69 (40); exact mass calcd for $C_{16}H_{23}NS$ 261.1581, found 261.1578.

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Registry No. 1, 56012-88-5; 2, 53822-96-1; 3, 53822-97-2; (±)-4, 127516-52-3; (±)-5, 127516-53-4; (±)-6, 127516-54-5; (±)-7, 139017-42-8; (±)-8, 139068-72-7; 9, 586-38-9; (±)-11, 114860-79-6; (±)-13, 139068-67-0; (±)-14, 139068-68-1; (±)-15, 139068-69-2; (±)-16, 139017-43-9; (±)-17, 139068-70-5; (±)-18, 139017-44-0; (±)-19, 139017-45-1; (±)-20 (isomer 1), 139017-46-2; (±)-20 (isomer 2), 139068-71-6; (±)-21, 139017-47-3; (±)-23, 139017-48-4; (±)-25, 139017-49-5; (±)-26, 139017-50-8; (±)-27, 139017-51-9; (±)-(*E*)-28, 139017-52-0; (±)-(*Z*)-28, 139017-65-5; 29, 5323-87-5; 30, 22627-45-8; (±)-31, 121363-31-3; (±)-32, 139017-53-1; (±)-33, 139017-54-2; (±)-34, 139017-55-3; (±)-35, 139017-56-4; (±)-36, 139017-57-5; (±)-37, 139017-58-6; (±)-39, 139017-59-7; (±)-40, 139017-60-0; (±)-(*E*)-41, 139017-61-1; (±)-(*Z*)-41, 139017-62-2; (±)-42, 127488-38-4; (±)-43, 127488-39-5; (±)-44, 127488-40-8; (±)-45, 127488-41-9; (±)-46, 127488-50-0; (±)-47, 127488-36-2; (±)-48, 127488-49-7; (±)-49, 127488-37-3; (±)-50, 127488-42-0; (±)-51, 127488-43-1; (±)-52a, 139040-97-4; (±)-52b, 139017-63-3; (±)-52c, 139017-64-4; (±)-52d, 106536-89-4; (±)-53, 127488-44-2; (±)-54, 127488-45-3; (±)-55, 127488-46-4; (±)-56, 127488-47-5; (±)-57, 127488-48-6; $(CH_3)_3SiCH_2CO_2Bu$-*t*, 41108-81-0.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for selected compounds, crystallographic data for compound 36, and experimental procedures for reactions presented in Schemes II and III (70 pages). Ordering information is given on any current masthead page.

A New Synthesis of Phthalides by Internal Trapping in Ortho-Lithiated Carbamates Derived from Benzylic Alcohols†

M. Rita Paleo, Carlos Lamas, Luis Castedo,* and Domingo Domínguez

Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago y Sección de Alcaloides del CSIC, 15706 Santiago de Compostela, Spain

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The addition of *t*-BuLi to a low-temperature THF solution of *o*-bromocarbamates **2** leads to *ortho*-lithiated intermediates **3**, in which internal trapping by the electrophile on the side chain then takes place. This novel Parham-type anionic cyclization procedure affords the variously substituted phthalides **5** in high yields and can also be used for the preparation of lactones **8**, which are useful for the synthesis of aristocularine alkaloids.

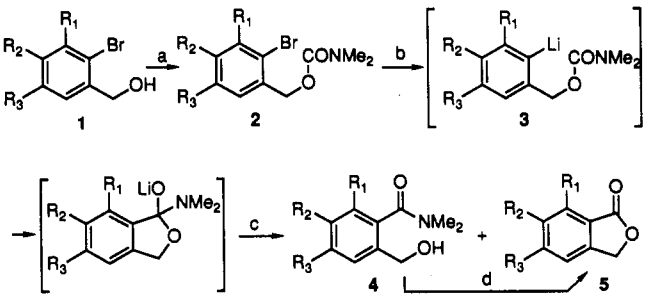
Introduction

Phthalides are versatile starting materials for the synthesis of a variety of structures. Carbanions derived from proton abstraction at the benzylic position have received considerable attention during the last decade as useful 1,4-dipole synthetic equivalents[1] for the preparation of linear and angular polycyclic aromatic systems[2] and some pharmacologically interesting isoquinoline alkaloids.[3] On the other hand, the electrophilic nature of the carbonyl of 3-halogenophthalides has been exploited by us for the assembly of isoindoloisoquinolines and benzo[*b*]-phenanthridines.[4] Phthalides are also appropriate precursors for isobenzofurans, which are highly reactive species, in synthetically useful cycloaddition reactions.[5]

