Bis(hydroxymethylation) of the Active Methylene Group of 1,3-Dicarbonyl and Related Compounds

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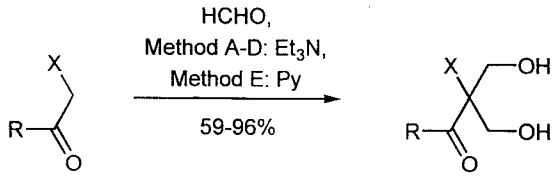
Treatment of dialkyl and di(aralkyl) malonates, alkyl cyano- and acetoacetates, and 1,3-diketones with formaldehyde in the presence of tertiary amines gives their 2,2-bis(hydroxymethyl) derivatives in 59 to 96% yield.

1,3-Dicarbonyl compounds and their cyano and nitro analogs react with aldehydes and ketones to give α,β-unsaturated condensation products (the Knoevenagel reaction), which are sometimes susceptible to further transformation.[1] Esters of malonic acid, for example, react with excess of formaldehyde to afford dialkyl 2,2-bis(hydroxymethyl)malonates.[2-7] However, only the reaction of dimethyl[2] and diethyl[3,4] malonates **(1a,b)** has been well established: in the presence of potassium carbonate, **2a,b** are obtained in 70 to 78% yield. The data on bis(hydroxymethylation) of other malonic esters is limited to 3 examples, the reactivity being in each case only moderate.[5] Use of either sodium hydroxide or copper acetate in acetic acid as a catalyst, has given even lower[6,7] or completely unsatisfactory[8] yields, respectively.

We have recently reported on novel applications of diethyl 2,2-bis(hydroxymethyl)malonate **(2b)** as a phosphate protecting group in the synthesis of oligonucleotide conjugates,[9] and as a starting material in preparation of phosphoramidite reagents.[10] Further development of these approaches requires a variety of analogous 1,3-diols. For this purpose, we have now developed a rather general method of bis(hydroxymethylation) of 1,3-diesters, 1,3-keto esters, 1,3-diketones and alkyl 2-cyanoacetates.

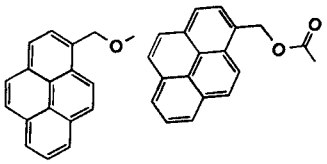
Attempts to prepare **2c–f** revealed that the recommended catalyst, potassium carbonate, gave complex reaction mixtures. In contrast, tertiary amines, e.g., triethylamine and pyridine, led to nearly quantitative yields of **2a,b** and good to excellent yields of **2c–f** (Table 1, Scheme 1). Crude cyanoacetate derivatives **(2e,f)**, for example, were ca 95% pure, according to ^{1}H NMR (Table 2), and hence they could be used further without any additional purification. Although a 2-alkyl substituent somewhat retards the deprotonation of H-2 of malonic esters and forms a steric obstacle to the nucleophilic attack on formaldehyde, diethyl methylmalonate **(1j)** was still found to undergo 2-hydroxymethylation in high yield (Scheme 2).



1a-i **2a-i**

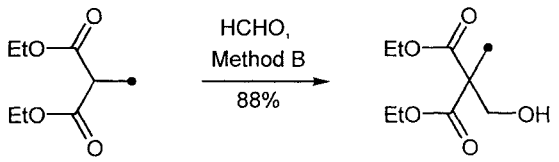
Scheme 1

Table 1. Preparation and Characterization of Compounds **2a–j**

Product[a]	R	X	Method	Workup	Yield (%)	mp (°C) solvent or n_D^{20}
2a	OMe	CO_2Me	A	F or H	91	78.0–78.5 (dec)[b]
			E	F	82	(benzene)
2b	OEt	CO_2Et	A	F or H	96	52–53 (*i*-Pr_2O)[c]
			E	F	95	
2c	OC_8H_{17}	$CO_2C_8H_{17}$	A	G	62	1.4553
			E	G	73	
2d			B	G	59	161 (dec)
2e	OMe	CN	A	F or H	90	–
2f	OEt	CN	A	F or H	94	–
			E	F	85	
2g	OBu-*t*	Ac	C	H	87	80–81 (dec)
			A	H	57	(hexane/benzene)
2h	Me	Ac	D	H	74	–
2i	Me	CH_2Ph	D	H	61	–
2j	OEt	CO_2Et	C	F or H	88	1.4332

