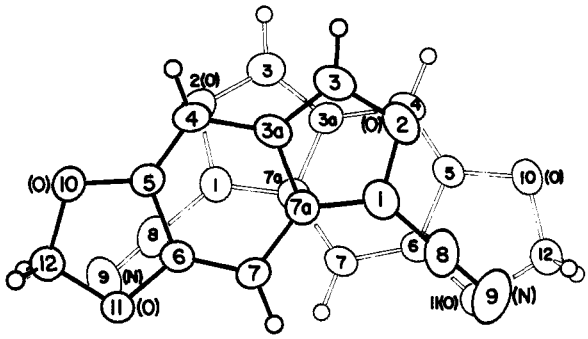


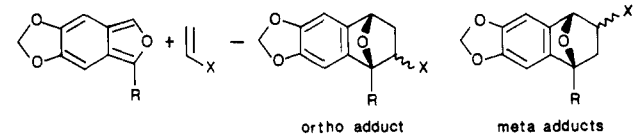
Figure 1. ORTEP diagram of two molecules of the asymmetric unit of **2**.

dione.[12] The data summarized in Table III appear to provide more powerful support for the representation of the isobenzofuran system as **14**.

The *cis*-butadiene moiety of the molecule, represented by C_4–C_7, can be compared with the conjugated C_1–C_4 system of 1,3-cyclohexadiene where the double bonds are 1.350 (4) Å and the intervening C_2–C_3 single bond is 1.468 (14) Å long.[13] In the nearest model for **2** that can be found in the literature, the 5,6-dimethylbenzotriazole glycoside (**16**), the cyclohexadiene ring possesses bond lengths that alternate in a similar fashion,[14] but C_4–C_5 is distinctly shorter and C_{3a}–C_4 distinctly longer in **2**.

This feature of the present X-ray result deserves further comment. Comparison of bonds O–C_6–C_7–C_{7a}–C_1 with O–C_5–C_4–C_{3a}–C_3 (i.e., the "bottom" side of **2** with the "top" side) shows that a slight mesomeric interaction between the oxygen atom at C-6 and the cyanide at C-1 as expressed in structure **17** is discernible. Corresponding changes in bond lengths are evident from the data although these are small. However, the packing of adjacent molecules in the asymmetric unit as shown in Figure 1 places the C-6 oxygen atom (O-11) of one molecule directly above the nitrogen (N-9) of the next and 3.456 (4) and 3.415 (4) Å apart at each contact.

Table IV. Diels–Alder Reactions of 2 and 3



R	X	total crude yield (%)	ortho adduct	(endo:exo)	ortho:meta
CN	$COCH_3$	95	**18**[a]	(7:3)	
	CN	95	**19**[a]	(3:2)	
	CO_2Me	95	**20**	(3:2)	8:1
	CHO	97	**21**	(1:1)	5:1
CO_2Me	$COCH_3$	95	**22**[a]	(7:2)	
	CN	90	**23**[a]	(2:1)	
	CO_2Me	90	**24**	(3:1)	
	CHO	90	**25**[a]	(1:1)	6.3:1

[a] One isomer crystallized, see text.

Diels–Alder Reactions of 2 and 3. The regiochemistry of the Diels–Alder reactions of common dienophiles with transient 1-substituted isobenzofurans generated in situ has attracted some recent interest. It has been generally observed that "ortho" adducts predominate in accordance with qualitative frontier orbital predictions.[15] The isobenzofurans investigated to date have carried mainly electron-donating substituents at C-1, ranging from amine[16] and alkoxy[17] to alkyl,[18,19] but in one instance the bromo and methoxycarbonyl derivatives were reported[19] to react sluggishly with a quinone monoketal to provide "ortho" adducts in moderate yield.

