mmol) was added. Then, L- or D-LDH (150–400 U) and FDH (40–50 U) immobilized on PAN gel[17] were added as a suspension in 100–200 mL of degassed H_2O. The flask was capped with septa, and Ar bubbled through the solution. HCl (2.56 N) added by a pH controller maintained the reaction near pH 7.5. The reaction progress was followed by measuring the volume of HCl consumed. Within 5 days the reaction was complete. The enzyme containing gel was isolated by centrifugation and washed with degassed H_2O. The aqueous layers were combined and concentrated by rotary evaporation to 70–80 mL, acidified to pH 2.0 with 6 N HCl, and extracted with 4 × 170 mL of ether. The ethereal layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure to give (*S*)-2-hydroxybutanoic acid (L-LDH used) (15.0 g, 95%) [>99% ee; mp 54.5–55.5 °C dec (lit.[28] mp 52.7–53.5 °C); $[\alpha]_D^{21}$ +7.15° (*c* 8.13, $CHCl_3$) (lit.[28] $[\alpha]_D^{16}$ +6.4° (*c* 11.03, $CHCl_3$)); ^1H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.75 and 1.88 (m, 1 H each, CH_2), 4.24 (dd, *J* = 4.5, 6.9 Hz, 1 H, CH), 6.72 (br, OH); IR (Nujol) 3500–2650 (OH), 1730 (C=O) cm^{-1}] or (*R*)-2-hydroxybutanoic acid (D-LDH used) (13.9 g, 89%) [>99% ee; mp 53–55 °C dec; $[\alpha]_D^{20}$ −5.6° (*c* 3.71, $CHCl_3$)]; the ^1H NMR and IR spectra were in agreement with those for the *S* enantiomer.

Conversion of (*R*)- and (*S*)-2-Hydroxybutanoic Acids to (*R*)- and (*S*)-Butane-1,2-diol. BH_3·THF[24] reduced the *R* and *S* hydroxy acids to (*R*)-butane-1,2-diol (9.7 g, 81%) [bp 122–125 °C (30 torr); $[\alpha]_D^{21}$ +12.6° (*c* 3.23, EtOH); ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.41 (m, 2 H, CH_3CH_2), 3.37 (m, 1 H, CH), 3.58 (m, 2 H, CH_2O), 3.67 (br s, 2 H, 2 × OH); IR (neat) 3350 (br, OH), 1045 (C–O) cm^{-1}] and (*S*)-butane-1,2-diol (11.7 g, 91%) [bp 94–96 °C (9 torr); $[\alpha]_D^{22}$ −15.35° (*c* 2.60, EtOH)]; the ^1H NMR and IR spectra were in agreement with those of the *R* enantiomer. Analytical data for both enantiomers agreed with the literature values.[29]

Conversion of (*R*)- and (*S*)-Butane-1,2-diol to (*R*)- and (*S*)-2-Acetoxy-1-bromobutane. Reaction of the diols with 30% HBr–AcOH[29,30] gave (*R*)-2-acetoxy-1-bromobutane (17.3 g, 82%) [bp 87–91 °C (21 torr); $[\alpha]_D^{21}$ +17.8° (*c* 2.73, ether); ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2), 1.69 (m, 2 H, CH_3CH_2), 2.07 (s, 3 H, CH_3CO), 3.45 (m, 2 H, CH_2O), 4.91 (m, 1 H, CH); IR (neat) 1735 (C=O) cm^{-1}] and (*S*)-2-acetoxy-1-bromobutane (22.3 g, 91%) [bp 68–70 °C (9 torr); $[\alpha]_D^{22}$ −23.16° (*c* 4.14, ether)]; ^1H NMR and IR spectra were in agreement with those for the *R* enantiomer. Analytical data for both enantiomers agreed with the literature values.[29,30] ^1H NMR spectroscopy indicated that the products contained approximately 7% 1-acetoxy-2-bromobutane.

Conversion of (*R*)- and (*S*)-2-Acetoxy-1-bromobutane to (*R*)- and (*S*)-1-Butene Oxide. Treatment of (*R*)- and (*S*)-2-Acetoxybromobutanes (5 M in dry 1-pentanol) with 1 equiv of 1.18 M $C_5H_{11}OK$ in 1-pentanol (added over 30–60 min at 0 °C) followed by distillation of the product through a 15-cm Vigreaux column equipped with a condenser cooled to −10 °C gave (*R*)-1-butene oxide (5.2 g, 81%) [>98% ee; bp 59–62 °C; $[\alpha]_D^{22}$ +14.80 (*c* 1.18, ether) (lit.[29] $[\alpha]_D^{21}$ +13.6° (*c* 1.135, ether)); ^1H NMR spectrum in agreement with that of 1 obtained from 2-chloro-1-butanol] and (*S*)-1-butene oxide (5.86 g, 71%) [>98% ee; bp 59–62 °C; $[\alpha]^{22}_D$ −12.00° (*c* 4.90, dioxane) (lit.[31] $[\alpha]^{16}_D$ −12.25 (*c* 6, dioxane)); ^1H NMR spectrum in agreement with that for the *S* enantiomer].