[a] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.2, N ± 0.25.
[b] Lit. mp 77–78°C,[2] 79.5–80.5°C.[5]
[c] Lit. mp 50–52°C,[3] 52–53°C.[6]

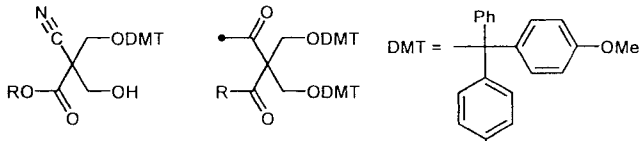
Hydroxymethylation of *tert*-butyl acetoacetate (**1g**) and 1,3-diketones **1h,i** was found to be more problematic. Nevertheless, high concentration of triethylamine (Method C) or its gradual addition (Method D) allows one to synthesize **2g** (Method C) and **2h,i** (Method D) in 60 to 90% yields.



1j **2j**

Scheme 2

Attempted purification by column chromatography revealed that **2e–i** decompose on silica gel columns. Of these compounds, **2g** could be recrystallized to afford a homogeneous material. The others, being liquid, were isolated ca 95% pure from the reaction mixtures, but they had to be converted into *O*-(4,4'-dimethoxytrityl) (DMT) derivatives **3e,f** and *O,O*-bis(DMT) derivatives **4h,i** for proper characterization[9] (Scheme 3).



3e: R = Me; **3f**: R = Et **4h**: R = Me; **4i**: R = Ph

Scheme 3

4,4'-Dimethoxytrityl chloride was obtained from Glen Research, and all the other reagents were purchased from Aldrich. Aq formaldehyde (20%) was prepared by dissolving an aliquot of paraformaldehyde in H_2O at 60–70°C in a pressure-resistant flask. Dioxane and pyridine were dried by distillation on CaH_2 before use. Column chromatography was carried out on silica gel 60 (Merck), eluting with a stepwise gradient of EtOAc in CH_2Cl_2 (**2a–c**) or benzene (**2d,3,4**). Columns for the isolation of **3** and **4** were successively prewashed with a mixture of pyridine and EtOAc (3:97), EtOAc and benzene (1:1). TLC was performed on silica gel plates 60 F_{254} (Merck), developing with a mixture of CH_2Cl_2 and EtOAc (2:3 for **2a–j**), or benzene and EtOAc (6:1 for **3e,f** and **4h,i**). All compounds were visualized by exposure to I_2 vapours. Additionally, upon heating spots of **2a–h** could be observed with UV light, and those of **3** and **4** developed an orange colour.

Dioctyl malonate (**1c**) was synthesised in 85% yield from octyl alcohol (7.16 g, 55 mmol) and malonyl dichloride (7.75 g, 25 mmol) in anhyd pyridine (150 mL) and dioxane (30 mL), followed by aqueous workup and vacuum distillation; bp 138–140°C/8 (Lit. bp 176–177°C/6,[11] 210–213°C/10–12[12]); n_D^{20} 1.4412 (Lit.[12] n_D^{20} 1.4412).

Bis(1-pyrenylmethyl) malonate (**1d**) was prepared by condensation of 1-pyrenylmethanol (3.90 g, 16.8 mmol) and malonic acid (830 mg, 8.0 mmol) in the presence of *N,N*-diisopropylcarbodiimide (2.12 g, 16.8 mmol) in anhyd pyridine (100 mL) for 24 h at +4°C. The solvent was evaporated, and the residue was refluxed with MeOH. The suspension was cooled to r.t. and filtered. The crystalline product was washed with MeOH and dried to give practically pure **1d** (3.07 g, 72%); mp 172.5–173.5°C (EtOH) (Lit.[13] mp 171–173°C).

Bis(hydroxymethylation) of Active Methylene Compounds; General Procedure:

Method A: Et_3N (1.0 M in THF; 0.20 mL, 0.2 mmol) was added to a stirred solution of **1a–e** (10 mmol) in 20% aq formaldehyde (3.3 g, 22 mmol) and dioxane (10 mL) at 4–6°C (ice-water bath), and the mixture was stirred for 20 min. (Old formaldehyde solutions may be contaminated with formic acid which neutralizes Et_3N. Either no reaction or extended formation of side products may be expected in this case). The water bath was removed, the mixture was kept for 40 min at r.t. (6–8 h for **2c**) and worked up as indicated in Table 1. Spectral data are given in Table 2.