Diels–Alder additions of **2** and **3** with four common olefinic dienophiles were carried out on a steam bath for

(11) Mata, F.; Martin, M. C.; Sorensen, G. O. *J. Mol. Struct.* **1978**, *48*, 157.
(12) Ahad, J.; Banham, R.; Whalley, W. B.; Ferguson, G.; Siew, P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2445.
(13) Oberhammer, H.; Bauer, S. H *J. Am. Chem. Soc.* **1969**, *91*, 10.
(14) de Lerma, J. L.; Hernandez, F.; Garcia-Blanco, S.; Martinez-Ripoll, M. *Acta Crystallogr., Sect. B*, **1976**, *32*, 3019.
(15) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.
(16) Beak, P.; Chen, C.-W. *Tetrahedron Lett.* **1983**, *24*, 2945.
(17) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 2734. Contreras, L.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2573.
(18) Smith, J. G.; Welankiwar, S. S.; Shantz, B. S.; Lai, E. H.; Chu, N. G. *J. Org. Chem.* **1980**, *45*, 1817.
(19) Warrener, R. N.; Hammer, B. C.; Russell, R. A. *J. Chem. Soc., Chem. Commun.* **1981**, 942.

Table V. 250-MHz ^{1}H NMR Spectra of Exo and Endo Isomers of Adduct 18

	exo			endo		
proton	δ	mult	J (Hz)	δ	mult	J (Hz)
2	2.93	dd	$2\alpha,3\alpha$ = 8.7 $2\alpha,3\beta$ = 4.6	3.66	dd	$2\beta,3\alpha$ = 4.0 $2\beta,3\beta$ = 9.9
3α	1.80	dd	$3\alpha,3\beta$ = 11.6 $2\alpha,3\alpha$ = 8.7	1.89	dd	$2\beta,3\alpha$ = 4.0 $3\alpha,3\beta$ = 11.5
3β	2.3–2.41	m[a]		2.38–2.45	m	
4	5.48	d	$3\beta,4$ = 4.8	5.40	d	$3\beta,4$ = 5.0
5, 8	6.79, 6.94	2 × s		6.76, 6.88	2 × s	
OCH_2O	6.0, 6.03	q	J_{AB} = 1.2	5.96, 6.01	q	J_{AB} = 1.2
$COCH_3$	2.36	s		2.23	s	

[a] Signals partially obscured by CH_3 signal at 2.36 ppm.

10 min to provide endo–exo mixtures of predominantly the ortho adducts in excellent yields. The crude reaction products were analyzed by ^{1}H NMR spectrometry to obtain the ratios reported in Table IV (see Experimental Section). In most instances the analysis was aided by the separation and crystallization of one or both ortho isomers. NMR-detectable amounts of meta regioisomers were formed in only three instances. No attempt was made to separate or isolate the endo and exo isomers of the meta products although their presence was especially evident in the acrolein adducts from the four aldehyde doublets in the spectrum of the crude adduct mixture. The reversibility of each reaction was not individually investigated but we did observe that both pure *endo*-**18** and pure *endo*-**19** were unaffected when heated on a steam bath for 10 min with excess dimethyl acetylenedicarboxylate. These Diels–Alder reactions therefore appear to be irreversible in contrast to reports[18,20] that some maleic anhydride adducts suffer cycloreversion when heated.

The 250-MHz ^{1}H NMR spectra of *exo*- and *endo*-**18**, briefly discussed and reported in Table V, are illustrative of the NMR properties of these compounds. Assignments and coupling constants which were confirmed by decoupling are in complete accord with the structure and stereochemistry of each compound and are typical of all the ortho adducts prepared. The shielding effect of the aromatic ring on the chemical shifts of endo groups (H-2α, 3α, and α-$COCH_3$) and the slight but distinct consequences of an endo $COCH_3$ group on resonances of H-8 and the 6,7-methylenedioxy group are noteworthy. Such effects are helpful in determining the stereochemistry of the adduct and have been observed before[4] in similar oxabicyclo systems.

Experimental Section

Melting points were determined with a Buchi SMP-20 apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-10 or a Perkin-Elmer 983 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker WP 80 or AM 250 spectrometer in deuteriochloroform unless otherwise indicated. Carbon spectra were run on the latter instrument operating at 62.87 MHz. Mass spectra were measured on a VG 7070 instrument and are reported in the order m/z, (relative intensity). Combustion analyses were carried out by the Guelph Chemical Laboratories, Guelph, Ontario.

