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LARGE SCALE MONOTRITYLATION OF WATER SOLUBLE COMPOUNDS CONTAINING MULTIPLE HYDROXYL GROUPS

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ABSTRACT: A procedure for the large scale monotritylation of watersoluble substrates containing multiple hydroxylgroups is reported; no elaborate purification procedures are required.

Protection of various functional groups is a fundamental requirement for the application of multifunctional compounds as synthons in multistep reaction sequences.[1] Hence, protection has to occur selectively and in good yield, furnishing an *educt* that is readily isolable and stable under the conditions of consecutive reactions. Moreover, quantitative and selective deprotection with preferably mild reagents should be possible. Apart from these 'chemical' requirements an additional condition has to be fulfilled when substantial amounts (*ca.* 50 grams) of the protected compound are needed: The protection should also be conveniently feasible on a large scale!

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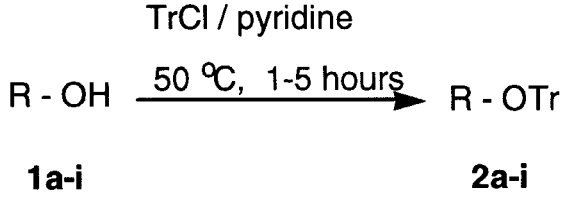
In connection with our work directed towards the synthesis of new ion-conductive materials, we recently reported a convenient synthesis of monodisperse oligo (ethylene glycols) using selective chain extension.[2] Paramount was the high yield synthesis of monotritylated mono- and diethylene glycol under solvolysis conditions.

A literature survey revealed that selective monotritylation of related watersoluble organic compounds containing multiple hydroxylgroups requires multistep reaction sequences in combination with elaborate purification procedures.[3-14] This prompted us to assess whether our solvolysis approach can be extended. In this paper we show that substrates such as triethylene glycol (**1a**), tetraethylene glycol (**1b**), 1,2- (**1c**) and 1,3-propanediol (**1d**), 1,2,3-propanetriol (**1e**), 1,4-butanediol (**1f**), 1,6-hexanediol (**1g**) and *cis*- (**1h**) and *trans*-1,4-cyclohexanediol (**1i**) can be regioselectively monotritylated in good to excellent yield. Neither column chromatography nor continuous extraction is required for the purification of any of the *educts* (Scheme and Table).

The following general procedure was used: To a 10-fold excess of substrate **1a-i**, 1 equivalent of TrCl and 1.5 equivalent dry pyridine was added and the reaction mixture was heated at 50 ^{o}C for 1 to 5 hours untill all TrCl was consumed (TLC). Upon workup excess substrate **1a-i** is readily isolated from the water layer and can be used again. Satisfactory analytical data were obtained for all *educts* **2a-i** (Cf. Table and Experimental Section). The yields are good to excellent and the following general conclusions can be drawn.

1) For substrates containing only primary hydroxylgroups, *i.e.* compounds **1a**, **1b**, **1d** and **1f**, respectively, only one hydroxylgroup is protected.

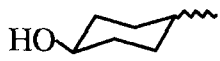
Scheme



2) For compounds **1c** and **1e**, which contain primary as well as secondary hydroxylgroups only one of the primary hydroxylgroups is tritylated.

3) In the case of 1,4-cyclohexanediol (**8**), which was used as the commercially available mixture of *cis* (**1h**) and *trans* (**1i**) isomers (capillary GC., *ratio* **1h**:**1i** 0.49:0.51), besides the monotrityl derivatives, some ditritylated **1i** (**3i**) is formed as a minor side-product (yield<5%); no ditritylated **1h** (**3h**) could be detected in the reaction mixture (^{1}H NMR). This is corroborated by the isolation of the monotritylated- (**2h** and **2i**) and ditritylated- (**3i**) derivatives using preparative column chromatography followed by ^{1}H NMR spectroscopic analysis. The characteristic *triplet of triplets* observed for the *methine* protons of **2h, 2i** and **3i**, respectively,[15,16] unequivocally reveal that only the *equatorial* hydroxylgroups of **1h** and **1i** are tritylated. The *ratio* **2h**:**2i** with respect to the *ratio* **1h**:**1i** (0.49:0.51) of the starting material was assessed by conversion of a sample of **2h** and **2i** into **1h** and **1i**, respectively, by treatment with a catalytic amount of acid in methanol (capillary GC; *ratio* **1h**:**1i** = 0.40:0.60). A moderate enrichment of the *trans* isomer **1i** is observed. Apparently, this is due to differences in the reaction