Classical methods for the preparation of phthalides depend on the chloromethylation of benzoic acids, but they usually give low yields and are not suitable for the regioselective preparation of substituted phthalides.[6] More recent syntheses are based on transition-metal-catalyzed carbonylation of ortho-substituted benzyl alcohols,[7] cyanation of *o*-halogenobenzyl alcohols,[8] or metalation–carboxylation of *m*-alkoxybenzyl derivatives. The latter strategy is based on the ortho-directing effect of alkoxy substituents[9] and is thus only suitable for the synthesis of 7-alkoxyphthalides, which are obtained in moderate yields.[10] Other routes based on ortho-lithiated aromatic derivatives of benzamides,[11] oxazolines,[12] or benzaldehydes[13] have also been reported.[14]

In this paper, we describe a new method by which a variety of phthalides can be obtained by lithium–halogen interchange followed by internal trapping from carbamates derived from *o*-bromobenzylic alcohols.

Scheme I[a]



[a] Reagents and conditions: (a) DMF, NaH, *N*,*N*-dimethylcarbamoyl chloride; (b) THF, *t*-BuLi, −95 °C; (c) MeOH, −95 °C to rt; (d) MeOH, rt or TFA, rt.

† Dedicated to Prof. M. P. Cava on the occasion of his 65th birthday.

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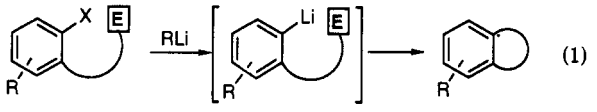
Table I. Preparation of Phthalides 5 from Carbamates 2 (Scheme I)

2	R_1	R_2	R_3	equiv of t-BuLi	% yield of 5[a]
a	H	OMe	OMe	1.1	93 (20)
b	H	OCH_2O		2.0	82 (12)
c	H	OCH_2Ph	OMe	1.5	85 (24)
d	H	OMe	OCH_2Ph	1.5	85 (24)
e	OMe	OMe	H	1.1	86 (36)[b]
f	$OCONMc_2$	OMe	H	2.0	78 (24)[b]
g	OMe	OMe	OMe	1.5	94 (36)[b]

[a] Yields after quenching with anhydrous methanol at the reaction temperature followed by stirring at room temperature for the time (h) specified in parentheses. [b] Addition of trifluoroacetic acid and stirring at room temperature were needed to completely transform the hydroxyamide 4 to its corresponding phthalide.

Results and Discussion

Our synthesis is based on Parham's "direct" protocol for annulations, in which an ortho-lithiated aromatic cyclizes by reaction with an electrophile present on the side chain (eq 1).[15] For this approach to be successful the electro-



(1)

phile must be resistant to the lithiation conditions but reactive enough for the subsequent intramolecular nucleophilic attack in the cyclization step. Such anionic aromatic annulations were first carried out on β-(o-bromophenyl)propanoic acid and its diisopropylamide to give 1-indanone in 76% and 61% yields, respectively,[16] and later extended to other (o-bromophenyl)alkanoic acids.[17] Besides the carboxyl and N,N-dialkylcarboxamide groups, other electrophiles such as epoxide,[18] bromo,[19] aldimino[20] and imide[21] groups have successfully been used for cyclization.

We report here a new synthesis of phthalides 5 (Scheme I) in which the lactone ring is assembled by lithium–halogen exchange in a bromo derivative 2 followed by Parham type cyclization of the lithiated intermediate 3, with the carbamate acting as the internal electrophile. The required substrates were prepared from commercially available aldehydes, which were readily converted to o-bromobenzyl alcohols 1 and then quantitatively transformed into the desired carbamates 2 by reaction with N,N-dimethylcarbamoyl chloride.

We first studied the dimethoxy derivative **2a**, which was converted to the reactive intermediate **3a** by treatment of a THF solution at −95 °C with 1.1 equiv of t-BuLi (1.7 M solution in pentane) added dropwise. A few minutes after the addition of t-BuLi the reaction mixture was quenched by anhydrous methanol, taken out of the cooling bath, and stirred at rt for 8 h. After workup, the crude product was shown by integration of NMR signals to be a 3:1 mixture of compound **4a** and lactone **5a**. When in the above experiment the quenched mixture was stirred for a longer period of time (14 h) the product ratio was 1:7 in favor of the lactone, and with 20 h of stirring the phthalide **5a** could be isolated in 93% yield (Table I). It is interesting to note that only 1.1 equiv of t-BuLi was needed in the metalation step and that no protonated derivative of **3a** was observed, showing that internal trapping in the lithiated intermediate **3a** was fast enough to prevent its reaction with the t-BuBr produced in the exchange reaction. Note also that reaction of the tertiary bromide with t-BuLi[22] is in this case not competitive with the very fast metal–halogen exchange between t-BuLi and the aryl bromide **2a**; this makes a second equivalent of metalating agent unnecessary.[23]