Enzymatic Preparation of (*R*)-Butane-1,2-diol. A three-necked, 500-mL, round-bottomed flask was charged with ammonium formate (3.78 g, 60 mmol), 1-hydroxy-2-butanone (4.56 g, 50 mmol), Tris–HCl (47 mg, 0.5 mmol), and 50 mL of water. The pH was adjusted to 7.5 with 1 N KOH. The flask was sealed with septa and fitted with an Ar inlet and outlet, a pH probe, and an inlet for 2.1 N HCl. The solution was degassed by bubbling Ar through it for 1 h and NAD (0.15 mmol) was added. FDH (67 U) and GDH (100 U) immobilized on PAN gel[17] were added as a suspension in 50 mL of H_2O. A pH controller maintained the pH at 7.7 ± 0.1 by adding 2.1 N HCl; Ar bubbled through the reaction. After 14 days, the enzyme-containing gels were removed by centrifugation (51 U of FDH and 44 U of GDH were recovered). The aqueous portion was continuously extracted with ether for 3 days, saturated with K_2CO_3, and extracted with 3 × 100 mL of ether. Concentration of the ethereal portions after drying over K_2CO_3 yielded a pale yellow liquid (3.5 g). Distillation through a short-path column [122–125 °C (30 torr)] yielded the diol (2.84 g, 64%), identified by ^1H NMR spectroscopy.

Conversion of (*R*)-Butane-1,2-diol to (*R*)-1-Butene Oxide. (*R*)-Butane-1,2-diol (from the GDH-catalyzed reaction) was converted to (*R*)-1-butene oxide by the same two-step method used with butane-1,2-diol from the LDH-catalyzed reactions. The yield was 3.90 g (47% from the diol): >98% ee; $[\alpha]_D^{21}$ +13.38° (*c* 1.225, ether).

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Substituent Effects on Rates of Inter- and Intramolecular Cycloaddition Reactions of Isobenzofurans

David Tobia and Bruce Rickborn*

Department of Chemistry, University of California, Santa Barbara, California 93106

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Isobenzofurans appear to be the *most reactive isolable dienes* known, and they exhibit unparalleled versatility in [4 + 2] reactions. Cycloadducts have been formed under relatively mild conditions with dienophiles ranging from the very poor (cyclohexene,[1] ethyl vinyl ether[1]) through common carbonyl-activated olefins (maleic anhydride etc.) to the extremely reactive arynes[2] and benzocyclobutadiene.[3] Recently Wege and Moursounidis[4] have determined that the parent unsubstituted isobenzofuran is ca. 10^6 times more reactive than 1,3-butadiene[5] with maleic anhydride.

Primarily because of advances in methodology, many new substituted isobenzofurans have recently become available. The ability to predict changes in reactivity imposed by substituents can be important in using these materials. Although relative rate data for cycloaddition reactions are not expected to transfer precisely from one dienophile to another, the literature[5] suggests that approximately parallel behavior would be found for similar dienophiles. *N*-Methylmaleimide (NMM) was chosen as a representative common dienophile for the present study. Its advantages are that it gives products cleanly and in high yield, and these materials are not susceptible to facile

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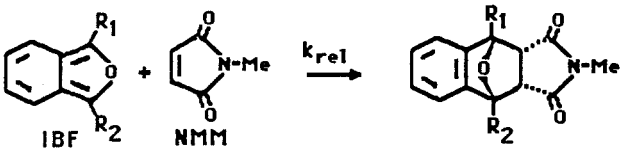
0022-3263/87/1952-2611$01.50/0

Table I



IBF	R_1	R_2	k_{rel}	cycloadduct % endo
1	OEt	H	3.8	>99
2	Me	H	2.2	97
3	*n*-Bu	H	1.8	>97
4	H	H	1	96
5	Ph	H	0.77	>99
6	OEt	$SiMe_3$	0.25	>99
7	Ph	Ph	0.088	>99
8	$SiMe_3$	$SiMe_3$	0.023	>99

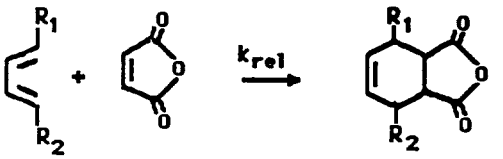
hydrolysis or retro-Diels–Alder reactions. Further, the cycloadditions of NMM with the isobenzofurans examined in this work all exhibited exceptionally high (>96%) endo selectivity, which simplified analysis. Although the *level* of endo selectivity in NMM reactions is unusual, there is no reason to believe that this behavior would obviate comparisons with similar dienophiles, e.g., maleic anhydride or *N*-phenylmaleimide, both of which gave ca. 3/1 endo/exo selectivity with isobenzofuran itself.

