Magnesium Methyl Carbonate-Activated Alkylation of Methyl Ketones with an ω-Halo Nitrile, Esters, and Amides

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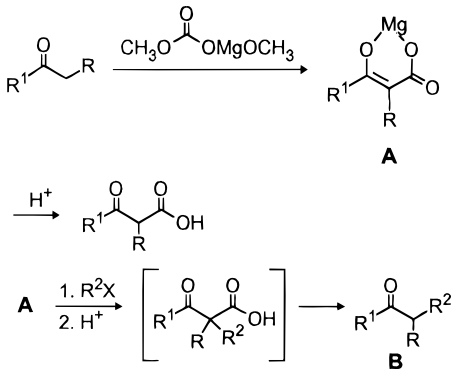
Terminally substituted, extended-chain derivatives of the 2-dibenzofuranyl methyl ketone **6** and its phenylethyl analogue **12** were readily obtained by converting the ketones to magnesium chelates of their β-carboxylated enolates with magnesium methyl carbonate (MMC, methyl methoxymagnesium carbonate, Stiles's reagent), followed by alkylation *in situ* with ω-halo compounds, $X(CH_2)_nY$ where X = Br and Y = CO_2Me, CN, $CONMe_2$, $CON(i\text{-}Pr)_2$, $CON(CH_2)_4$, or $CON(CH_2)_5$ for $n = 1$; X = Br or I, and Y = CO_2Me for $n = 2$; and X = Br and Y = CO_2Me for $n = 3$. Dimethylcarbamoyl chloride ($n = 0$) gave products derived from MMC and the solvent, *N*,*N*-dimethylformamide. The order of reactivity of the halides was α > β > γ and β-I > β-Br. β-Bromo amides were found to be unsuitable reactants. Lower reaction temperatures favored alkylation over competing elimination of HX from methyl β-halopropionate. No self-condensation products of the ketones were observed; however, bis-alkylation and monomethylation products were formed when reaction times were prolonged. In contrast to the unsubstituted β-keto acid **13**, all intermediate α-alkyl β-keto acids decarboxylated during the reaction or the workup.

Introduction

Methyl or substituted methyl (type RCH_2) ketones react with magnesium methyl carbonate (MMC) to give stable chelated adducts (**A**, Scheme 1), which are converted to β-keto carboxylic acids with aqueous HCl or to the methyl esters by reaction with methanolic HCl.[1,2] Stiles[1] has shown that certain MMC-adducts (*i.e.*, the magnesium chelate of the β-carboxylated enolate **A**, Scheme 1) can be alkylated in situ. Thus, MMC-activated 1-tetralone reacted with benzyl bromide to give, after decarboxylation, 2-benzyl-1-tetralone (72%). The MMC-adduct of acetophenone reacted with iodomethane to afford, after decarboxylation, the bis-alkylation product isobutyrophenone (**B**, $R^1 = C_6H_5$, $R = R^2 = CH_3$; 74%). In spite of the good yields and the simplicity of experimental procedure, such reactions in situ have apparently not been used for the introduction of α-substituents into other simple ketones, although a large number of hydantoin derivatives have been prepared by this method.[3,4] Surprisingly, this alkylation method is not even mentioned in some of the comprehensive treatises on organic reactions.[5] We report herein some results obtained when the MMC-adducts of the two methyl ketones **6** and **12** (Scheme 2) were treated with variously ω-substituted halides. The products (Table 1) are important intermediates in the synthesis of a series[6] of antagonists to leukotriene B_4 (LTB_4), a mediator of a variety of pathophysiological states that include tissue swelling and allergic reactions.[7]

Scheme 1



Results and Discussion

Chemical Syntheses. The starting aryl methyl ketone, 8-[1-(*tert*-butyldimethylsiloxy)-2-phenylethyl]-2-(1-oxoethyl)dibenzofuran (**6**), was prepared from dibenzofuran by the following series of reactions: (1) bromination to give 2-bromodibenzofuran (**1**, Scheme 2), (2) Friedel−Crafts acylation of **1** with phenylacetyl chloride, (3) reduction of the resulting ketone **2** with $NaBH_4$ to the racemic alcohol **3**, (4) protection of the OH group by reaction with *tert*-butylchlorodimethylsilane (*tert*-butyldimethylsilyl chloride, TBDMS-Cl) in the presence of imidazole,[8] (5) reaction with acetaldehyde of the Grignard reagent prepared from **4**, and (6) oxidation of the OH group of **5** with pyridinium chlorochromate (PCC) in the presence of alumina.[9] The ketone **12** was prepared from 2-bromo-8-[(2-phenylethyl)phenylacetyl]dibenzofuran[10] (**7**)

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† The University of Alabama.
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(1) Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598.
(2) Griffin, R. W., Jr.; Gass, J. D.; Berwick, M. A.; Shulman, R. S. *J. Org. Chem.* **1964**, *29*, 2109. Pelletier, S. W.; Chappell, R. L.; Parthasarathy, P. C.; Lewin, N. *J. Org. Chem.* **1966**, *31*, 1747. Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* **1968**, 3021. Whitlock, B. J.; Whitlock, H. W., Jr. *J. Org. Chem.* **1974**, *39*, 3144. Lansbury, P. T.; Vacca, J. P. *Tetrahedron* **1982**, *38*, 2797. Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686.
(3) Finkbeiner, H. L. *J. Am. Chem. Soc.* **1964**, *86*, 961.
(4) Finkbeiner, H. *J. Org. Chem.* **1965**, *30*, 3414.
(5) For example, March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985, and *Carbon−Carbon Bond Formation*; Augustine, R. L., Ed.; Dekker: New York, 1979; Vol. 1.
(6) Shoupe, T. S.; Baker, D. C.; Coutts, S. M.; Hand, E. S. U.S. Patent 5 019 573, 1991; *Chem. Abstr.* **1991**, *115*, 158949.
(7) Lehninger, A. L.; Nelson, D. L.; Cox, M. M. *Principles of Biochemistry*, 2nd ed.; Worth: New York, 1993, pp 258−259; 748.
(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

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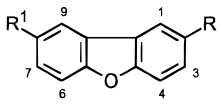
Scheme 2[a]



Compound No.[b]	R	R^1
1	Br	H
a. → 2	Br	$ArCH_2C(O)$
b. → 3	Br	$ArCH_2CH(OH)$
c. → 4	Br	$ArCH_2CH(OTBDMS)$
d. → 5	$CH(OH)CH_3$	$ArCH_2CH(OTBDMS)$
e. → 6	$C(O)CH_3$	$ArCH_2CH(OTBDMS)$
7	Br	$Ar^1CH_2C(O)$
b. → 8	Br	$Ar^1CH_2CH(OH)$
c. → 9	Br	$Ar^1CH_2CH(OTBDMS)$
d. → 10 + 11	$CH(OH)CH_3$ / H	$Ar^1CH_2CH(OTBDMS)$
10 e. → 12	$C(O)CH_3$	$Ar^1CH_2CH(OTBDMS)$

[a] Ar = C_6H_5; Ar^1 = 2-($C_6H_5CH_2CH_2$)C_6H_4; TBDMS = *tert*-butyldimethylsilyl. [b] Reagents: (a) $C_6H_5CH_2C(O)Cl$, $AlCl_3$, CS_2; (b) $NaBH_4$, 2-PrOH, H_2O; (c) TBDMSCl, imidazole, DMF; (d) 1. Mg, EtBr, THF; 2. CH_3CHO, THF; (e) PCC, alumina, CH_2Cl_2.

via the analogous intermediates **8**−**10**. Variable amounts of **11**, in which the bromine in **9** is replaced by hydrogen, and of **12** (oxidation of **10**) were also formed in the Grignard reaction.