In contrast with the above, the slow addition of 1.1 equiv of t-BuLi to the carbamate **2b** at −95 °C, followed by the usual MeOH treatment and chromatography, led to an inseparable mixture of lactone **5b**, starting material, and the debrominated derivative of the latter in an approximate ratio of 6:3:1, as determined by NMR integration. The presence of the debrominated compound shows that trapping of the aryllithio derivative **3b** is slower than in **3a**, due probably to the strain which is developed during the closure of a new ring fused to an aromatic ring that already contributes to an adjoining ring completed by the methylenedioxy group; **3b** is thus partially protonated by the t-BuBr generated. The unchanged starting material is the result of partial consumption of the metalating agent by the competitive reaction between t-BuLi and t-BuBr, which may indicate slower metal–halogen interchange than in **2a**. In keeping with these assumptions, the use of 1.3 equiv of t-BuLi led to an improved ratio of products (6:1:1), with less starting bromide remaining, while addition of 2 equiv of t-BuLi gave only lactone **5b** (82% isolated yield). Under the latter conditions the excess t-BuLi consumes all the t-BuBr, thus preventing it from quenching formation of the aryllithio intermediate.

Starting from carbamates **2c** and **2d**, good yields of the corresponding 5,6-dialkoxyphthalides **5c** and **5d** were obtained by using 1.5 equiv of t-BuLi (Table I).

Similarly, the 6,7-dimethoxyphthalide **5e** was prepared by treatment of **2e** with 1.1 equiv of t-BuLi. In this case, a mixture of **4e** and **5e** was still present even after 48 h of stirring at rt in the presence of methanol. Compound **4e** was finally converted to the desired phthalide by addition of trifluoroacetic acid and further stirring for 2 h. The

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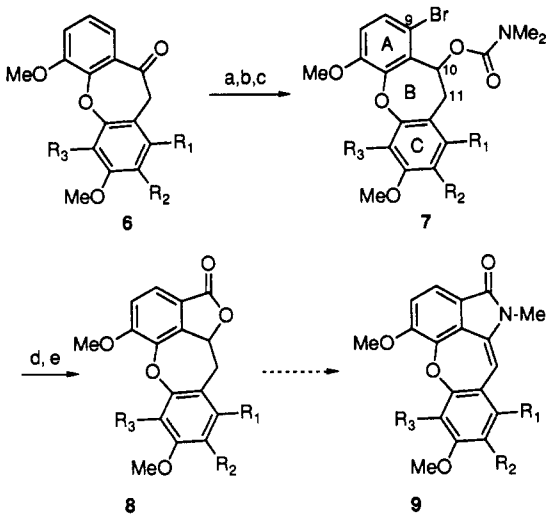
(23) When n-BuLi (1 equiv) was used in place of t-BuLi a very good yield of lactone **5a** was obtained (see ref 35).

Scheme II[a]



a, R_1=R_3=H, R_2=OMe; **b**, R_1=R_2=H, R_3=OMe; **c**, R_1=R_2=Br, R_3=OMe;

[a] Reagents and conditions: (a) $NaBH_4$, methanol; (b) NaH, DMF, $ClCO_2NMe_2$; (c) Br_2, NaOAc, AcOH; (d) *t*-BuLi, THF, −95 °C, 10 min; (e) MeOH.

need of acid to complete the conversion of **4e** can be ascribed to the presence of a substituent ortho to the carboxamide group of **4e**, which slows down the lactonization process.[24] Compound **5f**, in which a second urethane function acts as a protecting group for the phenolic hydroxyl, also formed only slowly in the presence of methanol and required the addition of acid. The intermediate aryllithio derivative **3f** is efficiently captured by the carbamate at the side chain with no interference by the *O*-aryl carbamate, which survives in the reaction conditions.[11b]

The trimethoxyphthalide **5g** was obtained in 94% yield by treatment of carbamate **2g** with 1.5 equiv of *t*-BuLi at −95 °C for 20 min, followed by addition of MeOH and acid and stirring at rt for 36 h.