Method B: A solution of **1d** (1.33 g, 2.5 mmol) in DMF (30 mL) was added dropwise to a stirred mixture of 20% aq formaldehyde (940 mg, 6.25 mmol), Et_3N (13 mg, 0.125 mmol) and DMF (5 mL) for 30 min at 40–50°C. The mixture was stirred for 2 h at the same temperature, cooled, and worked up by Method G.

Method C: Et_3N (1.0 M in THF; 0.50 mL, 0.5 mmol) was added to a stirred solution of **1g,j** (10 mmol) in 20% aq formaldehyde (3.75 g, 25 mmol) and dioxane (10 mL). At this point the temperature was raised up to 35–40°C. To prepare **2g**, the mixture was stirred for 45–60 min and worked up by Method H. Synthesis of **2j** required 4 h of stirring and workup by Method F or H.

Method D: Et_3N (1.0 M in THF; 0.50 mL, 0.5 mmol) was added to a stirred solution of **1h,i** (10 mmol) in 20% aq formaldehyde (3.75 g, 25 mmol) and dioxane (10 mL) as described in Method D. The pH of the mixture was monitored by the use of wet indicator paper and kept within the range 7.5–8.5 by further addition solution (0.20 mL, 0.2 mmol portions). Overall consumption of Et_3N was estimated to be 10–15 mmol, the reaction being completed in 50–75 min. The workup was effected by Method H.

Method E: A solution of **1** in 20% aq formaldehyde (3.75 g, 25 mmol) and pyridine (10 mL) was stirred at r.t. for 24 h and worked up as indicated in Table 1.

Workup F: The residue was coevaporated with dioxane (2 × 50 mL) and toluene (3 × 50 mL), dissolved in CH_2Cl_2 and separated on a silica gel column (30 × 100 mm), eluting with a gradient of EtOAc (0 to 10–50%) in CH_2Cl_2. The yields and physical constants of **2a–e** are presented in Table 1.

Workup G: The mixture was diluted with H_2O (150 mL) and the product was extracted (3 × 50 mL) with either benzene (**2c**) or EtOAc (**2d**). Organic extracts were dried (Na_2SO_4) and evaporated. The product was isolated by column chromatography as described above.

Workup H: The reaction mixture was diluted with H_2O (150 mL) and the side products were extracted with benzene (3 × 50 mL). The aqueous phase was evaporated at 30°C to one fourth of the initial volume and extracted with EtOAc (5 × 50 mL). The extracts were dried (Na_2SO_4) and evaporated. The residue was either separated by column chromatography (**2a,b,j**), or recrystallized (**2g**), or used without further purification (**2e,f,h,i**) for preparing mono- and bis(4,4'-dimethoxytrityl) derivatives (**3e,f** and **4h,i**, respectively).

Alkyl 2-Hydroxymethyl-2-[(4,4'-dimethoxytrityloxy)methyl]cyanoacetates 3e,f.

Crude **2e** and **2f** (2.8 mmol) were dried by evaporation with anhyd dioxane (5 × 10 mL), dissolved in the same solvent (10 mL) and treated with anhyd pyridine (174 mg, 2.2 mmol). Anhyd 4,4'-dimethoxytrityl chloride (680 mg, 2.0 mmol) was added in 4 equal portions over 2 h, and the mixture was left to stand overnight. The solution was separated from the viscous precipitate of pyridinium hydrochloride, diluted with 1% aq $NaHCO_3$ solution (50 mL), and the mixture was extracted with benzene (3 × 25 mL). The extracts were dried (Na_2SO_4) and evaporated. The residue was separated by column chromatography to give **3e,f** (75–85% on DMT-Cl) as a yellowish oil.

3,3-Bis[(4,4'-dimethoxytrityloxy)methyl]-2,4-butanediones **4h,i**:

These were prepared from **2h,i** as described for **3e,f**. Crude **2h** and **2i** (0.95 mmol) were dried and dissolved in anhyd dioxane as specified above. 4,4'-Dimethoxytrityl chloride (680 mg, 2.0 mmol) was added in one portion, followed by addition of anhyd pyridine

Table 2. Characteristic Spectroscopic Data of Compounds **1c, d, 2a–j, 3e, f, 4h, i**

