Use of Diphenylacetyl Chloride as Protective Reagent for Sugars

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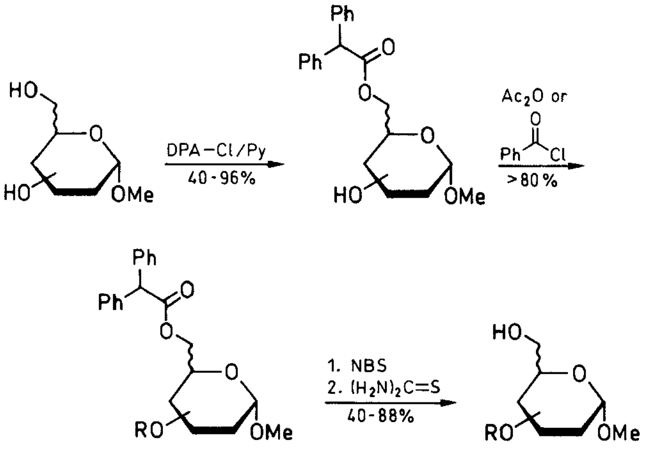
Diphenylacetyl chloride is used as a protective reagent for methyl α-D-glucopyranoside, methyl α-D-mannopyranoside, and α,α-trehalose showing a good regioselectivity. The obtained diphenylacetyl esters were readily removed under neutral and mild conditions with *N*-bromosuccinimide followed by thiourea, in a one-pot reaction, in the presence of acetyl or benzoyl groups.

Selective acylations of carbohydrate derivatives have been well studied employing a wide variety of acylating reagents.[1,2] The primary hydroxy groups of carbohydrates are considered to be the more reactive in esterification and alkylation than the secondary hydroxy groups.[1] Consequently, the synthesis of carbohydrates substituted at secondary hydroxy groups and containing a free primary hydroxy, usually requires the application of blocking–deblocking techniques.[3–5]

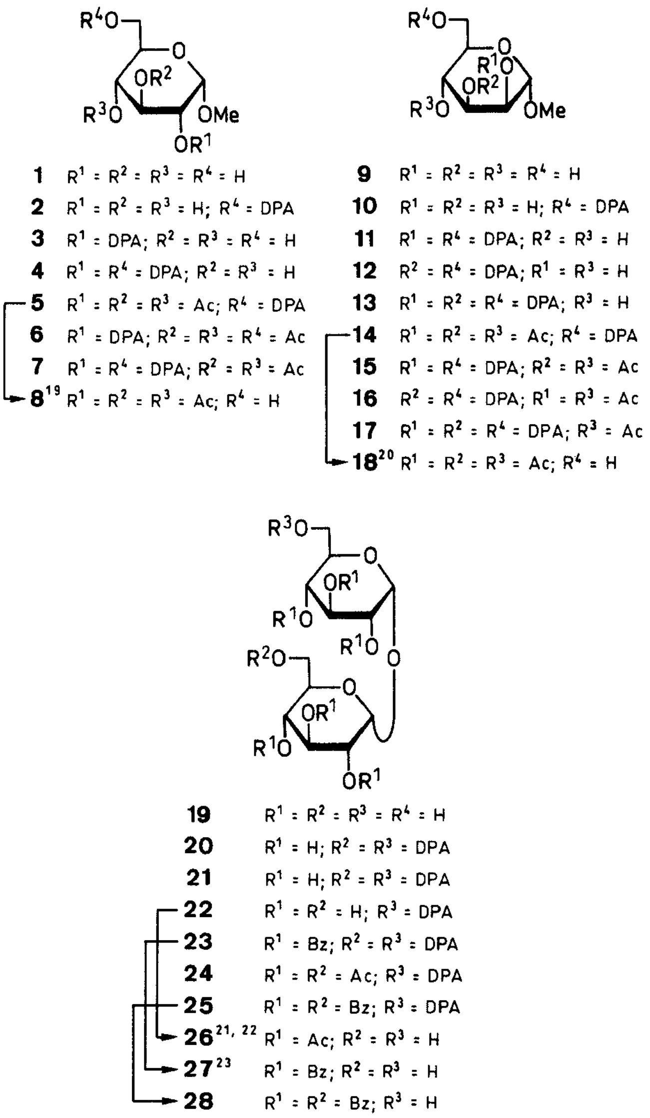
In the field of cyclomaltooligosaccharides (α, β, and γ-cyclodextrins), the *tert*-butylsilyl[6,7] and dimethylthexylsilyl (thexyl ≡ 1,1,2-trimethylpropyl)[8] groups have been used extensively for the protection of 6-HO of these compounds. In search of new protective groups for 6-HO that can be removed under mild and neutral conditions we envisaged that diphenylacetyl chloride (hereafter referred as DPA-Cl) could be an adequate reagent. This is a relatively bulky reagent because of the presence of two phenyl groups. Therefore, a high selectivity for primary hydroxy groups may be expected. In addition, the resulting esters will possess a benzylic hydrogen which can undergo free-radical bromination by treatment with *N*-bromosuccinimide (NBS). Reaction of the resulting bromoesters with thiourea[9–12] or hydrazinedithiocarbonate,[13,14] should allow the removal of the diphenylacetyl group under mild and neutral conditions (Scheme 1).