Having proved the feasibility of the lactonization procedure, we applied it to the preparation of the more complex lactones **8** (Scheme II); these are used as intermediates in the total synthesis of aristocularines **9**,[25] of which aristoyagonine (**9b**) is the only example to date of a natural cularine alkaloid incorporating a five-membered lactam ring.[26]

The precursor for lactone **8a** was prepared from the dibenzoxepinone **6a**[27] by sodium borohydride reduction (93% yield), carbamoylation (89%), and subsequent bromination to give the 9-bromo derivative **7a** selectively in 88% yield. Treatment of this carbamate under the general conditions for cyclization led after workup to a 92% yield of the desired lactone **8a**, which was converted to the nonnatural aristocularine **9a** in a straightforward manner.[25]

The preparation of the isomeric lactone **8b** needed for the synthesis of aristoyagonine met with some difficulties. In this case, attempted bromination at C-9 of the urethane derived from dibenzoxepinone **6b**[27] failed, giving a mixture of compounds with different degrees of bromination, which the use of 3.5 equiv of bromine transformed into the tribromide **7c** (76% yield). The presence of three bromine atoms was not, however, seen as an impediment to lactonization. We reasoned that *t*-BuLi treatment as above would bring about both the metalation of the ring A and the monometalation of the lower ring; the aryllithium on ring A would then be intramolecularly trapped by the carbamate, while the one on ring C was expected to be stable enough to survive at the reaction temperature. The reaction was carried out by treating a 0.015 M THF solution of **7c** at −90 °C with 4 equiv of *t*-BuLi for 10 min, followed by quenching with a few drops of methanol. The reaction mixture was then allowed to warm to rt and worked up to give the fully debrominated lactone **8b** (77% yield). The unexpected complete reduction of ring C is interpreted as the result of protonation of the corresponding aryllithium derivative by the substrate or *t*-BuBr, followed by the fast exchange of the second bromine for Li from *t*-BuLi and subsequent protonation by *t*-BuBr. In order to clarify these points, we carried out the metalation of **7c** followed by quenching with CD_3OD (10 equiv); the resulting lactone **8b** had no deuterium, showing that no lithiated derivatives were present when the quencher was added.[35] The use of more concentrated solutions of **7c** in the lactonization reaction led to lower yields of phthalide **8b** as the result of intermolecular processes involving the ring C aryllithium.

In conclusion, we have developed a high-yielding approach to the synthesis of phthalides which is based on a novel Parham-type cyclization in which a carbamate acts as an internal trap in an ortho-lithiated derivative generated by metal–halogen interchange.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 250 and 62.83 MHz in $CDCl_3$. Mass spectra were recorded at an ionization voltage of 70 eV. Melting points are uncorrected. All air-sensitive reactions were run under dried deoxygenated Ar, in oven-dried glassware, with magnetic stirring; reagents were added by syringe through septa. All solvents for air- or moisture-sensitive reactions were dried by standard procedures.[28] The concentration of commercial solutions of *t*-BuLi in pentane (Aldrich) was determined immediately prior to use by titration with diphenylacetic acid.[29] *N,N*-Dimethylcarbamoyl chloride (Aldrich) was distilled from CaH_2 prior to use.

o-Bromobenzyl alcohols **1a**–**1e** were prepared by $NaBH_4$ reduction in methanol of the corresponding *o*-bromobenzaldehydes: 2-bromo-4,5-dimethoxybenzaldehyde,[30] 2-bromo-4,5-(methylenedioxy)benzaldehyde,[31] 4-(benzyloxy)-2-bromo-5-methoxybenzaldehyde,[32] 5-(benzyloxy)-2-bromo-4-methoxybenzaldehyde,[32] and 2-bromo-3,4-dimethoxybenzaldehyde,[13b] respectively. Compound **1g** was obtained from commercially available 3,4,5-trimethoxybenzaldehyde by $NaBH_4$ reduction followed by bromination with *N*-bromosuccinimide in CCl_4.[10a]

Preparation of Carbamates 2. General Procedure. A 50-mL round-bottomed flask equipped with a stirring bar, septum cap, and Ar inlet was flame-dried under a stream of dry Ar and then cooled to rt. NaH (80% in mineral oil, 60 mmol) was added, washed twice with anhydrous THF, and cooled to 0 °C, and a solution of the benzyl alcohol **1** (20 mmol) in dry DMF (25 mL) was added dropwise. The mixture was stirred until H_2 evolution was complete, and then excess *N,N*-dimethylcarbamoyl chloride (40 mmol, 3.7 mL) was slowly added dropwise with a syringe. The

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resulting suspension was further stirred at rt for 3 h and then cooled to 0 °C. After addition of a few drops of methanol, it was diluted with CH_2Cl_2 (30 mL) and washed with water (4 × 15 mL). The organic extract was dried with anhydrous Na_2SO_4 and the solvent evaporated to leave the carbamate.