Product	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
1c	1755, 1738 (C=O)	4.14 (t, 4H, ^3J = 6.7, 2 × CH_2O), 3.37 (s, 2H, CH_2CO_2), 1.64 (m, 4H, 2 × ^3J = 6.7, 2 × CH_2CH_2O), 1.38–1.25 [m, 20H, 2 × $(CH_2)_5$], 0.88 (t, 6H, ^3J = 6.8, 2 × CH_3)	166.73 (C=O), 65.69 (CH_2O), 41.73 (CH_2CO_2), 31.81 (C-6), 29.20 (C-4, 5), 28.50 (C-2), 25.83 (C-3), 22.67 (C-7), 14.09 (CH_3)
1d	1732 (C=O)[a]	8.15–8.05 (m, 4H, 2 × H-6, 8), 8.01 (d, 2H, ^3J = 8.3, 2 × H-3), 7.97–7.92 (m, 10H, 2 × H-4, 5, 7, 9, 10), 7.86 (d, 2H, ^3J = 8.3, 2 × H-2), 5.81 (s, 4H, 2 × CH_2O), 3.47 (s, 2H, CH_2CO_2)	166.40 (C=O), 131.73 (C-1), 131.07, 130.53, 129.35, 128.19, 127.83, 127.55, 127.25, 126.00, 125.49, 124.42, 125.25, 124.70, 124.47, 122.58 (arom), 65.78 (CH_2O), 41.80 (CH_2CO_2)
2a	3505 (OH), 1732 (C=O)[a]	4.11 (s, 4H, 2 × CH_2OH), 3.79 (s, 6H, 2 × CH_3), 3.00 (br s, 2H, 2 × OH)	169.72 (C=O), 63.03 (CH_3), 61.15 (C), 52.83 (CH_2)
2b	3452 (OH), 1731 (C=O)	4.24 (q, 4H, ^3J = 6.9, 2 × CH_2O), 4.10 (br s, 4H, 2 × CH_2OH), 3.26 (br s, 2H, 2 × OH), 1.28 (t, 6H, ^3J = 6.9, CH_3)	169.48 (C=O), 63.37 (CH_2O), 61.89 (CH_2OH), 61.09 (C), 14.04 (CH_3)
2c	3435 (OH), 1732 (C=O)	4.15 (t, 4H, ^3J = 6.8, 2 × CH_2O), 4.09 (d, 4H, ^3J = 6.3, 2 × CH_2OH), 3.44 (br t, 2H, ^3J = 6.3, 2 × OH), 1.63 (m, 4H, 2 × ^3J = 6.8, 2 × CH_2CH_2O), 1.31–1.27 [m, 20H, 2 × $(CH_2)_5$], 0.88 (t, 6H, ^3J = 6.8, 2 × CH_3)	169.51 (C=O), 65.96 (CH_2O), 63.09 (CH_2OH), 61.22 (C), 31.83 (C-6), 29.22 (C-4, C-5), 28.45 (C-2), 25.97 (C-3), 22.68 (C-7), 14.10 (CH_3)
2d	3446 (OH), 1734 (C=O)[a]	8.21 (d, 2H, ^3J = 7.5, 2 × H-3), 8.20–8.08 (m, 4H, 2 × H-6, 8), 8.01–7.96 and 7.93–7.92 (m, 6H and 4H, 2 × H-4, 5, 7, 9, 10), 7.75 (d, 2H, ^3J = 7.5, 2 × H-2), 5.63 (s, 4H, 2 × CH_2O), 5.10 (t, 2H, ^3J = 5.2, 2 × OH), 3.97 (d, 4H, ^3J = 5.2, 2 × CH_2OH)[b]	168.40 (C=O), 130.85 (C-1), 130.85, 129.97, 128.47, 128.42 (C arom), 127.67, 127.49, 127.10, 127.04, 126.15, 125.39, 125.26, 124.29 (CH arom), 123.76 and 123.59 (C arom), 122.67 (CH arom), 64.82 (CH_2O), 61.49 (CH_2OH), 59.43 (C)[b]
2e	3384 (OH), 2255 (C≡N), 1740 (C=O)	3.87 (dd, 2H, ^2J = 11.0, ^3J = 6.2, 2 × CH^AH^BOH), 3.81 (dd, 2H, ^2J = 11.0, ^3J = 6.2, 2 × CH^AH^BOH), 3.79 (s, 3H, CH_3), 3.64 (t, 2H, ^3J = 6.2, 2 × OH)[c]	166.96 (C=O), 118.00 (CN), 62.09 (CH_2OH), 55.13 (C), 52.76 (CH_3)[c]
2f	3420 (OH), 2254 (CN), 1740 (C=O)	4.30 (q, 2H, ^3J = 7.0, CH_2O), 4.00 (d, 2H, ^2J = 12.6, 2 × CH^AH^BOH), 4.04 (d, 2H, ^2J = 12.6, 2 × CH^AH^BOH), 1.34 (t, 3H, ^3J = 7.0, CH_3)	166.60 (C=O), 117.58 (CN), 64.01 (CH_2O), 63.01 (CH_2OH), 54.18 (C), 13.90 (CH_3)
2g	3288 (OH), 1717 (C≡O)[a]	4.16 (dd, 2H, ^2J = 11.7, ^3J = 6.7, 2 × CH^AH^BOH), 4.03 (dd, 2H, ^2J = 11.7, ^3J = 7.0, 2 × CH^AH^BOH), 2.89 (br t, 2H, 2 × OH), 2.29 (s, 3H, CH_3), 1.48 (s, 9H, t-C_4H_9)	205.34 (C=O), 168.75 (O–C=O), 83.26 (C–O), 66.84 (C), 63.77 (CH_2OH), 27.77 (CH_3), 27.57 (H_3CC=O)