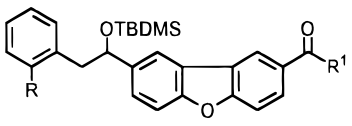
Adduct Formation. The MMC-adducts were prepared by heating the ketone **6** (or **12**) with MMC (generally 10 equiv) in *N*,*N*-dimethylformamide under nitrogen at 125 °C for 1.7−2 h, until formation of the adduct was complete, as demonstrated by TLC of ether aliquots which were diluted with water and acidified. The TLCs showed the presence of only minor amounts of **6** if the plates were developed immediately, but showed the reformation of increasing amounts of **6** if development was delayed. The reformation of **6** is due only to spontaneous or SiO_2-mediated decarboxylation of **13**. Acidic workup of the reaction mixture gave the free β-keto acid **13** (Table 1), which was isolated in 68% yield and was sufficiently stable as the pure solid to allow full characterization.

Alkylations. For the alkylations, a DMF solution of an excess of the halide (Table 2) was added to the cooled (25−50 °C) adduct solution, and the temperature was then raised until steady evolution of CO_2 commenced (for an exception, see below). The progress of most reactions was monitored by TLC of aliquots worked up as described above and, in some cases, by ^{1}H NMR spectral analysis of such aliquots. In general, since the amounts of side products relative to the desired monoalkylation product increased toward the end of the reaction time, the reaction was quenched even though the starting material

(9) The preparation of a reagent in which PCC is deposited on alumina has been reported by Cheng, Y.-S.; Liu, W.-L.; Chen, S.-h. *Synthesis* **1980**, 223. We simply added alumina to the mixture of compounds in dichloromethane.

(10) The synthesis of this compound will be published elsewhere.

Table 1. Reactants (6 and 12) and Products of MMC-activated Substitution Reactions



compd no.	R	R^1
6	H	CH_3
13	H	CH_2CO_2H
14	H	CH_2CH_3
15	H	OCH_3
16	H	$(CH_2)_2CO_2CH_3$
17	H	$(CH_2)_2CO_2CH_2CH_3$
18	H	$(CH_2)_2C(O)N(CH_3)_2$
19	H	$(CH_2)_2C(O)N(CH_2)_4$
20	H	$(CH_2)_2C(O)N(CH_2)_5$
21	H	$CH[CH_2C(O)N(CH_2)_5]_2$
22	H	$(CH_2)_2C(O)N[CH(CH_3)_2]_2$
23	H	$(CH_2)_2CN$
24	H	$(CH_2)_3CO_2CH_3$
25	H	$CH(CH_2CH_2CO_2CH_3)_2$
26	H	$(CH_2)_4CO_2CH_3$
12	$C_6H_5CH_2CH_2$	CH_3
27	$C_6H_5CH_2CH_2$	CH_2CH_3
28	$C_6H_5CH_2CH_2$	OCH_3
29	$C_6H_5CH_2CH_2$	$(CH_2)_2C(O)N(CH_2)_4$
30	$C_6H_5CH_2CH_2$	$(CH_2)_2C(O)N[CH(CH_3)_2]_2$
31	$C_6H_5CH_2CH_2$	$(CH_2)_3CO_2CH_3$
32	H	$CH_2CO_2CH_3$
33	H	$CH{=}CHN(CH_3)_2$
34	H	$C(CO_2CH_3){=}CHN(CH_3)_2$

6 (or **12**) was still detectable by TLC. Two of these side products were the ethyl ketone **14** (or **27**; Table 1) and the bis-alkylation product(s) which, in the case of compounds **21** and **25**, were characterized by elemental and ^{1}H NMR spectroscopic analyses. Analogous structures are attributed to materials formed in other reactions and which, like compounds **21** and **25**, had smaller R_f values than the monoalkylation products and ^{1}H NMR spectra interpretable in terms of keto−enol mixtures of the bis-alkylated products, e.g., **25**.

The ethyl ketones **14** and **27** (Scheme 1: **B**, R = H, R^2 = CH_3; Table 1) are believed to arise by reaction of the MMC adducts of **6** and **12** (Scheme 1: **A**, R = H) with bromomethane or iodomethane formed by reaction of MMC with the halide ion liberated during the alkylation and which are therefore present in higher concentration during the later stages of the reaction.

In all reactions a small amount of another side product, the methyl ester derivative **15** (or **28**; Table 1), was also formed. Since the ester **15** was also isolated from the reaction of **6** and MMC in the absence of halides, it presumably arises by formation of the methyl β-keto ester (rather than the β-keto carboxylate magnesium chelate **A**; Scheme 1), followed by retro-Claisen reaction induced by methoxide ion (Scheme 3).

Reactions of the MMC-adducts with α-halo compounds (ethyl ester, nitrile, and amides) gave the monoalkylation products **16**−**20**, **22**, **23**, **29**, and **30** in generally >65% yield when 3−4 equiv of halide were used. With ethyl bromoacetate and the adduct of **6**, ester exchange occurred, and a 4:1 mixture of the methyl **16** and ethyl **17** esters was obtained.

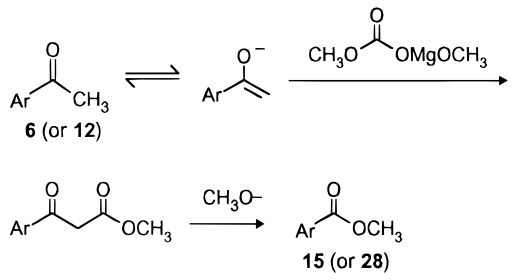
With β-halo esters the reaction was complicated by competing elimination of HX (X = Br or I), which, however, could be partially suppressed by using lower reaction temperatures (55−70 °C). Much longer reaction times and/or larger amounts of halide were required to obtain 40−76% yields of the monoalkylation products **24**

Table 2. Reagents, Conditions, and Product Distribution of MMC-Activated Reactions[a]

			product distribution %				
						alkylation products	
reagents	temp (°C)	time (h)	**6** or **12**	**14** or **27**	**15** or **28**	mono	bis
6, $BrCH_2CO_2Et$							
(18 equiv MMC)	100	2.3	< 2	< 2	< 2	80[b]	ND[c]
6, $BrCH_2CN$							
(7.5 equiv MMC)	90	2	23			**23**, 60	ca. 3
6, $BrCH_2CON(CH_3)_2$	120	1	ca. 8	trace	trace	**18**, 73	
6, $BrCH_2CON(CH_2)_4$	105	1	10	trace	2	**19**, 77	
6, $BrCH_2CON(CH_2)_4$	115	1.7					
	125	+0.1	ND[c]	8	trace	**19**, 61[d]	ca. 5
6, $BrCH_2CON(CH_2)_5$							
(2.7 equiv halide)	110	2.25	17	2	8	**20**, 66	**21**, 3
6, $BrCH_2CON(i\text{-}Pr)_2$	110	1.2	13	8	2	**22**, 66	ND[c]
6, $Br(CH_2)_2CO_2CH_3$	100	2.2	80[e]			**24**, 20[e]	
(+10.5 equiv halide)	100	+1.5	14[f]	trace	2	**24**, 50	**25**, 17
6, $Br(CH_2)_2CO_2CH_3$							
(16.5 equiv halide)	100	0.75	54	trace	trace	**24**, 40	trace
6, $Br(CH_2)_2CO_2CH_3$							
(8 equiv halide)	70	20					
(+8 equiv halide)	70	+2					
	100	+1	38	trace	trace	**24**, 60	ND[c]
6, $Br(CH_2)_2CO_2CH_3$							
(8 equiv halide)	65	2					
(+8 equiv halide)	65	24					
	100	+0.5	21	< 2	< 2	**24**, 49	ND[c]
6, $Br(CH_2)_2CO_2CH_3$							
(8 equiv halide)	55	24					
	100	+1	50	trace	trace	**24**, 42	<1
6, $I(CH_2)_2CO_2CH_3$							
(6.8 equiv halide)	55	20					
	100	+0.5	26	2.1	1.5	**24**, 60	1.9
6,							
$Br(CH_2)_2CON(CH_3)_2$[g]	105	1.5					
(+3 equiv halide)	85	0.5					
	105	+0.3	85	trace		7	
6, $Br(CH_2)_3CO_2CH_3$							
(4.3 equiv halide)	50	16	65[e]	trace	trace	**26**, 35	
	80−95	+6	ca. 28[f]	29	trace	**26**, 43	trace
12, $BrCH_2CON(CH_2)_4$							
(3.1 equiv halide)	105	1.5	33	2	trace	**29**, 64	trace
12, $BrCH_2CON(i\text{-}Pr)_2$							
(4 equiv halide)	110	0.51	−	< 2	< 1	**30**, 86	trace
12, $I(CH_2)_2CO_2CH_3$							
(8 equiv halide)	63	23	ca. 20	ca. 1		**31**, 76	ND[c]

[a] Unless otherwise stated, 10 equiv of MMC (2.0 M in *N*,*N*-dimethylformamide) and 3 equiv of halide were used. In some experiments additional halide was added and/or the temperature was increased as indicated. External temperatures are shown. [b] Mixture of **16** and **17**. [c] Not determined. [d] Ca. 10% additional product **19** contaminated with the disubstitution product was obtained. [e] ^1H NMR spectra analysis of an aliquot. [f] Impure. [g] Included for comparison.