Relative rates were obtained by the competition kinetics technique. Two isobenzofurans (ca. 1 equiv each) were allowed to vie for reaction with a limited amount (<1 equiv) of NMM at ca. 25 °C. The results are displayed in Table I.[6]

The reactions examined in this manner span a range of ca. 10^2 in relaive rate, with some derivatives more and some less reactive than the parent isobenzofuran (**4**). Of particular interest is the observation that **4** is 12 times more reactive than the commercially available and frequently used 1,3-diphenylisobenzofuran (**7**). In the only other comparison of these two materials in the literature, **7** was conversely found to be approximately 10 times more reactive than **4** with singlet oxygen.[7] However, as Clennan has shown,[8] the mechanism of singlet oxygen reactions with furans is complex and presumably not representative of typical [4 + 2] cycloadditions.

In general, the substituent effects shown in Table I are unexceptional in direction and magnitude for a normal electron demand diene component in Diels–Alder reactions. However, a more striking feature becomes evident when the Table I data are compared with the relative rates of cycloaddition of substituted 1,3-butadienes with maleic anhydride (at 30 °C). These values, taken from the review by Sauer and Sustmann,[5] are displayed in Table II. Two different dienophiles are involved in this comparison, but as already noted, this is not expected to cause large distortions in relative rates. The similarities in substituent effects are indeed remarkable in light of the ca. 10^6 difference in diene reactivity between isobenzofuran and butadiene.

Table II



1,3-butadiene R_1	1,3-butadiene R_2	k_{rel}[5]
OMe	H	12.4
Me	H	3.3
Ph	H	1.6
H	H	1
Ph	Ph	0.043

Some 1-arylisobenzofurans have been generated and used as reactive intermediates, but the isolation of 1-phenylisobenzofuran (**5**) has only recently been described.[9] Like the unsubstituted parent, **5** clearly lacks the shelf stability of **7**, but its reactivity is otherwise not well characterized. This study shows that **5** is only slightly less reactive than **4**, while the second phenyl substituent (in **7**) leads to significant depression in the rate of cycloaddition with NMM. Similar behavior is found for the analogous 1,3-butadienes and maleic anhydride listed in Table II, although the first phenyl substituent slightly enhances the rate in this instance.

It has previously been estimated that 1-methylisobenzofuran (**2**) is ca. 1.3 times as reactive as **4** when norbornene is employed as the dienophile.[10] A similar order of reactivity is maintained with the much more reactive dienophile NMM. Although the relative rate parallel is not exact, it is again the similarity rather than the difference which is noteworthy, given the large change in dienophile activity between NMM and norbornene (no direct comparison has been made, but maleic anhydride[4] is estimated to be ca. 4×10^6 more reactive than norbornene[10] with isobenzofuran).

1-Ethoxyisobenzofuran (**1**) appears to be the most reactive isolable [4 + 2] diene component prepared[11] to date. It is likely that the 1-(diisopropylamino)isobenzofuran recently described by Beak[12] would be even more reactive, but it has been generated only as an intermediate, under conditions not amenable to kinetic examination. Of course, *o*-xylylenes are more reactive than isobenzofurans but not isolable in the usual sense of this word.

The least reactive material studied is 1,3-bis(trimethylsilyl)isobenzofuran (**8**), which has proven to be a valuable substrate for trapping very reactive dienophiles such as arynes.[2c-h] Data are not available for quantitative comparison with the 1,3-butadiene analogue, but Fleming and co-workers have concluded that 1-(trimethylsilyl)-1,3-butadiene is less reactive than the unsubstituted parent.[13] The rate of the unsymmetrically disubstituted isobenzofuran **6** is explicable in terms of a modest rate enhancement caused by the 1-ethoxy substituent being more than offset by a larger rate depression caused by the 3-trimethylsilyl group.