Trimethylsilyl Cyanohydrin 7. The acetal **5**[4] (10 g, 44.6 mmol) was dissolved in dry methylene chloride (25 mL) in an atmosphere of dry nitrogen. Trimethylsilyl cyanide (4.15 g, 44.6 mmol) and a catalytic amount of potassium cyanide (0.25 g) were added, and the mixture was allowed to stir for 5 days at room temperature. Water was added, the organic layer separated, and the aqueous solution extracted with methylene chloride (2 × 25 mL). The combined organic phases were washed with water and dried (Na_2SO_4). Evaporation of the solvent left an oil which was distilled (120 °C/0.05 torr) to obtain **7** (11 g, 76%): ^{1}H NMR (80 MHz) δ 0.16 (s, 9 H, $SiMe_3$), 3.27, 3.28 (s, 3 H each, OMe), 5.24 (s, 1 H, C*H*$(OMe)_2$), 5.95 (overlapping m, 3 H, C*H*(CN)OSiMe_3 and OCH_2O), 6.91, 7.19 (s, 1 H each, Ar H).

Methoxyphthalans 10. The cyanohydrin **7** (10 g, 30.9 mmol) was dissolved in methanol (60 mL), 3 drops of 2 N hydrochloric acid were added, and the solution was stirred for 5 h. The methanol was removed on a rotary evaporator, saturated aqueous bicarbonate solution was added to neutralize the acid, and the product was extracted with methylene chloride (3 × 25 mL). The combined extracts were washed and dried (Na_2SO_4) and the solvent was removed to leave a mixture of cis and trans isomers of **10** (6.2 g, 91%). Recrystallization from ether gave the pure trans isomer: mp 177 °C; ^{1}H NMR (80 MHz) δ 3.45 (s, 3 H, OMe), 5.9 and 6.2 (d, 1 H each, H_1 and H_3, $J_{1,3}$ = 3.0 Hz), 6.06 (s, 2 H, OCH_2O) 6.8 (overlapping s, 2 H, Ar H); MS, 219 (20, M^+), 188 (100), 160 (16). Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.15; N, 6.39. Found: C, 60.45; H, 4.04; N, 6.12.

1-Cyano-5,6-(methylenedioxy)isobenzofuran (2). The cis–trans mixture of phthalans **10** (1 g, 4.56 mmol) was suspended in a 1:1 mixture of glacial acetic acid and *p*-xylene (5 mL) and heated under reflux for 3 h (with monitoring by thin layer chromatography for disappearance of **10**). The solvents were removed on a rotary evaporator, saturated aqueous sodium bicarbonate was added to neutralize any remaining acid, and the product was extracted with methylene chloride (3 × 10 mL). The extracts were washed and dried (Na_2SO_4), the solvent was removed, and the residue was filtered through a column of silica gel in ethyl acetate–hexane (1:1). Removal of the solvents left **2** (0.75 g, 88%) as a pale yellow solid. Sublimation at 60 °C and 10^{-5} torr produced a crystalline sample suitable for X-ray structure determination: mp (in a sealed evacuated tube) 137 °C; IR ($CHCl_3$) 2211 cm^{-1}; UV λ_{max} (MeOH) 316 (2119) nm; ^{1}H NMR (80 MHz) δ 5.99 (s, 2 H, OCH_2O), 6.71, 6.73 (s, 1 H each, H-4 and H-7), 7.86 (s, 1 H, H-3); MS, 187 (100, M^+), 159 (37), 129 (30), 101 (48), 75 (21), 93.5 (7, M^{2+}). Anal. Calcd for $C_{10}H_5O_3N$: C, 64.17; H, 2.69; N, 7.48. Found: C, 64.00; H, 3.09; N, 7.20.

Alternative One-Step Preparation of 2. The acetal **5** (2.25 g, 10 mmol) was dissolved in glacial acetic acid (25 mL), potassium cyanide (2.6 g, 40 mmol) was added, and the mixture was heated at 90 °C for 4.5 h. The solvent was removed under reduced pressure, a saturated aqueous solution of sodium bicarbonate was added, and the mixture was extracted with methylene chloride (3 × 25 mL). The dark colored extracts were combined, the solvent was removed, and the residue was chromatographed on a silica gel column in ethyl acetate–hexane (1:1). Removal of the solvents provided 0.62 g (30%) of **2** as the best yield.