Scheme 3



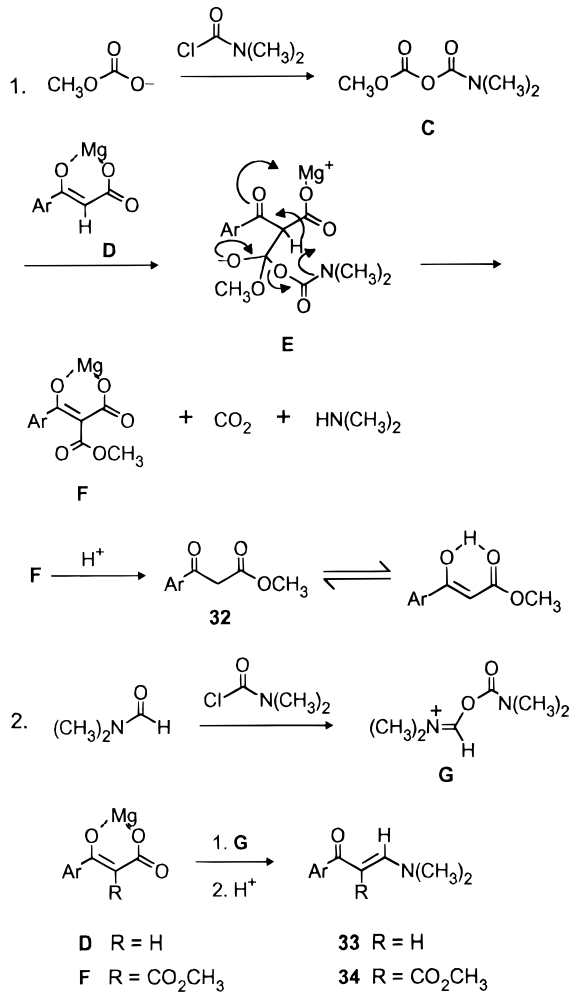
and **31**. Prior to workup, these solutions were heated at ca. 100 °C in order to convert any remaining halo ester to methyl acrylate which, in contrast to the starting halide, is easily removed from the other products by evaporation under reduced pressure. Crude product mixtures then lacked the ^1H NMR signals of the halo ester (Br-/I-$CH_2CH_2CO_2CH_3$), but showed the signals of the vinyl protons of residual methyl acrylate (which is also readily detectable by its characteristic odor).

Only a minor amount of the monoalkylation product was obtained in the reaction of *N*,*N*-dimethyl-3-bromopropionamide with the MMC-adduct of **6**. Reaction of the analogous pyrrolidino amide with the MMC-adduct of **6** gave numerous products which were not further investigated.

Although during the reaction of the MMC-adduct of **6** with the longer chain methyl 4-bromobutanoate evolution of CO_2 was not apparent, the desired alkylation product **26** was formed in 43% yield, together with a large amount (29%) of the methylation product **14**, most of which was formed during the later stages of the reaction at higher temperatures (periodic TLC analysis).

The reaction of the MMC-adduct of **6** with dimethylcarbamoyl chloride took a different course. Aside from the usual small amounts of the side products **14** and **15**, three compounds, **32**−**34** (Table 1), which cannot be directly derived from the carbamoyl chloride, were formed in similar amounts. Since such products were not observed in the MMC-mediated reactions of **6** with the other halogenated compounds, the carbamoyl chloride must have formed reactive intermediates with the solvent (DMF) and/or with MMC. Possible reaction sequences are shown in Scheme 4. Formation of the β-keto ester

Scheme 4



32 is attributed to initial reaction of the methyl carbonate anion (or MMC) with dimethylcarbamoyl chloride to form **C**. Reaction of the preformed MMC-adduct of **6** (**D**) with **C** results in the postulated intermediate **E**. Subsequent formation of the Mg-chelate **F** should be facile since, aside from CO_2, neutral dimethylamine could be formed by intramolecular proton transfer. (Note: Arrows indicated in **E** do not necessarily imply a concerted mechanism. These are intended to show only possible electronic transformations that are most likely complex. Numerous intermediates can be envisioned.) Under the acidic workup conditions, **F** is converted to **32** by loss of another CO_2 molecule. Formation of the vinylogous amides **33** and **34**, on the other hand, is attributed to the intermediacy of a Vilsmeier-type reagent, e.g., **G**, formed from the solvent (DMF) and dimethylcarbamoyl chloride and its reaction with the Mg-chelates **D** and **F**, respectively. It may be noted that in the reaction of MMC-activated 3-phenylhydantoin with benzoyl chloride and ethyl chloroformate (which like dimethylcarbamoyl chloride contain no α-hydrogen atoms), products of chlorine displacement were obtained in 53 and 41% yield, respectively. Although it has been reported that "in both cases ... considerable reaction between the acid chloride and DMF or MMC occurs",[5] products of these reactions were not indicated.

In conclusion, cyano and amide groups were stable toward the basic MMC reagent, but extensive ester exchange (by methoxide ion) occurred when an ethoxycarbonyl functional group was present. Good yields (60−80%) of monoalkylation products were obtained with 3 equiv of α-bromo compounds (1−2 h). β-Bromo amides were found to be unsuitable for the alkylation. Lower temperatures (55−70 °C), longer reaction times (20 h), and use of 7−8 equiv of the methyl β-iodo ester or 16 equiv of the methyl β-bromo ester gave good yields (60−76%) of the monoalkylation products of **6** and **12** (i.e., **24** and **31**), but ca. 25% of the monoalkylation product **24** was converted to the bis-alkylation product **25** when longer reaction times at 100 °C were used. The longer-chain γ-bromo ester gave the monoalkylation product **26** of **6** in fair (43%) yield. Except in the case of compound **24**, no attempts were made to optimize yields.

NMR Spectral Analyses. ^{1}H NMR chemical shift assignments (see Experimental Section) are based on HETCOR, COSY, NOE, and/or decoupling NMR experiments (details not reported). Two sets of signals were generally observed for the α and β protons of the *N*-substituents in the products, as is often observed in the spectra of amides. In NOE experiments when the $CH_2C(O)N$ protons of **22**, for example, were irradiated, enhancement of both (*E*)- and (*Z*)-C(O)NCH signals was observed. Signals showing greater enhancement in intensity compared to the other set were assigned to the functionalities *E* to the carbonyl group since these are proximate to the irradiated protons. Enhancement of the other signals is attributed to rotation about the amide bond during the time of irradiation.[11] Spectra of **5** and **10**, each of which contains two chiral carbon atoms, showed greater complexity in the aromatic region than that observed for the compounds with only one asymmetric center. Thus, for compound **5** at 360 MHz, H-1 (δ 7.96) gave rise to three signals (*J* ca. 2 Hz), and H-3 (δ ca. 7.45) and H-7 (δ 7.36) had the appearance of a triplet of doublets, rather than the usual doublet of doublets. Therefore, these protons in each component of the diastereomeric mixture have slightly different chemical shifts (ca. 1% in $CDCl_3$ solutions at 300 K). No evidence was obtained for differences in chemical shifts of the protons directly attached to the chiral carbon centers.