Table

Compound	R[a]	Reaction Time[b] (hours)	Product	Yield[c] (%)	Lit.
1a	**H-[O-CH_2-CH_2]3**	1	**2a**	94	4
1b	**H-[O-CH_2-CH_2]4**	1	**2b**	89	6
1c	**CH_3-CH(OH)-CH_2**	3	**2c**	81	7
1d	**HO-(CH_2)3**	2	**2d**	77	8, 9
1e	**HO-CH_2CH(OH)CH_2**	4	**2e**	41	10,11,12
1f	**HO-(CH_2)4**	1	**2f**	81	5,13
1g	**HO-(CH_2)6**	5	**2g**	75	5
1h[d]	 *cis*	5	**2h**	29	14
1i[d]	*trans*	5	**2i**	44	14

[a] Cf. Scheme. [b] The reaction was stopped after all TrCl was consumed (TLC). [c] Isolated yield with respect to TrCl. [d] 1,4-Cyclohexanediol is commercially available as a mixture of *cis* (**1h**) and *trans* (**1i**) isomers.

kinetics of compounds **1h** and **1i**, respectively, which is currently subject of a mechanistic investigation.

EXPERIMENTAL

All reagents were purchased from Janssen Chimica. Pyridine was freshly distilled from KOH powder. Tritylchloride (TrCl) was recrystallized from distilled petroleum-ether before use. All reactions were carried out under a nitrogen atmosphere. NMR Spectra were recorded on a Bruker AC 300 spectrometer (^{1}H: 300 MHz; ^{13}C: 75 MHz) using the solvent ($CDCl_3$: ^{1}H, 7.27 ppm; ^{13}C, 77.00 ppm) or TMS (δ = 0.00 ppm) as internal standard. FT-IR Spectra were measured on a Mattson Galaxy Series FTIR 5000 spectrophotometer using a diffuse reflection accessory; the samples were diluted with optically pure KBr. Mass spectra were measured with a JEOL JMS-AX505W mass spectrometer. Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus and are uncorrected. Elemental analysis were carried out by Dornis u. Kolbe, Microanalytical Laboratory, Mülheim a.d. Ruhr 1, Germany.

General Procedure for Monotritylation.

To a mixture of substrate **1a-i**, (1.25 Mole) and dry pyridine (0.188 Mole) tritylchloride (TrCl, 0.125 Mole) is added and the reaction mixture is heated to 50^{o}C. Depending on the substrate the reaction is finished in 1 to 5 hours (TLC; silica gel 60F254(Merck), eluens chloroform:acetone 10:1; disappearence of tritylchloride (TrCl)). After cooling to room temperature, toluene (300 mL) is added, afterwhich the reaction mixture is poured into water (1200 mL). The

organic phase is separated from the water layer, which is additionally extracted twice with toluene (150 mL). Subsequently, the combined organic layers are washed twice with water (125 mL), dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude product is triturated with methanol (100-300 mL) in which sideproducts, such as the ditritylated derivatives, are insoluble. To prevent acid catalyzed methanolysis of tritylated products, 1 mL of methanol saturated with gaseous ammonia is added to the solvent used for the trituration of the crude product. After filtration, the filtrate contains the monotritylated product which may be further purified by recrystallization from an appropriate solvent (*vide infra*). The excess substrate, which readily dissolves in the water layer, can be isolated and used again by concentration of the water layer under reduced pressure followed by purification with flash chromatography (Merck, 9358 Kieselgel 60 230-400 mesh ASTM, eluens chloroform:methanol 10:1).

10,10,10-Triphenyl-3,6,9-trioxadecanol (**2a**).[4] With triethyleneglycol (**1a**) both the mono- (**2a**) and ditritylated products dissolve in methanol at ambient temperature. However, upon cooling to -20°C the ditritylated byproduct crystallizes. After filtration, the filtrate is concentrated under reduced pressure giving pure **2a** as a pale yellow, viscous oil. ^{1}H NMR ($CDCl_3$): δ = 7.49-7.46 (m, 6H), 7.33-7.23 (m, 9H), 3.74-3.67 (m, 8H), 3.63 (X part of AA'XX', 2H), 3.26 (X part of AA'XX',2H), 2.16 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 144.1, 128.8, 127.7, 127.0, 86.6, 72.5, 70.8, 70.7, 70.5, 63.3, 61.9; IR 3439, 3058, 2936, 2872, 1596, 1490, 1449, 1080, 775, 707; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 415 (2, $[M+Na]^+$), 393 (3, $[M+H]^+$), 243 (90, $[\Phi_3C]^+$).