X-ray Data Collection and Structure Determination of 2. Colorless crystals of **2** were obtained by slow vacuum sublimation. All X-ray data were collected on a Syntex P2 diffractometer. A summary of data acquisition and structure refinement parameters is given in Table VI. Data were corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by direct methods (MULTAN 80) and refined by full-matrix least-squares methods. Scattering factors were taken from the International Tables[21] and for hydrogen the data of Stewart et al.[22] were used. Computer programs employed

(20) McCormick, J. P.; Shinmyozu, T. *J. Org. Chem.* **1982**, *47*, 4011.

(21) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England; 1974, Vol. IV.

Table VI. Summary of Crystal Parameters, Data Collection, and Refinement for 2, $C_{10}H_5NO_3$

formula	$C_{10}H_5NO_3$
fw	187.16
a, Å	7.070 (1)
b, Å	11.325 (4)
c, Å	21.107 (6)
β, deg	97.08 (2)
V, Å^3	1677.1 (8)
space group	$P2_1/c$
Z	8
density ρ_c, g cm^{-3}	1.482
crystal dimensions, mm	0.24 × 0.25 × 0.38
radiation	MoKα (λ = 0.71069 Å)
temperature, K	293 ± 1
μ (Mo Kα), cm^{-1}	1.213
2θ max, deg	50
scan type	θ–2θ
scan range	0.9° below Kα_1 to 0.9° above Kα_2
scan speed (deg min^{-1})	2.93–29.30
check reflections	008, 400
standard variation	±2%
unique data measured	2979
observed data	1525 ($I \geq 3\sigma(I)$)
no. of variables	148
max. shift/esd in final cycle	0.03
G.O.F.	1.47
maximum residuals, e Å^{-3}	0.13
R (= $\Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$)	0.035
R_w (= $[\Sigma w(\|F_o\| - \|F_c\|)^2/\Sigma w\|F_o\|^2]^{1/2}$	0.039
w^{-1}	$1.57 - 0.022\|F_o\| + 0.0075\|F_o\|^2$

have been described elsewhere.[23] Atomic coordinates, with bond lengths and angles, anisotropic thermal parameters, and least squares planes have been deposited (Tables S1–S4, supplementary material).

Keto Ester 6. The bromo acetal 4 (5.6 g, 20 mmol) was dissolved in dry ether (50 mL), and a solution of *n*-BuLi in hexane (1.6 M, 13 mL, 1.1 equiv) was added dropwise, under nitrogen at −78 °C with stirring. After a further 45 min at this temperature, diethyl oxalate (7.4 g, 5 equiv) was added quickly in one portion, and the reaction mixture was allowed to reach room temperature and then quenched with water. The ether layer was separated and the aqueous phase extracted further with ether (3 × 25 mL). The combined ethereal solutions were washed with water and dried (Na_2SO_4). The ether was removed and the excess diethyl oxalate removed in vacuo at 100 °C. The residual oil was crystallized from ether–hexane (1:1) to yield bright yellow crystals of **6** (4.7 g, 79%): mp 54 °C; IR ($CHCl_3$) 1690, 1725 cm^{-1}; ^{1}H NMR (80 MHz) δ 1.4 (t, 3 H, Me), 3.25 (s, 6 H, 2 × OMe), 4.3 (q, 2 H, CH_2), 5.6 (s, 1 H, C*H*(OMe)$_2$), 5.9 (s, 2 H, OCH_2O), 6.9 and 7.0 (s, 1 H each, Ar H); MS, 296 (9, M$^+$), 265 (12), 223 (100). Anal. Calcd for $C_{14}H_{15}O_7$: C, 56.95; H, 5.08. Found: C, 57.02; H, 5.52.