Experimental Section

General. Reagents, including MMC, were purchased from Aldrich Chemical Co. except for dibenzofuran (Lancaster Synthesis, Ltd), Silica Gel-60 for column chromatography (70−230 mesh, E. Merck) and analytical aluminum-backed silica gel TLC plates, 0.2-mm (E. Merck, Darmstadt), alumina (Fisher), Mg (Reade Manufacturing Co., Inc., RMC-3, 99.98% purity), N_2 (AIRCO, UN 1066), and Ar (AIRCO). Fourier-transform NMR spectra[12] were obtained for ca. 1% solutions in $CDCl_3$ with tetramethylsilane as internal standard, $\delta = 0$; general spectral information is given in refs 16, 18, and 22. GC analyses were conducted using a 30-m capillary DB-5 or a 10-m capillary CP Sil 19-CB column at 8.5 and 5 psi He, respectively, at the indicated oven temperature. Melting points are uncorrected. Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA. Solvents of occlusion in analytical samples of syrupy or waxy products have been confirmed by ^{1}H NMR spectroscopy.

Solvents were dried with and distilled from potassium benzophenone ketyl (THF, under N_2), CaH_2 (DMF, under

(11) Differences in enhancement of intensity of the O=CH resonance of DMF when protons of the proximate CH_3 group are irradiated at different temperatures have been used to determine the free energy of activation for rotation about the amide bond. See: Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect, Chemical Applications*; Academic Press: New York, 1971; p 160.

(12) Unless otherwise stated, ^{1}H NMR spectra of ω-halo compounds were determined at 200 MHz, and those of the dibenzofuran derivatives at 360 MHz.

reduced pressure and stored over 4 Å molecular sieves), or Mg(OMe)$_2$ (MeOH, under N_2). Nitrogen was dried by passage through a column (5 × 20 cm) of 4:1 Drierite−Linde 13X sieves. All organic solvent extracts were dried over $MgSO_4$ and evaporated under aspirator pressure with a rotary evaporator, and TLC analyses were done on silica gel plates with detection by means of a Mineralight lamp (UVS-54). Benzene (PhH) was frequently used as a chromatography solvent, and due caution (fume hood, proper disposal) should be exercised in its handling.

Preparation of 2-Bromodibenzofuran (1).[13] Bromine (18.8 g, 0.118 mol, 1.3 equiv) was added dropwise during 15 min to a warm solution (50 °C) of dibenzofuran (15 g, 0.089 mol) in glacial acetic acid (90 mL) at a rate such that the temperature did not exceed 60 °C. The mixture was stirred at ambient temperature overnight, and the yellow solid was filtered, rinsed with HOAc (9 mL), and triturated with H_2O until it was colorless. The moist solid was extracted with boiling heptane (3×), and the combined extracts were distilled to azeotropically remove H_2O, filtered, concentrated to ca. 50 mL, and cooled. The precipitate was filtered and rinsed with heptane (2×) and then consisted of 6% dibenzofuran, 82.5% **1**, 0.4% of another monobromo compound, and 11% of a dibromo compound (GC, DB-5, 200 °C: t_R 2.66, 4.90, 4.73, and 11.02 min, respectively). The yield of **1** was 47%; the mixture was suitable for the preparation of **2**.

Preparation of 2-Bromo-8-(phenylacetyl)dibenzofuran (2). Aluminum chloride (10.1 g, 0.076 mol) was added during 30 min (pressure-equalizing powder addition funnel) to a stirred solution of crude **1** [13.3 g containing ca. 11 g (0.044 mol) of **1**] and phenylacetyl chloride (8.2 mL, 0.062 mol) in CS_2 (100 mL, dried over Drierite). The mixture was stirred overnight and filtered, and the brown solid was rinsed with CS_2 (3×) and then gradually added to H_2O. The yellow paste was diluted with H_2O, filtered, and rinsed with H_2O. The wet solid was extracted with warm $CHCl_3$ (2×), and the extracts were washed with H_2O and saturated aqueous NaCl, dried, and concentrated under reduced pressure. Filtration gave a filtrate A and a solid, which was rinsed with $CHCl_3$ until it was nearly colorless and recrystallized ($CHCl_3$) to give **2** (8.84 g); fractional crystallization of materials in the mother liquor and the filtrate A gave a second crop of **2** (2.55 g, 71% total): mp (both crops) 161−162 °C (lit.[15] mp 158 °C); TLC (PhH) R_f 0.6; ^{1}H NMR[16] δ 8.58 (H-9), 8.17 (H-7), 8.10 (H-1), 7.58 (H-3, H-6), 7.45 (H-4), 4.38 (CH_2); GC (DB-5, 250 °C): t_R 21.9 min.

2-Bromo-8-(1-hydroxy-2-phenylethyl)dibenzofuran (3). A stirred mixture of **2** (16.14 g, 44.2 mmol) and 2-PrOH (65 mL) at 45 °C was treated with a solution of $NaBH_4$ (0.65 g, 17 mmol) in H_2O (6.5 mL) and then heated to reflux for 1 h, partly cooled, treated with acetone (2.5 mL), and stirred for 20 min. The upper layer was decanted, and the lower layer was extracted with 2-PrOH (3×). The combined organic solutions were evaporated, and ethereal extracts of the residue were percolated through silica gel (40 g). Evaporation of solvent gave syrupy **3** that was crystallized from heptane (15.8 g, 97%): mp 94−95.5 °C; TLC (PhH) R_f 0.3. A small second crop, which had the identical ^{1}H NMR spectrum ($CDCl_3$), was obtained as fluffy needles: mp 79−81 °C; ^{1}H NMR[16] δ 8.05 (H-1), 7.91 (H-9), 7.54 (H-3), 7.51 (H-6), 7.45 (H-7), 7.43 (H-4), 5.06 (7 lines, CH), 3.09 (7 lines, CH_2), 1.92 (OH). Anal. Calcd for $C_{20}H_{15}BrO_2$ [367.24]: C, 65.41; H, 4.12; Br, 21.76. Found: C, 65.47; H, 4.15; Br, 21.82.

2-Bromo-8-[1-(*tert*-butyldimethylsiloxy)-2-phenylethyl]dibenzofuran (4). A solution of **3** (10.8 g, 29.4 mmol), imidazole (5.0 g, 73 mmol), and *tert*-BuMe$_2$SiCl (5.32 g, 35.3 mmol) in DMF (35 mL), after standing for 20 h, was poured into ice−water. The mixture was extracted with Et_2O, and the organic layer was washed with H_2O (4×), dried, concentrated, and triturated with heptane to give pure **4** (10.5 g). Materials in the mother liquor were separated by chromatography (silica gel, 75 g); 1:19 PhH−heptane eluted trace impurities, 1:4 PhH−heptane eluted **4** (3.5 g, 99% total): mp 68−69.5 °C; TLC (1:4 PhH−heptane) R_f 0.75; ^{1}H NMR[16] δ 8.04 (H-1), 7.81 (H-9), 7.53 (H-3), 7.47 (H-6), 7.43 (H-4), 7.39 (H-7), 4.93 (dd, CH), 2.96 (7 lines, CH_2); GC (CP Sil 19-CB, 230 °C) t_R 16.07 min. Anal. Calcd for $C_{26}H_{29}BrO_2Si$ [481.50]: C, 64.86; H, 6.07; Br, 16.59. Found: C, 64.74; H, 6.09; Br, 16.51.