1-[(2-Bromo-4,5-dimethoxyphenyl)methoxy]-*N*,*N*-dimethylmethanamide (2a). Recrystallization from hexane–CH_2Cl_2 gave 6.04 g (95%): mp 73–75 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR δ 2.94 (s, 6 H, NMe_2), 3.88 (s, 6 H, 2xOMe), 5.13 (s, 2 H, $ArCH_2O$), 6.97 (s, 1 H, ArH), 7.04 (s, 1 H, ArH); ^{13}C NMR δ 35.60 and 36.12 (NMe_2), 55.75 (OMe), 55.86 (OMe), 66.29 ($ArCH_2$), 113.15, 113.85, 115.37, 127.96, 148.10, 149.23, 156.00 (CO).

1-[[2-Bromo-4,5-(methylenedioxy)phenyl]methoxy]-*N*,*N*-dimethylmethanamide (2b). The crude product was chromatographed on a column of silica gel; elution with CH_2Cl_2 followed by evaporation of solvent gave essentially pure **2b**, which was recrystallized from EtOAc–hexane: yield 5.4 g (90%): mp 76–77 °C; IR (KBr) 1700 cm^{-1}; ^1H NMR δ 2.95 (s, 6 H, NMe_2), 5.10 (s, 2 H, $ArCH_2O$), 5.98 (s, 2 H, OCH_2O), 6.92 (s, 1 H, ArH), 7.02 (s, 1 H, ArH); ^{13}C NMR δ 35.76 and 36.25 (NMe_2), 66.37 ($ArCH_2$), 101.71 (OCH_2O), 109.71, 112.64, 113.95, 129.31, 147.26, 148.04, 156.06 (CO).

1-[[4-(Benzyloxy)-2-bromo-5-methoxyphenyl]methoxy]-*N*,*N*-dimethylmethanamide (2c). Recrystallization from ether–EtOAc–hexane gave 7.7 g (98%): mp 94–96 °C; IR (KBr) 1705 cm^{-1}; ^1H NMR δ 2.94 (s, 6 H, NMe_2), 3.88 (s, 3 H, OMe), 5.12 (s, 4 H), 6.99 (s, 1 H, ArH), 7.09 (s, 1 H, ArH), 7.36–7.43 (m, 5 H); ^{13}C NMR δ 35.89 and 36.31 (NMe_2), 56.15 (OMe), 66.56 ($ArCH_2$), 71.29 ($ArCH_2$), 113.94, 113.99, 118.16, 127.39, 128.08, 128.61, 128.82, 136.41, 148.71, 149.06, 156.29 (CO).

1-[[5-(Benzyloxy)-2-bromo-4-methoxyphenyl]methoxy]-*N*,*N*-dimethylmethanamide (2d). Recrystallization from ether–EtOAc–hexane gave 7.5 g (95%): mp 61–62 °C; IR (KBr) 1705 cm^{-1}; ^1H NMR δ 2.85 and 2.91 (6 H, NMe_2), 3.88 (s, 3 H, OMe), 5.07 (s, 2 H), 5.14 (s, 2 H), 6.96 (s, 1 H, ArH), 7.05 (s, 1 H, ArH), 7.32–7.44 (m, 5 H); ^{13}C NMR δ 35.81 and 36.41 (NMe_2), 56.21 (OMe), 66.39, 71.23, 114.47, 115.90, 116.15, 127.27, 127.93, 128.22, 128.54, 136.71, 147.49, 150.15, 156.22 (CO).

1-[(2-Bromo-3,4-dimethoxyphenyl)methoxy]-*N*,*N*-dimethylmethanamide (2e). Purified by column chromatography on silica gel [CH_2Cl_2–MeOH (1%)] and recrystallized from hexane–CH_2Cl_2: yield 5.4 g (85%); mp 44–46 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR δ 2.93 (s, 6 H, NMe_2), 3.86 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 5.14 (s, 2 H, $ArCH_2O$), 6.86 (d, J = 8.5 Hz, 1 H, ArH), 7.15 (d, J = 8.5 Hz, 1 H, ArH); ^{13}C NMR δ 35.44 and 35.94 (NMe_2), 55.59 (OMe), 59.89 (OMe), 66.17 ($ArCH_2$), 110.68, 118.91, 124.91, 128.71, 146.21, 153.04, 155.83 (CO).