2h	3399 (OH), 1715 (C≡O)	4.19 (br s, 4H, 2 × CH_2OH), 2.70 (br s, 2H, 2 × OH), 2.22 (s, 6H, 2 × CH_3)	205.74 (C=O), 72.96 (C), 63.96 (CH_2OH), 28.12 (CH_3)
2i	3420 (OH), 1714 (C=O), 1671 (PhC=O)	7.9 – 7.4 (m, 5H, C_6H_5), 4.31 (s, 4H, 2 × CH_2OH), 3.70 (br s, 2H, 2 × OH), 2.22 (s, 3H, CH_3)	206.0 (MeC=O), 197.13 (PhC=O), 136.11, 133.29, 128.75, 128.29, (C-1, C-4, C-3, 5, C-2, 6 in Ph), 70.72 (C), 64.78 (CH_2OH), 28.20 (CH_3)
2j	3534 (OH), 1732 (C=O)	4.231 (q, 2H, ^3J = 7.1, CH_2CH_3), 4.228 (q, 2H, ^3J = 7.1, CH_2CH_3), 3.85 (d, 2H, ^3J = 7.1, CH_2OH), 2.93 (t, 1H, ^3J = 7.1, OH), 1.45 (s, 3H, CH_3C), 1.28 (t, 6H, ^3J = 7.1, 2 × CH_3CH_2)	171.61 (C=O), 66.71 (CH_2OH), 61.53 (CH_2O–), 55.73 (C), 17.49 (CH_3C), 13.94 (2 × CH_3CH_2)
3e	3462 (OH), 2251 (C≡N), 1750 (C=O)	7.45 – 7.2 (m, 9H, arom), 6.9 – 6.8 (m, 4H, arom), 4.00 (dd, 1H, ^2J = 11.2, ^3J = 7.3, CH^AH^BOH), 3.93 (dd, 1H, ^2J = 11.2, ^3J = 6.8, CH^AH^BOH), 3.82 (s, 3H, CO_2CH_3), 3.78 (s, 6H, 2 × $ArOCH_3$), 3.53 (d, 1H, ^2J = 8.7, CH^LH^M-ODMT), 3.48 (d, 1H, ^2J = 8.7, CH^LH^M-ODMT), 2.42 (t, 1H, ^3J = ~ 7, OH)	166.92 (C=O), 158.69, 134.72, 129.93, 113.31 (C-4, C-1, C-2, 6, C-3, 5 in anisole ring), 143.81, 128.29, 128.00, 127.08 [C-1, C-3, C-2, 6, C-4 in Ph (DMT)], 117.23 (CN), 86.88 (Ar_3C), 63.55 DMT-OCH_2), 62.99 (CH_2OH), 55.19 (CH_3OAr), 53.68 (CO_2CH_3), 52.28 (C)
3f	3480 (OH), 2251 (C≡N), 1748 (C=O)	in $CDCl_3$: 7.45 – 7.2 (m, 9H, arom), 6.9 – 6.8 (m, 4H, arom), 4.29 (m, 2H, CH_2CH_3), 4.03 (dd, 1H, ^2J = 11.2, ^3J = 7.2, CH^LH^MOH), 3.93 (dd, 1H, ^2J = 11.2, ^3J = 6.9, CH^LH^MOH), 3.79 (s, 6H, 2 × $ArOCH_3$), 3.53 (d, 1H, ^2J = 8.7, DMTO-CH^XH^Y), 3.51 (d, 1H, ^2J = 8.7, DMTO-CH^XH^Y), 2.17 (t, 1H, ^3J = ~ 7.1, OH), 1.32 (t, 3H, ^3J = 7.1, CH_3CH_2) in C_6D_6: 8.1 – 8.0 (m, 2H, arom), 7.95 – 7.85 (m, 4H, arom), 7.65 – 7.55 (m, 2H, arom), 7.5 – 7.4 (m, 1H, arom), 7.2 – 7.1 (m, 4H, arom), 4.34 (m, 1H, ^2J = 10.8, ^3J = 7.2, $CH^AH^BCH_3$), 4.29 (m, 1H, ^2J = 10.8, ^3J = 7.2, $CH^AH^BCH_3$), 4.125 (dd, 1H, ^2J = 10.9, ^3J = 7.0, CH^LH^MOH), 4.120 (d, 1H, ^2J = 8.5, DMTO-CH^XH^Y), 4.100 (d, 1H, ^2J = 8.5, DMTO-CH^XH^Y), 3.98 (dd, 1H, ^2J = 10.9, ^3J = 6.4, CH^LH^MOH), 3.70 (s, 6H, 2 × $ArOCH_3$), 1.98 (t, 1H, ^3J = ~ 6.7, OH), 1.30 (t, 3H, ^3J = 7.2, CH_3CH_2)	166.52 (C=O), 158.72, 134.83, 129.98, 113.33 (C-4, C-1, C-2, 6, C-3, 5 in anisole ring), 143.90, 128.02, 127.91, 127.11 [C-1, C-3, 5, C-2, 6, C-4 in Ph (DMT)], 117.40 (CN), 86.88 (Ar_3C), 63.56 DMT-OCH_2), 63.19, 63.13 (CH_2OH and CH_2CH_3), 55.23 (CH_3OAr), 52.43 (C), 14.02 (CH_3)
4h	1723 (C=O)	7.4 – 7.1 (m, 18H, arom), 6.9 – 6.8 (m, 8H, arom), 3.98 (s, 4H, 2 × CH_2), 3.75 (s, 12H, 4 × CH_3O), 1.65 (s, 6H, 2 × CH_3CO)	204.70 (C=O), 158.47, 135.16, 130.34, 113.04 (C-4, C-1, C-2, 6, C-3, 5 in anisole ring), 144.27, 128.30, 127.76, 126.78 [C-1, C-3, 5, C-2, 6, C-4 in Ph (DMT)], 86.28 (Ar_3C), 71.88 (C), 61.34 (DMT-OCH_2), 55.14 (CH_3OAr), 26.76 (CH_3CO)