Several interesting kinetic features emerge from the reactions of the ketal **9**, as outlined in Scheme I. The

(6) Isobenzofuran and many of its derivatives polymerize readily when concentrated or isolated neat. It was necessary to assume a (quantitative) yield in one or more preparative steps to obtain a value for the concentration of starting isobenzofuran in most cases. The validity of this assumption is bolstered by the high yields of cycloadducts formed in many related reactions, and the complete consumption of NMM also reinforces this conclusion. Error in this assumption will affect the relative rates only to the extent that *different* yields (initial concentrations) are involved for the two isobenzofurans paired in a given experiment.

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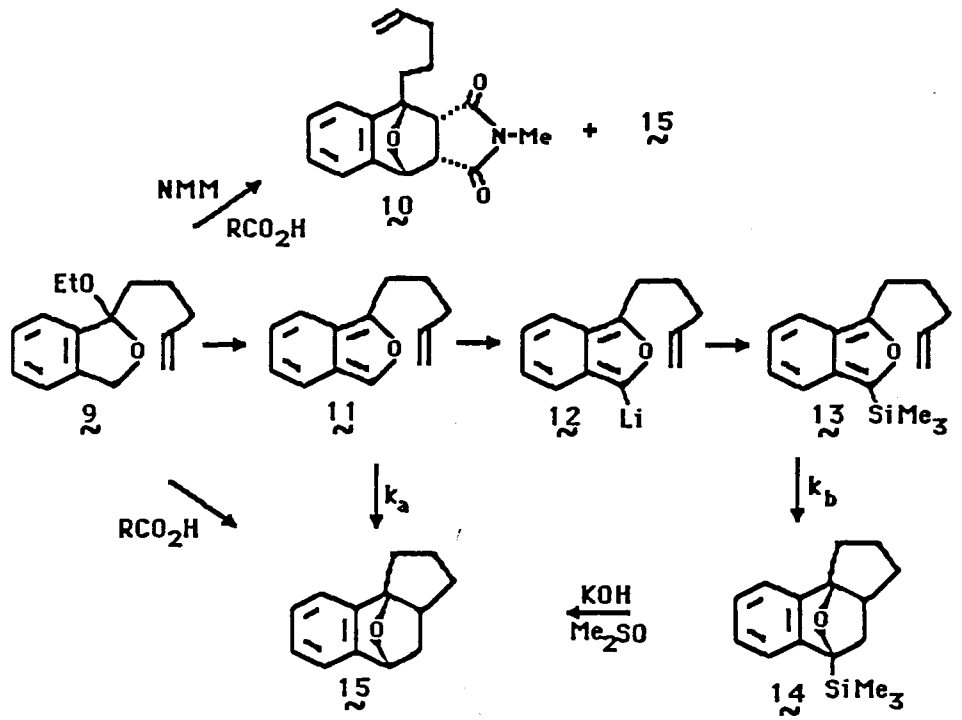
Scheme I



simple double bond which serves as the dienophile for intramolecular Diels–Alder reaction is poorly activated for this purpose, and the advantages of intramolecularity can be readily overcome by a second-order intermolecular process given a suitable concentration of a more reactive dienophile.

This is illustrated by the reactions of **9** in the absence and presence of NMM. Treatment of **9** with mesitoic acid catalyst[1] in refluxing $CHCl_3$ gave a single cycloadduct **15** in essentially quantitative yield. Although the stereochemistry of **15** has not been determined, Friedrichsen and co-workers[14] have recently shown that a similar intramolecular cycloadduct is formed with exclusive exo orientation. Repetition of the acid-catalyzed reaction of **9** (initial concentration = 0.30 M) in the presence of NMM (initial concentration = 0.31 M) gave the intermolecular cycloadduct **10** as the major product, accompanied by some **15** (**10**/**15** = 93/7 in this experiment). That this ratio results from kinetically controlled competition between intra- and intermolecular processes was shown by heating an isolated sample of **10** (131 °C, 24 h). No change was detected, and specifically no indication of formation of **15** was found. This shows that the NMM cycloadduct **10** does not undergo measurable retro-Diels–Alder reaction at the temperatures employed in this study.