1-[[2-Bromo-4-methoxy-3-[(*N*,*N*-dimethylcarbamoyl)oxy]phenyl]methoxy]-*N*,*N*-dimethylmethanamide (2f). A solution in DMF (4 mL) of 2-bromo-3-hydroxy-4-methoxybenzyl alcohol (0.5 g, 2.14 mmol), obtained by $NaBH_4$ reduction of the corresponding benzaldehyde,[33] was treated with NaH (0.26 g, 8.6 mmol) and *N*,*N*-dimethylcarbamoyl chloride (0.6 mL, 6.42 mmol) as above and stirred at rt for 48 h. The product was recrystallized from ether–hexane–EtOAc (0.74 g, 92%): mp 88–91 °C; IR (KBr) 1705, 1735 cm^{-1}; ^1H NMR δ 2.91 (s, 6 H, NMe_2), 3.02 and 3.16 (s each, 6 H, NMe_2), 3.82 (s, 3 H, OMe), 5.15 (s, 2 H, $ArCH_2O$), 6.89 (d, J = 8.5 Hz, 1 H, ArH), 7.25 (d, J = 8.5 Hz, 1 H, ArH); ^{13}C NMR δ 35.73, 36.13, 36.36 and 36.62 (NMe_2), 56.07 (OMe), 66.26 ($ArCH_2O$), 110.66, 119.45, 127.22, 128.64, 138.51, 152.79, 153.12, 156.06.

1-[(2-Bromo-3,4,5-trimethoxyphenyl)methoxy]-*N*,*N*-dimethylmethanamide (2g). Obtained as an oil in quantitative yield: IR (NaCl) 1710 cm^{-1}; ^1H NMR δ 2.94 (s, 6 H, NMe_2), 3.85 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 5.14 (s, 2 H, $ArCH_2$), 6.80 (s, 1 H, ArH); ^{13}C NMR δ 35.69 and 36.19 (NMe_2), 55.89 (OMe), 60.67 (OMe), 60.75 (OMe), 66.49 ($ArCH_2$), 108.84, 109.63, 131.50, 142.76, 150.83, 152.50, 155.97 (CO).

2,3,6-Trimethoxy-10-[(*N*,*N*-dimethylcarbamoyl)oxy]-10,11-dihydrodibenz[*b*,*f*]oxepine. The alcohol derived from $NaBH_4$ reduction of dibenzoxepinone **6a**[27] was treated with *N*,*N*-dimethylcarbamoyl chloride as indicated in the general procedure, giving the title carbamate as an oil in 89% yield: IR (NaCl) 1710 cm^{-1}; ^1H NMR δ 2.81 and 2.95 (s each, 6 H, NMe_2), 3.21 (dd, J = 14.6 and 8.3 Hz, 1 H, H-11), 3.40 (dd, J = 14.6 and 3.4 Hz, 1 H, H-11), 3.82 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 6.19 (dd, J = 8.3 and 3.4 Hz, 1 H, H-10), 6.63 (s, 1 H, ArH), 6.86 (s, 1 H, ArH), 6.85–6.94 (m, 2 H, ArH), 7.03 (t, J = 7.8 Hz, 1 H, ArH); ^{13}C NMR δ 35.62 and 36.28 (NMe_2 and C-11), 55.95 (OMe), 56.07 (OMe), 56.17 (OMe), 71.44 (C-10), 105.26, 111.51, 113.03, 119.28, 120.94, 123.74, 131.50, 145.65, 145.82, 147.91, 150.72, 151.16, 155.82 (CO).

9-Bromo-2,3,6-trimethoxy-10-[(*N*,*N*-dimethylcarbamoyl)oxy]-10,11-dihydrodibenz[*b*,*f*]oxepine (7a). To a solution of the above carbamate (0.93 g, 2.49 mmol) and anhydrous NaOAc (0.31 g, 3.74 mmol) in AcOH (6 mL) was added dropwise a solution of Br_2 (0.50 g, 3.11 mmol) in 5 mL of AcOH contained in a pressure-compensating funnel. After being stirred for 8 h at rt the mixture was poured into an aqueous solution of sodium metabisulfite and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with water, dried with anhydrous Na_2SO_4, and concentrated to dryness. The crude product was chromatographed on a silica gel column and crystallized from CH_2Cl_2–hexane (1.00 g, 88%): mp 185–189 °C; IR (KBr) 1700 cm^{-1}; ^1H NMR δ 2.70 and 2.97 (s each, 6 H, NMe_2), 3.45 (m, 2 H, H-11), 3.87 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 6.20 (dd, J = 5.6 and 3.5 H, 1 H, H-10), 6.70 (s, 1 H, ArH), 6.83 (d, J = 8.3 Hz, 1 H, ArH), 6.86 (s, 1 H, ArH), 7.33 (d, J = 8.6 Hz, 1 H, ArH); ^{13}C NMR δ 33.90 (C-11), 35.80 and 36.27 (NMe_2), 56.04 (OMe), 56.27 (2xOMe), 72.82 (C-10), 105.05, 112.80, 112.90, 116.17, 120.18, 128.03, 129.40, 146.05, 148.03, 148.27, 150.88, 151.16, 155.78 (CO).