Hydroxy Acetal 8. The keto ester **6** (2 g) was dissolved in methanol (50 mL) in a two-necked flask and solid potassium hydroxide (20 mg) was added. The catalyst (1 g, 5% Pd–charcoal) was added under a nitrogen atmosphere and the nitrogen was replaced by a hydrogen atmosphere by flushing the flask with hydrogen three times. Hydrogenation at room temperature and pressure was allowed to proceed with monitoring by TLC for disappearance of the starting material. At completion of the reaction the mixture was filtered through Celite, the filtrate treated with saturated sodium bicarbonate (20 mL), and the methanol removed on the rotary evaporator. The aqueous residue was extracted with methylene chloride (3 × 20 mL). The combined extracts were washed and dried (Na_2SO_4), and the solvent was removed to yield the product **8** (1.82 g, 95%) as an oil which was used without further purification: ^{1}H NMR (80 MHz) δ 3.3, 3.35 (s, 3 H each, CH(O*Me*)$_2$), 3.65 (d, 1 H, $J_{H,OH}$ = 4 Hz, exchanges with D_2O, CHO*H*), 3.75 (s, 3 H, CO_2*Me*), 5.5 (d, 1 H, $J_{H,OH}$ = 4 Hz, collapses to singlet with D_2O, C*H*OH), 5.6 (s, 1 H, C*H*(OMe)$_2$, 5.9 (s, 2 H, OCH_2O), 6.83 and 7.13 (s, 1 H each, Ar H); IR ($CHCl_3$) 3528 (br), 1736 cm^{-1}; MS, 284 (4, M$^+$), 232 (25), 221 (49), 193 (100).

Methoxyphthalans 11. The hydroxy acetal **8** (2 g) was dissolved in dry methanol (10 mL), a catalytic quantity of *p*-toluenesulfonic acid (50 mg) was added, and the mixture was stirred at room temperature with periodic monitoring by TLC. Upon completion of the reaction powdered anhydrous sodium carbonate (1 g) was added and stirring continued for 1 h. The methanol was removed under reduced pressure, and the residue was mixed with water (10 mL) and extracted with methylene chloride (3 × 10 mL). The combined extracts were washed, dried (Na_2SO_4), and evaporated to leave the phthalans **11** as a mixture of cis and trans isomers (90% total). Crystallization from ether provided prisms of the pure trans isomer: mp 110 °C; ^{1}H NMR (80 MHz) δ 3.46, 3.80 (s, 3 H each, OMe), 5.69, 6.29 (d, 1 H each, H-1 and H-3 respectively, $J_{1,3}$ = 2.5 Hz), 6.01 (s, 2 H, OCH_2O), 6.79 and 6.86 (s, 1 H each, Ar H); IR ($CHCl_3$) 1757 cm^{-1}; MS, 252 (9, M$^+$), 221 (15), 220 (21), 193 (100). Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.76. Found: C, 56.59; H, 4.61.

5,6-(Methylenedioxy)-1-carbomethoxyisobenzofuran (3). The mixture of phthalans **11** (or the hydroxy acetal **8**) (100 mg) was dissolved in THF (20 mL), *p*-toluenesulfonic acid (5 mg) was added, and the mixture was heated under reflux for 3 min. The acid was neutralized with saturated aqueous sodium bicarbonate, THF was removed under reduced pressure, and the residue was extracted with methylene chloride (3 × 10 mL). The combined extracts were washed, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column in ethyl acetate/hexane (4:3) and the isobenzofuran **3** obtained as a pale yellow solid upon removal of the solvents (50%). Attempts at recrystallization and elemental analysis were unsuccessful, presumably due to decomposition of the material: IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR (80 MHz) δ 3.95 (s, 3 H, OMe), 5.95 (s, 2 H, OCH_2O), 6.65, 7.15, 7.85 (s, 1 H each, H-4, H-7, and H-3, respectively).

General Procedure for Diels–Alder Reactions of 2 and 3. The isobenzofuran (**2** or **3**, 100 mg) was added to the freshly distilled dienophile (1 mL) stabilized with hydroquinone (1% wt), and the solution was heated on a steam bath for 10 min (when TLC indicated no remaining isobenzofuran). Excess dienophile was removed at 0.05 torr, and the residue was analyzed by ^{1}H NMR (Table IV) and processed further as described for each adduct below.

Adducts 18. Crystallization of the endo–exo mixture from ether yielded the pure endo isomer (mp 146 °C) and from the mother liquors the exo isomer (mp 167 °C): ^{1}H NMR in Table V; MS (endo isomer), 257 (25), 187 (100), 159 (21), 101 (15); IR ($CHCl_3$) 1717 cm^{-1}. Anal. Calcd for $C_{14}H_{11}O_4N$: C, 65.36; H, 4.31; N, 5.45. Found: C, 64.94; H, 4.59; N, 5.29.