The base-induced reactions of ketal **9** gave especially interesting results. A solution of 1-(4-pentenyl)isobenzofuran (**11**) was formed by treatment of **9** with excess MeLi and catalytic LDA, followed by destruction of excess strong bases through the addition of *tert*-butyl alcohol. Direct examination of the ^1H NMR spectrum of the resultant ethereal solution of **11** exhibited the expected singlet for the furan proton, and the loss of this signal over time gave the rate constant, $k_a = 1.3 \times 10^{-3}$ s^{-1} (ca. 32 °C), for the intramolecular cycloaddition of **11** to **15**. This reaction is quite rapid, with a half-life of just a few minutes at this probe temperature. In order to gather the rate data, it was necessary to obtain NMR spectra immediately *after the addition of tert-butyl alcohol.* Very interestingly, the lithiated isobenzofuran **12** appears to be stable toward cycloaddition, and in effect the lithium atom serves as a protecting group to prevent Diels–Alder reaction, at least over the time span examined. While the exact cause of this behavior is not known, cycloaddition would require conversion of a basic compound (the lithioisobenzofuran) to a much stronger base (the bridgehead lithiated cycloadduct), and this pK_a factor may inhibit reaction. Although not necessarily related, this observation is also reminiscent of unsuccessful attempts to obtain cycloadducts from arynes with furans and isobenzofurans under strongly basic conditions.[2a,c]

Addition of Me_3SiCl to the solution of **12** gave 1-(4-pentenyl)-3-(trimethylsilyl)isobenzofuran (**13**). The disappearance of this material was also followed by NMR (see Experimental Section), and the rate constant, $k_b = 1.4 \times 10^{-4}$ s^{-1} (ca. 32 °C), was obtained for the conversion of **13** to cycloadduct **14**. Thus the Me_3Si substituent depresses the rate of the intramolecular cycloaddition by approximately an order of magnitude relative to the unsubstituted **11**, a result in keeping with the relative rates given in Table I. The proof of structure of **14** in part rests on its facile protiodesilylation (KOH/Me_2SO)[2c] to form **15**, as shown in Scheme I.

When **14** is formed in the manner just described, it is contaminated with **15**, formed by intramolecular cycloaddition of **11**; this process apparently occurs in competition with the second order lithiation of **11** to form **12**. In a typical experiment, the ratio of **14**/**15** was 73/27. It should be possible to exercise some control over this ratio by altering the concentration of base employed, although this feature was not examined. Instead, an effort to circumvent the early closure reaction was made by adding **9** to a mixture of lithium tetramethylpiperidide (LTMP) and Me_3SiCl.[15] This was only partially successful, giving **14**/**15** in a ratio of 82/18, even though a relatively large excess of LTMP had been employed. The intramolecular

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Diels–Alder reaction of **11** is thus competitive with the rapid but second-order deprotonation reactions of the isobenzofuran, for both MeLi/LDA and LTMP.

Experimental Section

Commercial 1,3-diphenylisobenzofuran (**7**) was used as received. Other isobenzofurans were formed in ether solution by treatment of the appropriate acetal or ketal with MeLi and a catalytic amount of lithium diisopropylamide, as already described for **1**,[11] **4**,[10] **6**,[2g] and **8**.[2c] The method developed for the preparation of **9** and similar ketal precursors for isobenzofurans **2**, **3**, and **5** will be presented in a later publication. *N*-Methylmaleimide (NMM) was prepared by the method of Mehta et al.[16] NMR spectra were recorded on Varian EM-360A (in ether solvent) and/or Nicolet NT-300 instruments; products were characterized on the latter, in $CDCl_3$ solvent. MS data were obtained on a VG 70-250 instrument by Dr. Hugh Webb. Combustion analyses were performed by MicAnal, Tucson, AZ.

Competition Kinetics. Approximately equimolar mixtures of the following pairs of isobenzofurans were prepared, either by separate reactions following by mixing, or by simultaneous treatment of both precursors: **1** + **4**; **2** + **4**; **3** + **4**; **4** + **5**; **4** + **6**; **4** + **7**; **4** + **8**; **7** + **8**. The assumption was made that the yields of both isobenzofurans were identical (quantitative); error is introduced to the extent that the yields in any given pair are different, but separate control experiments support the view that yields are high in all cases.[6] This assumption was also checked by direct examination of the ^1H NMR spectra of the ethereal solutions of **2** + **4**, **3** + **4**, and **4** + **5**; the ratio of furan proton singlet integrals gave an independent measure, which supported the conclusion that equal yields were obtained. The preparations were carried out under an inert atmosphere, and the isobenzofuran solutions were either washed with saturated NaCl solution or treated with *tert*-butyl alcohol (for 1-ethoxyisobenzofurans **1** and **6**) to destroy strong bases. NMM was then added (ca. 0.25 equiv per equiv of total isobenzofuran, at 25 °C), the solvent was evaporated, and the crude product mixture was analyzed by NMR. The cycloaddition reactions are rapid, complete (no residual NMM), and irreversible. The ratio of products was determined by integration of the N–Me absorptions, which were identified by comparison with the spectra of samples prepared separately from the individual isobenzofurans. Relative rates were calculated from the relationship $k_1/k_2 = \ln([1]_t/[1]_0)/\ln([2]_t/[2]_0)$, where **1** and **2** represent two starting materials with concentrations determined initially (0) and at the conclusion of the reaction (t).