13,13,13-Triphenyl-3,6,9,12-tetraoxatridecanol (**2b**).[6] In the case of tetraethyleneglycol (**1b**) the crude product mixture was triturated with *n*-hexane (150-200 mL), instead of methanol in which the undesired ditrytilated side product dissolves readily (Cf. General Procedure for Monotritylation). ^{1}H NMR ($CDCl_3$): δ = 7.50-7.47 (m, 6H), 7.33-7.21 (m, 9H), 3.69 (m, 12H), 3.58 (X part of AA'XX'system, 2H), 3.26 (X part of AA'XX'system, 2H), 2.50 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ = 144.1, 128.7, 127.8, 126.9, 86.7, 72.5, 70.7, 70.4, 63.4, 61.8; IR 3465, 3075, 2880, 1605, 1495, 1455, 1100, 760, 705; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 459 (2, $[M+Na]^+$), 436 (0.3, $[M]^{+\cdot}$), 243 (90, $[\Phi_3C]^+$); $C_{27}H_{32}O_5$ (436) calc. C 74.29 H 7.39 O 18.32, found C 74.29 H 7.46 O 18.25.

5,5,5-Triphenyl-4-oxapenta-2-ol (**2c**).[7] Racemic mixture mp. 99-100 °C, Lit. 96-97 °C.[7] ^{1}H NMR ($CDCl_3$): δ = 7.48-7.45 (m, 6H), 7.35-7.23 (m, 9H), 4.00 (dddq, ^{3}J(HH) = 9.0 Hz, ^{3}J(HH) = 3.0 Hz, ^{3}J(HH) = 6.0 Hz, ^{3}J(HH) = 6.0 Hz, 1H), 3.18-3.00 (AB system, δ(A) = 3.16 , δ(B) 3.03, J(AB) = 9.0 Hz, ^{3}J(HH) = 3.0 Hz, ^{3}J(HH) = 6.0 Hz, 2H), 2.39 (d, ^{3}J(HH) = 3.0 Hz, 1H), 1.13 (d, ^{3}J(HH) = 9.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 144.1, 128.8, 128.0, 127.3, 86.8, 69.2, 67.2, 19.2; IR 3338, 3100, 2975, 2910, 1595, 1500, 1447, 1100, 763, 700; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 318, (7, $[M]^{+\cdot}$), 243 (100, $[\Phi_3C]^+$).

5,5,5-Triphenyl-4-oxapentanol (**2d**).[8,9] Mp. 118-119 °C, Lit. 115-117 °C[8], 119-120 °C.[9] ^{1}H NMR ($CDCl_3$): δ = 7.47-7.44 (m, 6H), 7.35-7.23 (m, 9H), 3.78 (td, ^{3}J(HH) = 6.0 Hz, ^{3}J(HH) = 6.0 Hz, 2H), 3.29 (t, ^{3}J(HH) = 6.0 Hz,

2H), 2.18 (t, ^{3}J(HH) = 6.0 Hz, 1H), 1.88 (tt, ^{3}J(HH) = 6.0 Hz, ^{3}J(HH) = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 144.2, 128.7, 128.1, 127.4, 87.1, 62.3, 61.4, 32.6; IR 3231, 3020, 2949, 2885, 1596, 1489, 1445, 1076, 767, 703; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 318, (4, $[M]^{+\cdot}$), 243 (95, $[\Phi_3C]^+$).

5,5,5-Triphenyl-4-oxapenta-1,2-diol (**2e**).[10,11,12] With 1,2,3-propanetriol (**1e**) the yield of **2e** is markedly improved if the toluene extraction is done in quadruplicate. Racemic mixture mp. 94-96 °C, Lit. 92 °C,[10] 110-112 °C,[11] 108-109 °C.[12] ^{1}H NMR ($CDCl_3$): δ = 7.45-7.42 (m, 6H), 7.35-7.23 (m, 9H) 3.87 (m., 1H), 3.71-3.57 (AB system, δ(A) = 3.68, δ(B) 3.59, J(AB) = 12.0 Hz, 3.31-3.20 (AB system, δ(A) = 3.27, δ(B) 3.24, J(AB) = 9.0 Hz, ^{3}J(HH) = 3.0 Hz, ^{3}J(HH) = 6.0 Hz, 2H), 2.52 (bs, 1H), 1.99 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ = 143.7, 128.7, 128.0, 127.2, 87.0, 71.1, 65.1, 64.3; IR 3400, 3057, 2962, 2872, 1596, 1490, 1446, 1090, 746, 699; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 357 (2, $[M+Na]^+$), 334 (5, $[M]^{+\cdot}$), 243 (100, $[\Phi_3C]^+$); $C_{22}H_{22}O_3$ (334) calc. C 79.02 H 6.63 O 14.35 found C 79.12 H 6.71 O 14.17.

6,6,6-Triphenyl-5-oxahexanol (**2f**).[5,13] Mp. 72-74 °C, Lit. 65-67 °C.[5] ^{1}H NMR ($CDCl_3$): δ = 7.49-7.45 (m, 6H), 7.35-7.22 (m, 9H), 3.63 (t, ^{3}J(HH) = 6.0 Hz, 2H), 3.15 (t, ^{3}J(HH) = 6.0 Hz, 2H), 1.81 (bs, 1H), 1.72-1.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 144.3, 128.7, 127.8, 126.9, 86.7, 63.5, 62.8, 29.9, 26.6; IR 3209, 3080, 2940, 2865, 1595, 1500, 1448, 1086, 765, 704; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 332 (1, $[M]^{+\cdot}$), 243 (54, $[\Phi_3C]^+$).