Adducts 19. Crystallization of the exo–endo mixture from methanol afforded the pure endo isomer: mp 200 °C; ^{1}H NMR (250 MHz) δ 1.76 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 3.9, J_{gem} = 11.7), 2.74 (ddd, 1 H, H-3β, $J_{3\beta,4}$ = 4.8, $J_{2,3\beta}$ = 10.8, J_{gem} = 11.7), 3.54 (dd, 1 H, H-2, $J_{2,3\alpha}$ = 3.9, $J_{2,3\beta}$ = 10.8), 5.53 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.8), 6.06 (q, 2 H, OCH_2O, J_{AB} = 1.3), 6.81, 7.09 (2 × s, 1 H each, ArH); MS, 240 (9), 187 (100), 159 (16), 101 (16). Anal. Calcd for $C_{13}H_8O_3N_2$: C, 65.00; H, 3.36; N, 11.66. Found: C, 64.53; H. 3.55; N, 11.53. ***exo*-19**: ^{1}H NMR (250 MHz) δ 2.02 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 8.4, J_{gem} = 11.8), 2.58 (ddd, 1 H, H-3β, $J_{3\beta,4}$ = 4.8, $J_{2,3\beta}$ = 4.4, J_{gem} = 11.8), 2.9 (dd, 1 H, H-2, $J_{2,3\beta}$ = 4.4, $J_{2,3a}$ = 8.4), 5.58 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.8), 6.04 (q, 2 H, OCH_2O), 6.79, 6.97 (2 × s, 1 H each, Ar H).

Adducts 20. Adducts could not be separated or crystallized but the ^{1}H NMR spectrum of the mixture (250 MHz) could be interpreted to show the existence of a 8:1 ratio of regioisomers and a 3:2 endo–exo ratio of ortho stereoisomers.

***endo*-20**: ^{1}H NMR (250 MHz) δ 1.95 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 3.8, J_{gem} = 11.7), 2.5 (m, H-3β, overlapping with H-3β of exo adduct), 3.66 (s, 3 H, *endo*-CO_2*Me*), 3.6 (m, 1 H, H-2, obscured by ester methyl), 5.42 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.95), 6.0 (q, 2 H, OCH_2O), 6.77, 6.85 (2 × s, 2 × Ar H).

***exo*-20**: ^{1}H NMR (250 MHz) δ 1.81 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 8.5, J_{gem} = 11.7), 2.5 (m, H-3β), 2.84 (dd, 1 H, H-2, $J_{2,3\alpha}$ = 8.5, $J_{2,3\beta}$ = 4.5), 3.85 (s, 3 H, *exo*-CO_2Me), 5.49 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.9), 6.0 (q, 2 H, OCH_2O), 6.78, 6.92 (2 × s, 2 × Ar H); MS (mixture), 273 (7), 187 (100), 159 (13), 101 (7).

(22) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

(23) Carty, A. J.; Mott, G. N.; Taylor, N. J.; Yule, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 3051.

Adducts 21. The ^1H NMR spectrum (80 MHz) of the crude adduct mixture showed four separated doublets in the 9–10-ppm region from the aldehyde resonances of the four isomers. The meta adduct doublets (1:1) were found at 9.15 (endo) and 9.76 ppm (exo). The crude mixture was chromatographed on silica gel (230–440 mesh) in ethyl acetate–hexane (3:5) and two fractions containing pure *exo*-**21** and mainly *endo*-**21** were collected but neither fraction yielded any crystals.

***exo*-21**: ^1H NMR (80 MHz) δ 1.75 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 8.3, J_{gem} = 12.0), 2.3–2.9 (complex m, 2 H, H-2 and H-3β), 5.51 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.6), 6.02 (q, 2 H, OCH_2O, J_{AB} = 1.3), 6.8, 6.95 (2 × s, 1 H each, Ar H), 9.85 (d, 1 H, CHO, J = 2.9); IR ($CHCl_3$) 2780, 2740 (w), 1727 cm^{-1}; MS, 243 (15), 187 (100), 159 (15), 101 (9).