8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]-2-(1-hydroxyethyl)dibenzofuran (5). A solution (0.5 M) of an initiator for the Grignard reaction was prepared as follows. A 3-mL portion of a solution of EtBr (0.79 mL, 10.5 mmol, purified by the H_2SO_4 method in ref 17) in THF (10 mL) was added to Mg turnings (0.29 g, 12 mmol) under N_2. After the exothermic reaction had started, the remainder of the EtBr was added during 15 min, and the stirred mixture was then heated at 60 °C for 45 min and diluted with THF (10 mL). The reagent, kept in a septum-stoppered flask, retained excellent initiator properties for at least 1 week.

A mixture of Mg (0.63 g, 26 mmol), **4** (7.34 g, 15.2 mmol, dried 20 h at 0.1 torr), THF (27 mL), and EtMgBr (9 mL, 0.5 M) was stirred under N_2 for 90 min at 65 °C and then cooled to 0 °C. A solution of CH_3CHO (8.5 mL of a 3.1 M solution in THF, dried over Drierite) was added during 5 min. After 20 h at ambient temperature, the mixture (which contained excess Mg) was treated dropwise with saturated aqueous NH_4Cl (18 mL) and stirred for 1 h. The top layer was decanted, the bottom layer was extracted with Et_2O, and the combined organic layers were dried and evaporated under reduced pressure (up to 60 °C) to give a residue that was fractionated on silica gel (230 g); PhH eluted impurities; 1:19 Et_2O−PhH gave **5** (7.2 g) as a syrup which contained 1 equiv of PhH (calcd yield, 90%): TLC (PhH) R_f 0.25; ^{1}H NMR[16] δ 7.96 (H-1), 7.87 (H-9), 7.52 (H-4), 7.46 (H-6), 7.45 (H-3), 7.36 (H-7), 5.08 (m, C*H*OH), 4.94 (dd, C*H*OTBDMS), 2.98 (8 lines, CH_2). Drying at 60 °C, 0.1 torr, gave an analytical sample. Anal. Calcd for $C_{28}H_{34}O_3Si$ [446.67]: C, 75.29; H, 7.67. Found: C, 75.42; H, 7.76.

8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]-2-(1-oxoethyl)dibenzofuran (6). A mixture of the syrup **5** (3.79 g, ca. 7.8 mmol), alumina (10 g), pyridinium chlorochromate (PCC, 3.4 g, 16 mmol, 2 equiv), and CH_2Cl_2 (80 mL), protected with a Drierite-filled drying tube, was stirred overnight. Solids were removed by filtration and rinsed with CH_2Cl_2 and PhH. The combined filtrates were evaporated, and the PhH-soluble portion of the residue was percolated through alumina (60 g) to give a colorless syrup that was crystallized from heptane to give analytically pure **6** (3.00 g, 93%): mp 93−94.5 °C; TLC (PhH) R_f 0.7; ^{1}H NMR[16] δ 8.58 (H-1), 8.10 (H-3), 7.92 (H-9), 7.69 (H-4), 7.51 (H-6), 7.42 (H-7), 4.96 (dd, CH), 2.98 (7 lines, CH_2), 2.73 (s, CH_3). Anal. Calcd for $C_{28}H_{32}O_3Si$ [444.65]: C, 75.64; H, 7.25. Found: C, 75.73; H, 7.31.

2-Bromo-8-[1-hydroxy-2-(2-phenylethyl)phenylethyl]-dibenzofuran (8). The reduction of **7**[10] (2.5 g, 5.3 mmol) was carried out as previously described for the synthesis of **3** from **2**, but after evaporation of 2-PrOH the residue was diluted with $CHCl_3$ and washed with H_2O (3×). The solution was dried and evaporated to give a syrup, which on trituration with heptane (2×) gave **8**[18] as a solid (2.46 g, 98%): mp 84−85 °C;

(13) The methods of refs 14 and 15 were more time-consuming and gave lower yields and/or less pure **1**; use of catalytic amounts of I_2[15] failed to improve the yield.

(14) Mayer, F.; Krieger, W. *Ber.* **1922**, *55*, 1659; see also Gilman, H.; Brown, G. E.; Bywater, W. G.; Kirkpatrick, W. H. *J. Am. Chem. Soc.* **1934**, *56*, 2473.

(15) Buu-Hoi, Ng Ph.; Roger, R. *Rec. Trav. Chim.* **1948**, *67*, 175.

(16) H-1, H-4, H-6, and H-9 each appear as doublets; H-3 and H-7 each appear as a doublet of doublets. Typical apparent first-order coupling constants are $J_{1,3}$ and $J_{7,9}$ = 1.7−2.2 Hz, $J_{3,4}$ and $J_{6,7}$ = 8.2−8.7 Hz, $J_{CH,OH}$ = 2.4 Hz (**3**, **8**), and $J_{CH,CH3}$ = 6.4 Hz (**5**, **10**). Other signals: the benzylic CH_2 protons (δ ca. 3.0 Hz) gave an ABX pattern (7 or 8 lines) when adjacent to C*H*OH (δ ca. 5.06) or C*H*OTBDMS (δ ca. 4.95) or a singlet (δ ca. 4.4) when adjacent to C=O; phenyl protons gave multiplets centered about 7.2 ppm; *tert*-butyl, δ ca. 0.80 and SiMe$_2$, δ ca. −0.22 and −0.27.

(17) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: New York, 1980; p 253.

(18) ^{1}H NMR spectra of **8**−**10** and **12** were nearly the same as those of the corresponding compounds **3**−**6**, except for the additional signals of the $C_6H_5CH_2CH_2$ protons at δ ca. 7.2 (m, 9 H total) and ca. 2.85 (m, 4 H).

TLC (PhH) R_f ca. 0.4. Anal. Calcd for $C_{28}H_{23}BrO_2$ [471.40]: C, 71.34; H, 4.92; Br, 16.95. Found: C, 71.28; H, 4.88; Br, 16.86.

2-Bromo-8-[1-(*tert*-butyldimethylsiloxy)-2-(2-phenylethyl)phenylethyl]dibenzofuran (9). This compound was prepared from **8** (2.86 g, 5.2 mmol) as previously described for the synthesis of **4** from **3**. Purification by chromatography (silica gel, 90 g, 1:9 and 1:4 PhH−heptane), followed by crystallization from Et_2O, gave **9**[18] as a solid (2.90 g, 95%): mp 82−85 °C; TLC (3:7 PhH−heptane) R_f ca. 0.6. Anal. Calcd for $C_{34}H_{37}BrO_2Si$ [585.66]: C, 69.73; H, 6.37; Br, 13.64. Found: C, 69.84; H, 6.41; Br, 13.60.

8-[1-(*tert*-Butyldimethylsiloxy)-2-(2-phenylethyl)-phenylethyl]-2-(1-hydroxyethyl)dibenzofuran (10). Prior to use, a solution of **9** (1.80 g, 3.07 mmol) in THF (7.5 mL) was kept over 4 Å molecular sieves, and a solution of CH_3-CHO (1 mL, 0.75 g, ca. 17 mmol) in THF (5 mL) was kept over Drierite for ca. 4 h. A portion (1 mL) of a solution of purified EtBr[17] (0.24 mL in 3.0 mL THF) was added to Mg turnings (0.18 g, 7.4 mmol) under Ar with stirring. After the mixture had become hot, solutions of **9** and the remainder of EtBr were added alternately during 20 min; the mixture was then heated to reflux for 70 min and cooled to 0 °C. A portion (45 mL) of the CH_3CHO solution was added dropwise during 5 min. After 40 min, saturated aqueous NH_4Cl (4.5 mL) was added, stirring was continued for 15 min, the top layer was decanted, and the bottom layer was extracted with THF (3×). The combined THF solutions were filtered and evaporated to give a syrup, which was fractionated on silica gel (150 g) eluting first with 2:3 PhH−heptane (400 mL) and then with PhH. Early fractions contained **11** (90 mg) and traces of **12**; later fractions contained **10**,[18] obtained as a syrup (1.64 g) which retained ca. 1 equiv of PhH (calcd yield 85%): TLC (PhH) R_f ca. 0.2. Compound **10** failed to crystallize from Et_2O or heptane. Anal. Calcd for $C_{36}H_{42}O_3Si$ [550.82]: C, 78.50; H, 7.69. Found: C, 78.39; H, 7.72.