The endo NMM cycloadducts of **2** and **5** have been previously characterized.[9]

The new cycloadducts of the various isobenzofurans and NMM had the following characteristics.

***endo*-4,9-Epoxy-4-ethoxy-2-methyl-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione** (from **1**): mp 111–113 °C; ^1H NMR δ 1.39 (t, 3 H, J = 7 Hz), 2.26 (s, 3 H), 3.58 (d, 1 H, J = 8 Hz), 3.85–3.96 (m, 2 H), 3.98–4.09 (m, 1 H), 5.56 (d, 1 H, J = 6 Hz), and 7.23–7.32 (m, 4 H). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53. Found: C, 66.06; H, 5.46.

***exo*-2,4-Dimethyl-4,9-epoxy-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione** (from **2**): mp 175–176.5 °C; ^1H NMR δ 1.95 (s, 3 H), 2.78 (d, 1 H, J = 7 Hz), 3.03 (s, 3 H), 3.05 (d, 1 H, J = 7 Hz), 5.61 (s, 1 H), 7.24–7.27 (m, 3 H), and 7.32–7.36 (m, 1 H); MS, calcd for $C_{14}H_{13}NO_3$ 243.0933 found 243.0914.

***endo*-4-(1-Butyl)-4,9-epoxy-2-methyl-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione** (from **3**): mp 105–106 °C; ^1H NMR δ 0.96 (t, 3 H, J = 7 Hz), 1.39–1.62 (m, 4 H), 2.24 (s, 3 H), 2.24–2.36 (m, 1 H), 2.46–2.59 (m, 1 H), 3.37 (d, 1 H, J = 8 Hz), 3.80 (dd, 1 H, J = 8 and 6 Hz), 5.63 (d, 1 H, J = 6 Hz), 7.12–7.16 (m, 1 H), and 7.19–7.27 (m, 3 H). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.43; H, 6.73.

***endo*-4,9-Epoxy-2-methyl-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione** (from **4**): mp 190–192 °C; the ^1H NMR spectrum of product prior to recrystallization was identical with that shown by Warrener,[17] including minor absorptions due to the small amount of exo isomer that is also formed in this reaction.

***endo*-4,9-Epoxy-4-ethoxy-2-methyl-3a,4,9,9a-tetrahydro-9-(trimethylsilyl)-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione** (from **6**): mp 153–155 °C; ^1H NMR δ 0.36 (s, 9 H), 1.38 (t, 3 H, J = 7 Hz), 2.23 (s, 3 H), 3.53 (d, 1 H, J = 8 Hz), 3.73 (d, 1 H, J = 8 Hz), 3.85–4.06 (m, 2 H), and 7.13–7.29 (m, 4 H). Anal. Calcd for $C_{18}H_{23}NO_4Si$: C, 62.58; H, 6.71. Found: C, 62.59; H, 6.69.

***endo*-4,9-Diphenyl-4,9-epoxy-2-methyl-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione** (from **7**): mp 224–225.5 °C; ^1H NMR δ 2.40 (s, 3 H), 4.07 (s, 2 H), 6.94–6.98 (m, 2 H), 7.14–7.18 (m, 2 H), 7.42–7.55 (m, 6 H), and 8.01–8.05 (m, 4 H). Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02. Found: C, 78.34; H, 4.75. The endo stereochemical assignment in this instance is based on δ 2.4 for the NMe group, which is characteristic of the other endo adducts examined; this absorption occurs at $\geq$3.0 ppm in related exo isomers.

***endo*-4,9-Bis(trimethylsilyl)-4,9-epoxy-2-methyl-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione** (from **8**): mp 172–173 °C; ^1H NMR δ 0.32 (s, 18 H), 2.20 (s, 3 H), 3.49 (s, 2 H), and 7.08–7.17 (m, 4 H). Anal. Calcd for $C_{19}H_{27}NO_3Si_2$: C, 61.08; H, 7.28. Found: C, 60.72; H, 7.36. The endo stereochemical assignment was confirmed by protiodesilylation (treatment with tetrabutylammonium fluoride in THF[2c]), which yielded the endo derivative of **4** described above.