Table 2. (continued)

Product	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
4i	1716 (C=O), 1674 (Ph–C=O)	7.7 – 7.0 (m, 23 H, arom), 6.8 – 6.6 (m, 8 H, arom), 3.79 (s, 2 H, CH_2), 3.76 (s, 12 H, $4 \times CH_3O$), 3.71 (s, 2 H, CH_2), 1.90 (s, 3 H, CH_3CO), 7.9 – 7.4 (m, 5 H, C_6H_5)	204.78 (Me*C*=O), 196.06 (Ph*C*=O), 158.44, 135.21, 129.97, 113.03 (C-4, C-1, C-2, 6, C-3, 5 in anisole ring), 144.27, 128.55, 127.74, 126.54 [C-1, C-3, 5, C-2, 6, C-4 in Ph (DMT)], 136.27, 132.74, 129.09, 128.19, (C-1, C-4, C-3, 5, C-2, 6 in Ph 85.85 (Ar_3C), 70.36 (C), 61.65 (DMT-OCH_2), 55.15 (CH_3OAr), 27.19 (CH_3)

[a] Recorded as Nujol mull. [b] Recorded in DMSO-d_6. [c] Recorded in CD_3CN.

(170 mg, 2.2 mmol). The mixture was worked up as described for **3e,f** to give after the column purification **4h,i** (70–75 %) as a yellow oil.

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