8,8,8-Triphenyl-7-oxaoctanol (**2g**).[5] Mp. 74-75 °C, Lit. 68-69 °C.[5] ^{1}H NMR ($CDCl_3$): δ = 7.47-7.43 (m, 6H), 7.33-7.20 (m, 9H), 3.63 (t, ^{3}J(HH) = 6.0 Hz, 2H), 3.07 (t, ^{3}J(HH) = 6.0 Hz, 2H), 1,60 (tt, ^{3}J(HH) = 6.0 Hz, ^{3}J(HH) = 6.0 Hz, 2H), 1.52 (^{3}J(HH) = 6.0 Hz, ^{3}J(HH) = 6.0 Hz, 2H), 1.46-1.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 144.7, 128.9, 127.9, 127.0, 86.5, 63.7, 63.1, 32.9, 30.2, 26.3, 25.8; IR 3298, 3075, 2935, 2864, 1616, 1491, 1462, 1069, 756, 716; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 360 (4, $[M]^{+\cdot}$), 243 (100, $[\Phi_3C]^+$).

cis-(**2h**) *and trans-4-(Triphenylmethoxy)cyclohexanol* (**2i**).[14] In the case of 1,4-cyclohexanediol (**1h** and **1i**) dioxane (125 mL) is added to obtain a homogeneous reaction mixture. After completion of the reaction (TLC) and cooling to room temperature of the reaction mixture, dioxane is removed under reduced pressure before the addition of toluene (Cf. General procedure for Monotrytilation). To determine the ratio **2h** : **2i**, a sample (1 g) of monotritylated cyclohexane-1,4-diol was deprotected to **1h** and **1i**, respectively, by treatment with methanol (5 mL) in the presence of acetyl chloride (0.15 mL) and subjected to capillary gas chromatography analysis (column; 30 m x 0.309 mm, type DB-5; injector temperature 340 °C, FID detector temperature 250 °C, temperature program 120 °C isotherm; carrier gas N_2, flow 1.5 $mLmin^{-1}$). For spectroscopic analyses, pure samples of compounds **2h** and **2i**, respectively, were obtained by column chromatography (Merck, 9358 Kieselgel 60 230 - 400 mesh ASTM; eluens chloroform:acetone 10:1). Mixture of compounds **2h** and **2i**; $C_{25}H_{26}O_2$ (358) calc. C 83.76 H 7.31 O 8.93 found C 83.68 H 7.27 O 9.05.

cis-4-(Triphenylmethoxy)cyclohexanol (**2h**).[14] ^{1}H NMR ($CDCl_3$): δ = 7.56-7.52 (m, 6H), 7.33-7.21 (m, 9H), 3.64 (tt, ^{3}J(HH) = 5.0 Hz, ^{3}J(HH) = 2.5 Hz, 1H), 3.58 (tt, ^{3}J(HH) = 8.8 Hz, ^{3}J(HH) = 5.0 Hz, 1H), 1.81 - 1.70 (m, 2H), 1.58-1.50 (m, 3H), 1.36-1.32 (m, 2H), 1.12-1.03 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 145.4, 129.0, 127.7, 126.9, 86.7, 68.9, 68.3, 30.8, 29.5; IR 3327, 3064, 2923, 2859, 1616, 1469, 1447, 1055, 774, 703; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 358 (1.5, $[M]^{+\cdot}$), 243 (98, $[\Phi_3C]^+$).

trans-4-(Triphenylmethoxy)cyclohexanol (**2i**).[14] ^{1}H NMR ($CDCl_3$): δ = 7.56-7.52 (m, 6H), 7.33-7.22 (m,9H), 3.61 (tt, ^{3}J(HH) = 10.9 Hz, ^{3}J(HH) = 5.5 Hz, 1H), 3.47 (tt, ^{3}J(HH) = 10.9 Hz, ^{3}J(HH) = 5.5 Hz, 1H), 1.84-1.79 (m, 2H), 1.38-1.23 (m, 5H), 1.14-1.06 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 145.4, 128.9, 127.9, 126.9, 86.6, 71.5, 69.3, 32.9, 30.8; IR 3320, 3063, 2936, 2859, 1595, 1490, 1466, 1068, 778, 709; FABMS [Xe; matrix: *m*-nitrobenzyl alcohol] *m/z* (%, fragment) = 358 (5.5, $[M]^{+\cdot}$), 243 (100, $[\Phi_3C]^+$).

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