***endo*-21**: ^1H NMR (80 MHz) δ 1.82 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 3.9, J_{gem} = 11.7), 2.5 (complex m, 1 H, H-3β), 3.53 (m, 1 H, H-2, $J_{2,CHO}$ = 1.47, $J_{2,3\alpha}$ = 3.9, $J_{2,3\beta}$ = 10.1), 5.47 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.6), 6.0 (q, 2 H, OCH_2O, J_{AB} = 1.0), 6.8, 6.92 (2 × s, 1 H each, Ar H), 9.30 (d, 1 H, CHO, $J_{2,CHO}$ = 1.47).

Adducts 22. Crystallization of the crude endo–exo mixture from ether yielded the endo isomer of **22**: mp 144 °C; ^1H NMR (250 MHz) δ 1.83 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 4.05, J_{gem} = 11.3), 2.09 (s, 3 H, $COCH_3$), 2.40 (ddd, 1 H, H-3β, $J_{3\beta,4}$ = 4.9, $J_{2,3\beta}$ = 9.7, J_{gem} = 11.3), 3.61 (dd, 1 H, H-2, $J_{2,3\alpha}$ = 4.05, $J_{2,3\beta}$ = 9.7), 3.95 (s, 3 H, OMe), 5.39 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.9), 5.96 (q, 2 H, OCH_2O, J_{AB} = 1.05), 6.77, 6.98 (s, 2 × Ar H); MS, 290 (23), 220 (100), 189 (40), 162 (29), 133 (11); IR ($CHCl_3$) 1746, 1712 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.06; H, 4.82. Found: C, 62.06; H, 4.95.

Adducts 23. The crude mixture of adducts was chromatographed on a silica gel column in ethyl acetate/ligroin (1:1) and the pure endo isomer crystallized from ether–methanol: mp 175 °C; ^1H NMR (80 MHz) δ 1.73 (dd, 1 H, H-3α, J_{gem} = 11.2 Hz, $J_{2,3\alpha}$ = 3.9), 2.7 (ddd, 1 H, H-3β, J_{gem} = 11.2, $J_{2,3\beta}$ = 10.6, $J_{3\beta,4}$ = 4.7), 3.34 (dd, 1 H, H-2, $J_{2,3\alpha}$ = 3.9, $J_{2,3\beta}$ = 10.6), 4.02 (s, 3 H, OMe), 5.5 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.7), 6.05 (q, 2 H, OCH_2O, J = 1.5), 6.8, 7.15 (s, 2 × Ar H); IR (KBr) 2325, 1770 cm^{-1}; MS, 273 (8), 220 (100), 189 (20), 162 (16), 133 (8). Anal. Calcd for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.03; N, 5.13. Found: C, 61.57; H, 4.09; N, 4.90.

Adducts 24. The endo–exo mixture of ortho adducts could not be separated by chromatography or crystallization: MS (mixture), 306 (12), 275 (6), 220 (100), 189 (30), 162 (19), 133 (6).

Adducts 25. The mixture of ortho and meta adducts (6.3:1) was chromatographed on a silica gel column in ethyl acetate–hexane (7:3) and the ortho,endo isomer crystallized from ether–methylene chloride: mp 129 °C; ^1H NMR (80 MHz) δ 1.8 (dd, 1 H, H-3α, $J_{2,3\alpha}$ = 4.0, J_{gem} = 12.0), 2.42 (ddd, 1 H, H-3β, $J_{3\beta,4}$ = 4.8, J_{gem} = 12.0, $J_{2,3\beta}$ = 10.1), 3.28 (m, 1 H, H-2), 4.0 (s, 3 H, OMe), 5.45 (d, 1 H, H-4, $J_{3\beta,4}$ = 4.8), 5.95 (q, 2 H, OCH_2O), 6.8, 6.92 (s, 2 × Ar H), 9.3 (d, 1 H, C*H*O, J = 2.5); MS, 276 (14), 220 (100), 189 (32), 162 (21), 133 (10). Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.35. Found: C, 60.78, H, 4.36.

Acknowledgment. We thank the National Sciences and Engineering Research Council of Canada for support of this work.