3,4,6-Trimethoxy-10-[(*N*,*N*-dimethylcarbamoyl)oxy]-10,11-dihydrodibenz[*b*,*f*]oxepine. The alcohol obtained by $NaBH_4$ reduction of dibenzoxepinone **6b**[27] was converted to its corresponding carbamate, which was obtained as an oil in 96% yield: IR (NaCl) 1700 cm^{-1}; ^1H NMR δ 2.74 and 2.94 (s each, 6 H, NMe_2), 3.26 (dd, J = 14.1 and 7.9 Hz, 1 H, H-11), 3.40 (dd, J = 14.1 and 3.3 Hz, 1 H, H-11), 3.84 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 3.99 (s, 3 H, OMe), 6.10 (dd, J = 7.9 and 3.3 Hz, 1 H, H-10), 6.64 (d, J = 8.4 Hz, 1 H, ArH), 6.82–6.93 (m, 3 H, ArH), 7.01 (t, J = 7.8 hz, 1 H, ArH); ^{13}C NMR δ 35.47 (C-11), 35.71 and 36.36 (NMe_2), 56.22 (2xOMe), 61.43 (OMe), 71.77 (C-10), 108.25, 112.03, 122.12, 122.79, 123.74, 124.25, 130.83, 141.17, 145.87, 151.37, 151.50, 152.53, 156.01 (CO).

1,2,9-Tribromo-3,4,6-trimethoxy-10-[(*N*,*N*-dimethylcarbamoyl)oxy]-10,11-dihydrodibenz[*b*,*f*]oxepine (7c). The above carbamate (0.83 g, 2.79 mmol) and anhyd NaOAc (0.72 g, 8.78 mmol) in AcOH (10 mL) were treated with a solution of Br_2 (1.41 g, 8.82 mmol) in AcOH (10 mL). The mixture was stirred at rt for 40 h and worked up and the product purified by column chromatography on silica gel, giving 1.00 g (75%) of tribromide **7c**, which was crystallized from ether: mp 147–149 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR δ 2.60 and 2.95 (s each, 6 H, NMe_2), 3.63 (dd, J = 14.5 and 2.1 Hz, 1 H, H-11), 3.84 (dd, J = 14.5 and 5.8 Hz, 1 H, H-11), 3.90 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 6.19 (dd, J = 5.8 and 2.1 Hz, 1 H, H-10), 6.83 (d, J = 8.8 Hz, 1 H, ArH), 7.34 (d, J = 8.8 Hz, 1 H, ArH); ^{13}C NMR δ 35.34 (C-11), 35.68 and 36.47 (NMe_2), 56.30 (OMe), 61.08 (OMe), 61.83 (OMe), 71.49 (C-10), 113.18, 116.73, 117.80, 121.07, 128.38, 128.55, 128.84, 129.75, 145.30, 147.30, 150.98, 151.05, 155.52 (CO).

Preparation of Phthalides 5. General Procedure for the Cyclization of Carbamates 2. A solution of carbamate **2** (0.3 mmol) in 3 mL of anhydrous THF was stirred under Ar and cooled in a bath at between −95 and −100 °C (liquid nitrogen/ether) and treated dropwise with 1.1–2.0 equiv (see Table I) of *t*-BuLi (1.7 M in pentane), producing a yellowish solution which was further stirred for 30 min and quenched by addition of a few drops of anhydrous methanol. The reaction mixture was taken out of the cooling bath and stirred at rt. TLC showed one spot corresponding to the intermedite hydroxyamide **4**, which after stirring for a further 12–36 h (see Table I) evolved to the more mobile phthalide **5**. This transformation is considerably accelerated during workup (evaporation of the solvent, addition of water, extraction with CH_2Cl_2 and concentration to dryness) due to heating during evaporation of solvents, so in some cases good yields of phthalides

(33) Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 4694.

(34) Nzué, S. E.; Bodo, B.; Molho, D. *Bull Mus. Nat. Hist. Natural* **1977**, *14*, 65.

(35) We thank one of the reviewers for suggesting this experiment.

were obtained by workup shortly after addition of methanol. The physical properties of the new phthalides, which were obtained in yields ranging from 78 to 94% (see Table I), are described below.

6-(Benzyloxy)-5-methoxyisobenzofuran-1(3*H*)-one (5c). Recrystallized from CH_2Cl_2–hexane: mp 144–145 °C; IR (KBr) 1745 cm^{-1}; ^1H NMR δ 3.95 (s, 3 H, OMe), 5.16 (s, 2 H), 5.18 (s, 2 H), 6.91 (s, 1 H, H-4), 7.31–7.45 (m, 6 H, ArH); ^{13}C NMR δ 56.25 (OMe), 68.98, 71.00, 103.82, 108.32, 117.45, 127.32, 128.11, 128.59, 136.00, 141.36, 149.49, 155.49, 171.25 (CO).