5,9b-Epoxy-2,3,3a,4,5,9b-hexahydrobenz[*e*]indene (15). A mixture of 275 mg (1.2 mmol) of the ketal **9** and 22 mg (0.13 mmol) of mesitoic acid in 3 mL of $CHCl_3$ was refluxed for 19 h. Rotary evaporation of the solvent followed by silica gel chromatography (20% Et_2O/hexanes) gave 212 mg (95%) of **15** as a pale yellow oil. Distillation [bp 83 °C (0.02 Torr)] returned 172 mg (77%) of pure **15** as a colorless oil: ^1H NMR δ 1.50–1.70 (m, 2 H), 1.80–2.20 (m, 6 H), 2.38–2.52 (m, 1 H), 5.36 (d, 1 H, J = 5 Hz), and 7.10–7.25 (m, 4 H). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.45; H, 7.67.

***endo*-4,9-Epoxy-2-methyl-4-(4-pentenyl)-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (10).** A mixture of **9** (189 mg, 0.813 mmol), NMM (102 mg, 0.921 mmol), and mesitoic acid (14.8 mg, 0.090 mmol) in 3 mL of $CHCl_3$ was refluxed for 16 h (the reaction appeared to be complete after 6 h). Rotary evaporation and silica gel chromatography (graded elution, pentane to Et_2O) afforded 186 mg (77%) of pure **10** and 9 mg (6%) of the intramolecular cycloadduct **15**. **10** had mp 109–110 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 1.60–1.74 (m, 2 H), 2.15–2.40 (m, 3 H), 2.23 (s, 3 H), 2.48–2.62 (m, 1 H), 3.37 (d, 1 H, J = 8 Hz), 3.80 (dd, 1 H, J = 8 and 6 Hz), 4.97–5.11 (m, 2 H), 5.63 (d, 1 H, J = 6 Hz), 5.76–5.92 (m, 1 H), 7.12–7.16 (m, 1 H), and 7.19–7.27 (m, 3 H). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44. Found: C, 72.68; H, 6.60.

5,9b-Epoxy-2,3,3a,4,5,9b-hexahydro-5-(trimethylsilyl)-benz[*e*]indene (14). A solution of **9** (150 mg, 0.64 mmol) and 11 μL of diisopropylamine in 1 mL of ether was treated with 1.94 mmol (1.35 mL of ethereal solution) of MeLi. This homogeneous solution was stirred for 0.3 h, and then 0.25 mL (1.94 mmol) of Me_3SiCl was added (precipitate formed). The resulting slurry was stirred overnight, then washed with brine, dried over K_2CO_3, and rotary evaporated to give 159 mg of crude product as an oil. Chromatography (silica gel, 10% Et_2O/hexanes) afforded 79 mg (48%) of **14** and 22 mg (18%) of **15**. Essentially pure **14** was an oil: ^1H NMR δ 0.24 (s, 9 H), 1.42–1.60 (m, 2 H), 1.78–2.20 (m, 6 H), 2.37–2.48 (m, 1 H), and 7.09–7.20 (m, 4 H); MS, calcd for $C_{16}H_{22}OSi$ 258.1436, found 258.1438.

A sample of **14** (43 mg, 0.17 mmol) was added to ca. 150 mg of crushed KOH pellets in 1.5 mL of Me_2SO, with stirring for 2 h. This mixture was taken up in water, and the product was extracted into CH_2Cl_2. The usual washing, drying, and evaporation gave 19 mg (61%) of essentially pure **15**, as shown by its NMR spectrum.

In a separate experiment, a solution of LTMP (2.2 mmol) and Me_3SiCl (2.2 mmol) was rapidly added to **9** (167 mg, 0.72 mmol) in ether (total volume ca. 3.2 mL). The ^1H NMR spectrum of this ethereal solution indicated that **9** had been consumed within 15 min, leading to a mixture consisting of cycloadduct(s) and the

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silylated isobenzofuran 13, with little if any unsilylated 11 present. The conversion of 13 (m at δ 6.7–6.9, 2 H) to 14 (a single sharper downfield absorption, 4 H) was monitored by NMR and judged to be complete in ca. 6 h. Workup and chromatography as before gave 96 mg (52%) of 14 and 14 mg (11%) of 15.

Rate Constants for Intramolecular Cycloadditions. Two separate reactions were carried out in which solutions of 9 in ether were treated with 0.1 equiv of diisopropylamine followed by 2.4 equiv of MeLi. The concentration of 9 after addition of these reagents was 0.24 M.