In a similar experiment, where (evidently) moisture was not rigorously excluded, considerable amounts (14%) of **11**, obtained as a syrup, were formed: TLC (1:2 PhH−heptane) R_f ca. 0.6. Anal. Calcd for $C_{34}H_{38}O_2Si$ [506.76]: C, 80.59; H, 7.56. Found: C, 80.65; H, 7.59.

8-[1-(*tert*-Butyldimethylsiloxy)-2-(2-phenylethyl)-phenylethyl]-2-(1-oxoethyl)dibenzofuran (12). Oxidation of **10** (0.74 g, 1.3 mmol) by the procedure described for the synthesis of **6** from **5**, except that the reaction time was 5.5 h, gave **12**[18] (0.66 g, 90%): mp 79 °C; TLC (PhH) R_f ca. 0.6. Anal. Calcd for $C_{36}H_{40}O_3Si$ [548.80]: C, 78.79; H, 7.35. Found: C, 78.89; H, 7.38.

MMC-Adduct Formation and Isolation of 3-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]dibenzofuranyl]]-3-oxopropionic Acid (13). A stirred solution of **6** (0.78 g, 1.75 mmol) in DMF (3 mL) and MMC (15 mL, 2 M in DMF, 17 equiv) was heated at 125 °C under N_2 for 110 min and cooled. This provides the MMC adduct used in the following section. The MMC adduct was poured into ice and water (60 g) and treated with HCl (47 mL, 1.4 N) to pH < 2. Ethereal extracts (2×) were washed with ice−water, dried, and evaporated to give a residue consisting of **13** (78%) and **6** (22%) according to its ^{1}H NMR spectrum. Trituration of the residue with heptane gave **13** (0.58 g, 68%) as a pure solid: mp 105−106.5 °C dec; TLC (1:4 MeOH−$CHCl_3$) R_f ca. 0.4; ^{1}H NMR[19] (200 MHz) (85% keto:15% enol mixture) δ 12.55 (OH), 8.60 (H-1, keto), 8.43 (H-1, enol), 5.83 (s, =CH), 4.22 (s, O=CCH_2); OH, CH_2, and =CH exchange with D_2O; CO_2H not observed. Anal. Calcd for $C_{29}H_{32}O_5Si$ [488.66]: C, 71.28; H, 6.60. Found: C, 71.20; H, 6.66.

Alkylation Reactions. For relative amounts of MMC, ω-halides, and conditions used for the alkylations, see Table 2. Unless otherwise stated, 1.75 mmol of **6** was used. Stirred solutions of the adducts, prepared as described in the preceding section and cooled to 25−50 °C, were treated with the halide that was diluted with an approximately equal volume of DMF and then heated as indicated in Table 2. The cooled reaction solution was poured into ice−water and acidified with HCl (1.4 M) to pH 4−5. For the workup of the β-halo ester reactions only ca. 1/10 the amount of the acid was required to achieve pH 4−5; crude alkylation products were isolated by filtration or, if a gum was then present, by extraction with Et_2O or $CHCl_3$.

Methyl and Ethyl 4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]dibenzofuranyl]]-4-oxobutanoate (16 and 17). The crude products (from 0.74 g, 1.7 mmol of **6**) were percolated through silica gel (65 g). PhH eluted **14**, **15**, and **6**; 1:19, 1:9, and 1:3 $CHCl_3$−PhH eluted mixtures of **17** and **16** (0.66 g syrup, ca. 80%). The last fractions contained primarily **16**, which crystallized from heptane as a colorless solid: mp 85.5−87 °C; TLC (developed 2 × with PhH) R_f 0.4; ^{1}H NMR[19] δ 3.75 (OCH_3), 3.46 [t, $ArC(O)CH_2$], 2.84 (t, CH_2-CO_2). Anal. Calcd for $C_{31}H_{36}O_5Si$ [516.72]: C, 72.06; H, 7.02. Found: C, 72.10; H, 7.03.

Data for **17**: TLC (developed 2 × with PhH) R_f 0.45; ^{1}H NMR[19] δ 3.46 [t, $ArC(O)CH_2$], 2.84 (t, CH_2CO_2), 2.20 (q, CH_2-CH_3), 1.29 (t, CH_2CH_3).

***N*,*N*-Dimethyl 4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]dibenzofuranyl]]-4-oxobutanamide (18).** The reagent, *N*,*N*-dimethyl bromoacetamide, was prepared according to method IIb of ref 20.; bp 70 °C/0.5 torr (lit.[20] bp 63−65 °C/1 torr). ^{1}H NMR δ 3.88 (s, $BrCH_2$), 3.11 and 2.99 (singlets, NMe_2). Chromatography (silica gel, 50 g, $CHCl_3$) of the alkylation products gave **18** as a syrup (0.68 g, 73%): TLC ($CHCl_3$) R_f ca. 0.4; ^{1}H NMR (200 MHz)[19] δ 3.48 [t, $ArC(O)$-CH_2], 3.10 (s, (*Z*)-CH_3), 3.00 (s, (*E*)-CH_3), 2.85 [t, $CH_2C(O)N$]. Anal. Calcd for $C_{32}H_{39}NO_4Si$ [529.76]: C, 72.55; H, 7.42; N, 2.64. Found: C, 72.51; H, 7.48; N, 2.55.

***N*-[4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]-dibenzofuranyl]]-4-oxobutanoyl]pyrrolidine (19).** The reagent, *N*-(bromoacetyl)pyrrolidine, was prepared by gradual addition of pyrrolidine (6.0 mL, 73 mmol, 1.8 equiv)[21] dissolved in ethanol-free $CHCl_3$ (20 mL, prepared by passage through alumina) to a stirred solution of bromoacetyl bromide (3.5 mL, 40 mmol) in $CHCl_3$ (30 mL) at 0 °C; after 20 min, the solution was washed with H_2O (4×) and $NaHCO_3$ (20 mL, 0.02 M), dried, and evaporated. Kugelrohr distillation (140 °C, 0.6 torr) of the residue gave the reagent (3.4 g, 49%) as a colorless solid: mp 30−33 °C; ^{1}H NMR (360 MHz) δ 3.83 (s, $BrCH_2$), 3.52 (m, 4 H, CH_2NCH_2), 1.97 (m, 4H, CCH_2CH_2C). Anal. Calcd for $C_6H_{10}BrNO$ [192.06]: C, 37.52; H, 5.25; Br, 41.60; N, 7.29. Found: C, 37.39; H, 5.28; Br, 41.60; N, 7.20.

Chromatography (silica gel, 35 g) of the crude alkylation products gave **14** and **15** (PhH), **6** (1:9 Et_2O−PhH), and **19** (1:1 Et_2O−PhH and Et_2O), which separated from heptane as a flocculent solid (0.75 g, 76%): mp 91−101 °C; TLC (Et_2O) R_f ca. 0.4; ^{1}H NMR[18] δ 3.5 [m, 6 H, $ArC(O)CH_2$ and CH_2NCH_2], 2.75 [t, 2 H, $CH_2C(O)N$], 1.96 (m, 4 H, CCH_2CH_2C). Anal. Calcd for $C_{34}H_{41}NO_4Si$ [555.8]: C, 73.48; H, 7.44; N, 2.52. Found: C, 73.52; H, 7.45; N, 2.52.