5-(Benzyloxy)-6-methoxyisobenzofuran-1(3*H*)-one (5d). Recrystallized from CH_2Cl_2–hexane: mp 139–140 °C; IR (KBr) 1750 cm^{-1}; ^1H NMR δ 3.92 (s, 3 H, OMe), 5.15 (s, 2 H), 5.23 (s, 2 H), 6.90 (s, 1 H, H-4), 7.30–7.42 (m, 6 H, ArH); ^{13}C NMR δ 56.20 (OMe), 69.00, 71.09, 105.57, 106.57, 117.96, 127.13, 128.26, 128.74, 135.80, 140.76, 151.03, 154.01, 171.32 (CO).

6-Methoxy-7-[(*N*,*N*-dimethylcarbamoyl)oxy]isobenzofuran-1(3*H*)-one (5f). Recrystallized from CH_2Cl_2–hexane: mp 112–114 °C; IR (KBr) 1730, 1775 cm^{-1}; ^1H NMR δ 3.01 and 3.17 (s, 6 H, NMe_2), 3.87 (s, 3 H, OMe), 5.16 (s, 2 H, H-3), 7.21 (d, J = 8.3 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 36.68 (broad, NMe_2), 56.88 (OMe), 68.49 (C-3), 119.21, 119.49, 119.62, 138.56, 138.76, 152.45, 153.70, 167.96.

Phthalide 8a. A THF solution of bromide **7a** (0.67 g, 1.49 mmol) was cooled to −90 °C and treated dropwise with *t*-BuLi (1 mL, 1.64 mmol). Workup as before gave essentially pure lactone **8a** (92% yield), which was further purified by crystallization from CH_2Cl_2–hexane: mp 219–221 °C; IR (KBr) 1750 cm^{-1}; ^1H NMR δ 3.10 (dd, J = 13.3 and 11.3 Hz, 1 H), 3.46 (dd, J = 13.3 and 3.3 Hz, 1 H), 3.87 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 5.44 (dd, J = 11.3 and 3.3 Hz, 1 H), 6.62 (s, 1 H, ArH), 6.82 (s, 1 H, ArH), 7.07 (d, J = 8.2 Hz, 1 H, ArH), 7.56 (d, J = 8.2 Hz, 1 H, ArH); ^{13}C NMR δ 39.48, 56.02 (OMe), 56.24 (OMe), 56.65 (OMe), 76.00, 105.37, 112.14, 113.14, 114.53, 118.16, 120.41, 136.78, 138.68, 145.25, 147.59, 148.98, 153.26, 169.37 (CO).

Phthalide 8b. A solution of carbamate **7c** (50 mg, 0.08 mmol) in 5 mL of THF was cooled to −90 °C, and 0.2 mL of *t*-BuLi (0.32 mmol) was added. After solution was warmed to −70 °C for 10 min, a few drops of MeOH were added. Workup and purification by column chromatography on silica gel gave 20 mg of **8b** (77%), which was recrystallized from CH_2Cl_2–hexane: mp 131–135 °C; IR (KBr) 1780 cm^{-1}; ^1H NMR δ 3.12 (t, J = 11.9 Hz, 1 H), 3.53 (dd, J = 13.3 and 3.2 Hz, 1 H), 3.89 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 5.44 (dd, J = 11.5 and 3.2 Hz, 1 H), 6.69 (d, J = 8.6 Hz, 1 H, ArH), 6.91 (d, J = 8.6 Hz, 1 H, ArH), 7.10 (d, J = 8.2 Hz, 1 H, ArH), 7.59 (d, J = 8.2 Hz, 1 H, ArH); ^{13}C NMR δ 39.69, 56.25 (OMe), 56.83 (OMe), 61.11 (OMe), 76.09, 107.88, 113.62, 115.41, 118.09, 120.83, 126.58, 137.31, 138.45, 140.72, 148.43, 153.19, 153.86, 169.37 (CO).

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Supplementary Material Available: Mass spectra and analytical data for all compounds and full spectroscopic and analytical data for known phthalides **5a**,[13b] **5b**,[13b] **5e**,[13b] and **5g**[34] and ^1H and ^{13}C NMR spectra of 2,3,6-trimethoxy-10-[(*N*,*N*-dimethylcarbamoyl)oxy]-10,11-dihydrodibenz[*b*,*f*]oxepine and 3,4,6-trimethoxy-10-[(*N*,*N*-dimethylcarbamoyl)oxy]-10,11-dihydrodibenz[*b*,*f*]oxepine (9 pages). Ordering information is given on any current masthead page.