In the first run, an aliquot examined by NMR after 15 min exhibited a pattern in the aromatic region attributed to cycloadduct 15 (ca. 38%) and lithiated isobenzofuran 12 (62%). After 37 min, *tert*-butyl alcohol was added, and this caused the appearance of a singlet at δ 7.9, the furan proton of 11. This signal disappeared with a half-life of ca. 9 min, corresponding to a rate constant (11 → 15) of $k_a = 1.3 \times 10^{-3}$ s^{-1} (ca. 32 °C). This experiment was repeated to confirm the stability of 12. Substrate 9 was added to MeLi (4.5 equiv)/LDA (0.1 equiv), and no change in the NMR spectrum of 12 was observed over a period of 3 h. Addition of *tert*-butyl alcohol gave 11 as before.

In the second reaction, the solution of 12 (m at δ 6.3–6.45, 2 H) was allowed to stand for 0.5 h (no change in the spectrum was seen), before being treated with 2.4 equiv of Me_3SiCl. This gave a spectrum attributed to a mixture of 15 and the silylated isobenzofuran 13; the m at δ 6.7–6.9 for the latter was integrated vs. total aromatic absorption to obtain the rate constant for the process (13 → 14), $k_b = 1.4 \times 10^{-4}$ s^{-1} (ca. 32 °C). Repetition of this experiment at a controlled NMR probe temperature gave $k_b = 6.5 \times 10^{-5}$ s^{-1} (25 °C).

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A New Synthetic Approach to 1-(Hydroxymethyl)-8-methoxy-1,2,3,4-tetrahydroisoquinolin-4-one

Robert M. Williams,*† Paul P. Ehrlich, Weixu Zhai, and James Hendrix

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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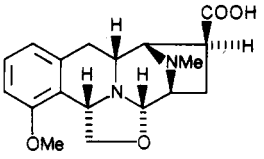
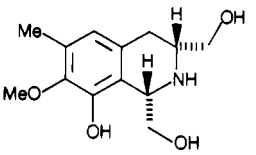
The tetrahydroisoquinoline moiety occurs as the structural nucleus of a wide variety of naturally occurring alkaloids.[1] As a result, numerous methods[2] have been developed and employed in the construction of natural alkaloids constituted of this ring system. Perhaps the most widely used synthetic construction is the classic Pictet–Spengler isoquinoline synthesis,[1] which involves the condensation of β-arylethylamines and carbonyl compounds. Cyclization occurs via the intermediacy of the putative Schiff base, furnishing the tetrahydroisoquinoline. The related Bischler–Napieralski reaction furnishes the corresponding 3,4-dihydroisoquinolines through an electronically similar electrophilic aromatic substitution. In both instances, rate-accelerating electron-releasing substituents generally induce cyclization to occur (ortho/para) at the less hindered (para) position to a significant extent. In the case of a *m*-methoxy-substituted β-arylamine, cyclization occurs to give the 6-methoxy regioisomer as the major and, often times, exclusive product.[1]

As part of a program to construct and study the rare tetrahydroisoquinoline antitumor alkaloid quinocarcin (DC-52, 1)[3] and the β-adrenergic receptor antagonist MY



1, quinocarcin



2, MY 336-a

336-a,[4] we needed a reliable and unambiguous synthetic protocol that would embrace the 8-oxygenated 1,2,3,4-tetrahydroisoquinoline nucleus.[5] Our approach is related to the classic Pomeranz–Fritsch reactions, wherein an appropriately substituted benzylic amine serves as the template for the penultimate C-4a/C-4 bond construction.[6]

2-Bromoanisole is lithiated (*n*-BuLi, THF) and condensed with the *N*-methoxy-*N*-methylamide[7] of (benzyloxy)acetic acid[8] (4) to furnish the ketone 5 in 90% yield (Scheme I). This coupling proved to be significantly superior to condensations of 3 with (benzyloxy)acetyl chloride,[8] the corresponding tertiary alcohol resulting from further reaction of 5 and 3 being the predominant product. However, preparatively useful quantities of 5 could also be obtained by coupling (benzyloxy)acetyl chloride and 3 in the presence of $CdCl_2$.[9]

Reductive amination of the ketone using the Borch[10] procedure (65%) followed by hydrogenolytic removal of the benzyl ether furnished the amino alcohol 7 (81%). Alkylation of the amine with ethyl bromoacetate (8; 95%) and formation of the cyclic urethane furnished the ethyl ester 9 (77%). Selective basic hydrolysis of the ethyl ester furnished the crystalline acid (75%; mp 165–166 °C), which was converted to the acid chloride with thionyl chloride. The crucial intramolecular Friedel–Crafts acylation proved to be extremely difficult and required extensive experimentation. Low yields (<10%) were obtained under classical conditions (hot CS_2, $AlCl_3$), but eventually the conditions reported by Uggeri[11] ($AlCl_3$, $Cl_2CH_2CH_2Cl_2$, 25

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