***N*-[4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]-dibenzofuranyl]]-4-oxobutanoyl]piperidine (20).** The reagent, *N*-(bromoacetyl)piperidine, was prepared by dropwise addition of a solution of piperidine (1.42 g, 16.7 mmol, 1.7 equiv)[21] in dry PhH (5 mL) to a cold, stirred solution of $BrCH_2$-COBr (2.0 g, 10 mmol) in PhH (10 mL). The mixture was filtered after 20 min. The solvent was evaporated, and a $CHCl_3$ solution of the residue was washed with H_2O (4×), $NaHCO_3$ (15 mL, ca. 0.3 M), H_2O, and saturated aqueous NaCl, dried, and evaporated. The residue was distilled (Kugelrohr, 140 °C, 0.4 torr) to give a colorless liquid (1.39 g, 81%); ^{1}H NMR δ 3.87 (s, $BrCH_2$), 3.56 (t, (*Z*)-NCH_2), 3.45 (b, (*E*)-NCH_2), 1.7−1.5 (m, 6 H, $C(CH_2)_3C$).

The crude alkylation products (from 1.0 g, 2.25 mmol of **6**) were fractionated on silica gel (75 g); PhH eluted side products and **6**, 1:3 EtOAc−PhH eluted mixtures of **6** and **20**, pure **20**, and **21** (50 mg). The mixtures were rechromatographed, eluting first with $CHCl_3$ to obtain **6** (0.17 g total, 17%) and

(19) Chemical shifts of aromatic protons are nearly the same as those of **6** (or **12**).

(20) Weaver, W. E.; Whaley, W. M. *J. Am. Chem. Soc.* **1947**, *69*, 515.

(21) The use of 2 equiv of amine(s), described in ref 20, in our hands led to partial displacement of the alkyl halide, in addition to displacement of the acyl halide.

then with 1:3 EtOAc−$CHCl_3$ to obtain **20** (0.85 g total, 66%) as a syrup: TLC (1:3 EtOAc−$CHCl_3$) R_f ca. 0.7; ^{1}H NMR[19] δ 3.58 (t, (*Z*)-NCH_2), 3.53 (t, (*E*)-NCH_2), 3.47 [t, $ArC(O)CH_2$], 2.85 [t, $CH_2C(O)N$], 1.65 (m, 4 H, (*E*)-NCH_2CH_2 and $CH_2CH_2CH_2$-CH_2CH_2), 1.56 (m, 2H, (*Z*)-NCH_2CH_2). Anal. Calcd for $C_{35}H_{43}NO_4Si + 0.26C_6H_6 + 0.3H_2O$ [FW 578.61]: C, 73.19; H, 7.64; N, 2.42. Found: C, 73.19; H, 7.71; N, 2.44.

After trituration with Et_2O, compound **21** was obtained as a colorless solid: mp 148−149 °C; TLC (1:3 EtOAc−$CHCl_3$) R_f ca. 0.2; ^{1}H NMR (200 MHz)[19] δ 4.63 [p, $ArC(O)CH$], 3.5 and 3.4 (b, 8 H, 2 × CH_2NCH_2), 2.79 (ABX, 4 H, 2 × CH_2CO), 1.5 [b, 12 H, 2 × $C(CH_2)_3C$]. Anal. Calcd for $C_{42}H_{54}N_2O_5Si$ [694.99]: C, 72.59; H, 7.83; N, 4.03. Found: C, 72.33; H, 7.84: N, 4.01.

***N,N*-Diisopropyl 4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]dibenzofuranyl]]-4-oxobutanamide (22).** The reagent, *N*,*N*-diisopropyl bromoacetamide, was prepared by dropwise addition of (*i*-Pr)$_2$NH (7.27 g, 72 mmol, 1.8 equiv, dried over 4 Å molecular sieves)[21] dissolved in CH_2Cl_2 (10 mL) to a stirred solution of $BrCH_2COBr$ (3.5 mL, 40 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 20 min the mixture was filtered, and the filtrate was washed with ice−water (4×), $NaHCO_3$ to give pH 8−9, and ice−water, dried, and evaporated; the orange residue was triturated with heptane to give the reagent as colorless, long needles (0.51 g, 63%): mp 64−65.5 °C (lit.[20] liquid); ^{1}H NMR δ 3.96 (h, (*Z*)-NCH), 3.81 (s, $BrCH_2$), 3.43 (h, (*E*)-NCH), 1.39 [d, (*E*)-$NCH(CH_3)_2$], 1.25 [d, (*Z*)-$NCH(CH_3)_2$]. Anal. Calcd for $C_8H_{16}BrNO$ [222.13]: C, 43.26; H, 7.26; Br, 35.97; N, 6.31. Found: C, 43.31; H, 7.30; Br, 36.05; N, 6.25.

The filtered, crude alkylation product (from 1.00 g, 2.25 mmol of **6**) was purified by chromatography on silica gel (75 g) eluting first with PhH to remove **14**, **15**, and **6** and then with $CHCl_3$ to obtain **22**, followed by impure **22**, which was rechromatographed (silica gel, 50 g) with 1:33 EtOAc−$CHCl_3$. The product was obtained as a syrup (0.73 g, 55% total): TLC (1:15 EtOAc−$CHCl_3$) R_f ca. 0.5; ^{1}H NMR (200 MHz)[19] δ 4.17 (h, (*Z*)-NCH), 3.55 (h, (*E*)-NCH), 3.49 [t, $ArC(O)CH_2$], 2.82 [t, $CH_2C(O)N$], 1.40 [d, (*E*)-$NCH(CH_3)_2$], 1.27 [d, (*Z*)-$NCH(CH_3)_2$]. Anal. Calcd for $C_{36}H_{57}NO_4Si + 0.2Et_2O + 0.3H_2O$ [FW 610.90]: C, 73.14; H, 8.18; N, 2.29. Found: C, 73.19; H 8.13; N, 2.29.

4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]-dibenzofuranyl]]-4-oxobutanenitrile (23). The crude alkylation products were fractionated on silica gel (60 g) with PhH. The product **23** (0.51 g, 60%) crystallized from Et_2O as a colorless solid: mp 139−140 °C; TLC (PhH) R_f ca. 0.4; ^{1}H NMR (200 MHz)[19] δ 3.52 (t, O=CCH_2), 2.85 (t, CH_2CN). Anal. Calcd for $C_{30}H_{33}NO_3Si$ [483.69]: C, 74.50; H, 6.88; N, 2.90. Found: C, 74.41; H, 6.92; N, 2.86.

Methyl 5-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]dibenzofuranyl]]-5-oxopentanoate (24). The reagent, methyl 3-iodopropionate, was prepared by stirring a solution of NaI (5.8 g, 38.7 mmol) and 3-bromopropionate (3.3 mL, 30.2 mmol) in acetone (20 mL) for 2 h, heating the mixture at 50 °C for 45 min, cooling, and filtering; the filtrate was concentrated under reduced pressure, diluted with Et_2O, extracted with ice-cold H_2O (2×), dried, and evaporated to give a liquid (6.57 g, ca. 95%) consisting of 19:1 $ICH_2CH_2CO_2CH_3$−$BrCH_2CH_2CO_2CH_3$, according to a ^{1}H NMR spectrum [δ 3.73 (s, OCH_3), 3.59 (t, $BrCH_2$), 3.34 (t, ICH_2), 2.99 (t, ICH_2CH_2), 2.96 (t, $BrCH_2CH_2$)].

A heptane solution of the crude alkylation products (from 1.64 g, 3.7 mmol of **6**) was partially evaporated to give **24** (0.90 g), mp 69−72 °C. Materials in the mother liquor were fractionated on silica gel (75 g); PhH eluted side products and **6** (ca. 26%), 1:20 Et_2O−PhH eluted **24** (0.47 g), which was recrystallized from heptane to give a second crop (0.28 g, 60% total): TLC (PhH) R_f 0.35; ^{1}H NMR (200 MHz)[19] δ 3.69 (s, OCH_3), 3.12 [t, $ArC(O)CH_2$], 2.42 (t, CH_2CO_2), 1.80 (p, CH_2CH_2-CH_2). Anal. Calcd for $C_{32}H_{38}O_5Si$ [530.74]: C, 72.42; H, 7.22. Found: C, 72.55; H, 7.28.