Registry No. **2**, 104172-43-2; **3**, 104172-48-7; **4**, 74879-22-4; **5**, 87850-43-9; **6**, 104172-44-3; **7**, 104172-40-9; **8**, 104172-45-4; *cis*-**10**, 104172-41-0; *trans*-**10**, 104172-42-1; *cis*-**11**, 104172-46-5; *trans*-**11**, 104172-47-6; **18** (isomer 1), 104172-49-8; **18** (isomer 2), 104264-05-3; **19** (isomer 1), 104172-50-1; **19** (isomer 2), 104264-06-4; **20** (isomer 1), 104172-51-2; **20** (isomer 2), 104264-07-5; **20** (isomer 3), 104172-56-7; **20** (isomer 4), 104264-13-3; **21** (isomer 1), 104172-52-3; **21** (isomer 2), 104264-08-6; **21** (isomer 3), 104172-57-8; **21** (isomer 4), 104264-14-4; **22** (isomer 1), 91758-99-5; **22** (isomer 2), 104264-09-7; **23** (isomer 1), 104172-53-4; **23** (isomer 2), 104264-10-0; **24** (isomer 1), 104172-54-5; **24** (isomer 2), 104264-11-1; **25** (isomer 1), 104172-55-6; **25** (isomer 2), 104264-12-2; **25** (isomer 3), 104172-58-9; **25** (isomer 4), 104264-15-5.

Supplementary Material Available: Tables S1–S4 and X-ray crystallographic data for **2** (4 pages). Ordering information is given on any current masthead page.

New Derivatizing Agents for Amino Acids and Peptides. 1. Facile Synthesis of N-Substituted 1-Cyanobenz[*f*]isoindoles and Their Spectroscopic Properties

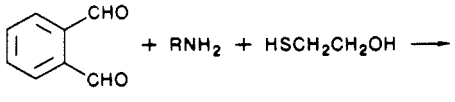
R. G. Carlson,* K. Srinivasachar, R. S. Givens, and B. K. Matuszewski

Center for Bioanalytical Research and Department of Chemistry, The University of Kansas, Lawrence, Kansas 66045-0046

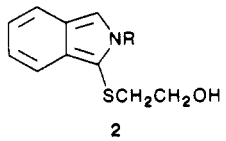
Received March 31, 1986

2,3-Naphthalenedicarboxaldehyde (NDA) is shown to be a very useful reagent for the derivatization of primary amines, amino acids, and small peptides. The reaction of these amino compounds with NDA and cyanide ion produces highly fluorescent 2-substituted 1-cyanobenz[*f*]isoindoles that are relatively stable. The physical and fluorescent properties of a variety of 1,2-disubstituted benz[*f*]isoindoles are presented.

The reaction of the fluorogenic reagent, *o*-phthalaldehyde (OPA, 1), with a primary amine function and a nucleophile such as 2-mercaptoethanol to produce a highly fluorescent N-substituted isoindole has become a standard method for the very low-level analysis of amines and amino acids.[1] Despite the widespread analytical application of this reagent, a number of drawbacks make it less than an ideal method. For example, the isoindoles **2** produced in the derivatization are relatively unstable and decompose to nonfluorescent products.[2a] Furthermore, it has been reported that OPA fails to give fluorescent products with small peptides,[2b] thus limiting the applications to simple amino acids.



1



2

At the onset of this work, it was our goal to develop new derivatizing reagents that would retain the desirable

(1) (a) Roth, M. *Anal. Chem.* **1971**, *43*, 880. (b) Simons, S. S., Jr.; Johnson, D. F. *J. Am. Chem. Soc.* **1976**, *98*, 7098. (c) Simons, S. S., Jr.; Johnson, D. F. *J. Chem. Soc., Chem. Commun.* **1978**, 374. (d) Simons, S. S., Jr.; Johnson, D. F. *J. Org. Chem.* **1978**, *43*, 2886. (e) Lee, K. S.; Drescher, D. G. *Int. J. Biochem.* **1978**, *9*, 457.

(2) (a) For leading references see: Stobaugh, J. F.; Repta, A. J.; Sternson, L. A. *J. Org. Chem.* **1984**, *49*, 4306. (b) For leading references see: de Montigny, P.; Sternson, L. A. *Anal. Lett.* **1984**, *17*, 1893.

0022-3263/86/1951-3978$01.50/0