In the experiment with methyl 3-bromopropionate (3 + 10.5 equiv), the bis-alkylation product **25** (0.18 g, 17%) was isolated from the last column eluates (1:20 Et_2O−PhH) as a syrup: TLC (1:20 Et_2O−PhH) R_f ca. 0.2. Anal. Calcd for $C_{36}H_{44}O_7Si$ [616.83]: C, 70.10; H, 7.19. Found: C, 70.24; H, 7.15.

Methyl 6-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-phenylethyl]dibenzofuranyl]]-6-oxohexanoate (26). The reagent was prepared by dropwise addition of 4-bromobutanoyl chloride (3.5 mL, 30 mmol) to a cold solution of anhydrous MeOH (5 mL) in dry PhH (10 mL). After 1 h, the solution was diluted with PhH, washed with ice−water (4×), dried, and evaporated under reduced pressure to give methyl 4-bromobutanoate as a colorless liquid which contained ca. 0.35 equiv of PhH (6.2 g, 100%).

The crude alkylation products (from 3.1 g, 7.0 mmol of **6**) were fractionated on silica gel (275 g) with PhH; early fractions gave **14** as a syrup (0.62 g, 19%): TLC (PhH) R_f 0.75; ^{1}H NMR[19] δ 3.16 (q, CH_2CH_3), 1.3 (t, CH_2CH_3). Anal. Calcd for $C_{29}H_{34}O_3Si$ [458.68]: C, 75.94; H, 7.47. Found: C, 75.95; H, 7.52.

Middle fractions contained **6** and methyl 4-bromobutanoate. Late fractions gave **26** (1.62 g, 43%), which crystallized from heptane as a colorless solid: mp 69−71 °C; TLC (PhH) R_f ca. 0.2; ^{1}H NMR[19] δ 3.68 (OCH_3), 3.12 [t, $ArC(O)CH_2$], 2.42 (t, CH_2CO_2), 1.80 (m, CCH_2CH_2C). Anal. Calcd for $C_{33}H_{40}O_5Si$ [544.77]: C, 72.76; H, 7.40. Found: C, 72.91; H, 7.44.

***N*-[4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-(2-phenylethyl)phenylethyl]dibenzofuranyl]]-4-oxobutanoyl]pyrrolidine (29).** The crude products (from 0.70 g, 1.27 mmol of **12**) were fractionated on silica gel (100 g). $CHCl_3$ eluted the minor side products, **27** and **28**, and **12** (0.12 g, 17%); 1:9 and 1:3 EtOAc−$CHCl_3$ eluted **29**[19,22] (0.54 g, 64%) as a hygroscopic syrup, which failed to crystallize from heptane: TLC (1:3 EtOAc−$CHCl_3$) R_f ca. 0.7. Anal. Calcd for $C_{42}H_{49}NO_4Si$ + 0.14heptane + $0.2H_2O$ [FW 677.88]: C, 76.19; H, 7.69; N, 2.07. Found: C, 76.13; H, 7.79; N, 2.06.

***N,N*-Diisopropyl 4-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-(2-phenylethyl)phenylethyl]dibenzofuranyl]]-4-oxobutanamide (30).** The crude products (from 0.81 g, 1.5 mmol of **12**) were fractionated on silica gel (65 g), eluting with $CHCl_3$, to give **30** and impure **30**, which was rechromatographed. A heptane solution of the product was left to evaporate to give **30**[19,22] as a waxy solid (0.88 g, 86%): mp 98−103 °C; TLC ($CHCl_3$) R_f ca. 0.2. Anal. Calcd for $C_{44}H_{55}NO_4Si + 0.3H_2O$ [FW 695.42]: C, 76.00; H, 8.06; N, 2.01. Found: C, 76.03; H, 8.10; N, 1.98.

Methyl 5-[2-[8-[1-(*tert*-Butyldimethylsiloxy)-2-(2-phenylethyl)phenylethyl]dibenzofuranyl]]-5-oxopentanoate (31). The crude products (from 0.76 g, 1.4 mmol of **12**) were fractionated on silica gel (60 g); PhH eluted **27** (15 mg, 2%) and **12** (0.12 g, 16%); $CHCl_3$ eluted **31**[19,22] which was obtained as a syrup (0.67 g, 76%): TLC (PhH) R_f ca. 0.2. Anal. Calcd for $C_{40}H_{46}O_5Si + 0.3H_2O$ [FW 640.30]: C, 75.03; H, 7.34. Found: C, 75.04; H, 7.38.

Reaction of 6 with *N,N*-Dimethylcarbamoyl Chloride. A solution of the MMC-adduct formed from **6** (0.78 g, 1.75 mmol), DMF (3 mL), and MMC (4.4 mL, 2 M in DMF, 5 equiv), was treated with a solution of Me_2NCOCl (0.48 mL, 5.25 mmol, 3 equiv) in DMF (0.9 mL) and heated for 40 min at 65 °C and then at 120 °C for 45 min, cooled, treated with additional Me_2-NCOCl (0.32 mL, 2 equiv), and heated at 115 °C for 1 h. The cooled orange-red solution was poured into ice−water and acidified to pH 3 with HCl (5.5 mL, 1.4 N). Filtration gave a solid (0.94 g) which was fractionated on silica gel (60 g). PhH eluted **15** (ca. 15 mg), **14** (ca. 15 mg), **6** (0.17 g, 22%), and **32** (tough gum, 0.16 g, 18%); Et_2O eluted **34** (glass, 0.12 g, 12%) and 1:19 MeOH−Et_2O eluted **33** (hard glass, 0.17 g, 16%).

Data for **32**: TLC ($CHCl_3$) R_f ca. 0.7; MS m/z = 411 [(M − $PhCH_2$)$^+$, base]; ^{1}H NMR (200 MHz) (9:1 keto−enol mixture) δ (keto) 8.57 (H-1), 4.14 (CH_2), 3.79 (OCH_3); δ (enol) 8.42 (H-1); 5.79 (=CH), 3.84 (OCH_3); CH_2 and =CH exchange with D_2O. Anal. Calcd for $C_{30}H_{34}O_5Si$ [502.69]: C, 71.68; H, 6.82. Found: C, 71.79; H, 6.86.

Data for **33**: TLC (1:33 MeOH−Et_2O) R_f ca. 0.3; MS m/z = 499 (M^+, 0.2%), 408 [(M − $PhCH_2$)$^+$, base]; ^{1}H NMR[19] δ 7.90 (d, J = 12.5 Hz, =CHN), 5.86 (d, J = 12.5 Hz, O=CC(H)=), ca. 3.18 (b, ca. 3 H, NCH_3), ca. 3.0 (b, overlayed by two sharp

(22) Chemical shifts of the amide and ester side chain protons in **29**−**31** were about the same as in the corresponding compounds **19**, **22**, and **24**.

peaks, ca. 5 H, NCH_3 and $PhCH_2$); at 55 °C the broad peaks coalesce to a singlet 3.08 (6 H, $N(CH_3)_2$) and the ABX pattern of $PhCH_2$ is apparent at δ 2.98; the O=CCH proton exchanges with D_2O, and the =CHN signal is then a singlet. Anal. Calcd for $C_{31}H_{37}NO_3Si + 0.38Et_2O$ [FW 526.0]: C, 74.20; H, 7.52; N, 2.66. Found: C, 74.40; H, 7.50; N, 2.67.

Data for **34**: TLC (Et_2O) R_f ca. 0.4; MS: m/z = 466 [$(M - PhCH_2)^+$, base]; ^{1}H NMR (200 MHz) (55 °C) δ 7.79 (s, =CHN), 3.54 (s, OCH_3), 2.98 (intense singlet overlapping with ABX, 8 H, $N(CH_3)_2$ and $PhCH_2$). Anal. Calcd for $C_{33}H_{39}NO_5Si + 0.6Et_2O + 0.033CHCl_3$ [FW 606.22]: C, 70.20; H, 7.49; N, 2.31. Found: C, 70.23; H, 7.30; N, 2.29.

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Supporting Information Available: ^{1}H NMR spectra of compounds **22**, **29**, **31**, **33**, and **34** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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