R = Ac, Bz
DPA = Ph$_2$CHCO

Scheme 1

In order to study the applicability and versatility of DPA-Cl as a new protective reagent, we have assayed first the protection reactions on methyl α-D-glucopyranoside (**1**), methyl α-D-mannopyranoside (**9**) and α,α-trehalose (**19**).



1 $R^1 = R^2 = R^3 = R^4 = H$
2 $R^1 = R^2 = R^3 = H$; $R^4 = DPA$
3 $R^1 = DPA$; $R^2 = R^3 = R^4 = H$
4 $R^1 = R^4 = DPA$; $R^2 = R^3 = H$
5 $R^1 = R^2 = R^3 = Ac$; $R^4 = DPA$
6 $R^1 = DPA$; $R^2 = R^3 = R^4 = Ac$
7 $R^1 = R^4 = DPA$; $R^2 = R^3 = Ac$
8[19] $R^1 = R^2 = R^3 = Ac$; $R^4 = H$

9 $R^1 = R^2 = R^3 = R^4 = H$
10 $R^1 = R^2 = R^3 = H$; $R^4 = DPA$
11 $R^1 = R^4 = DPA$; $R^2 = R^3 = H$
12 $R^2 = R^4 = DPA$; $R^1 = R^3 = H$
13 $R^1 = R^2 = R^4 = DPA$; $R^3 = H$
14 $R^1 = R^2 = R^3 = Ac$; $R^4 = DPA$
15 $R^1 = R^4 = DPA$; $R^2 = R^3 = Ac$
16 $R^2 = R^4 = DPA$; $R^1 = R^3 = Ac$
17 $R^1 = R^2 = R^4 = DPA$; $R^3 = Ac$
18[20] $R^1 = R^2 = R^3 = Ac$; $R^4 = H$

19 $R^1 = R^2 = R^3 = R^4 = H$
20 $R^1 = H$; $R^2 = R^3 = DPA$
21 $R^1 = H$; $R^2 = R^3 = DPA$
22 $R^1 = R^2 = H$; $R^3 = DPA$
23 $R^1 = Bz$; $R^2 = R^3 = DPA$
24 $R^1 = R^2 = Ac$; $R^3 = DPA$
25 $R^1 = R^2 = Bz$; $R^3 = DPA$
26[21,22] $R^1 = Ac$; $R^2 = R^3 = H$
27[23] $R^1 = Bz$; $R^2 = R^3 = H$
28 $R^1 = R^2 = Bz$; $R^3 = H$

Scheme 2

The acylation experiments were performed at low temperature (~ −10 °C) by addition of DPA-Cl in anhydrous pyridine to a solution of the corresponding sugar in anhydrous pyridine. The reaction conditions applied are summarized in Table 1.

Treatment of methyl α-D-glucopyranoside (**1**) with 1.5 equivalents of DPA-Cl gave a mixture of three products (TLC) which were fractioned by column chromatography to yield the 6-*O*-diphenylacetate **2** (40 %), as major product, and the 2-*O*-diphenylacetate **3** (6 %) and the 2,6-di-*O*-diphenylacetate **4** (25 %) as minor compounds.

Similar acylation of methyl α-D-mannopyranoside (**9**) yielded a crude product which was purified by column chromatography. The most mobile component was the 3,6-di-*O*-diphenylacetate **12** (14 %). Eluted next were the 2,6-di-*O*-diphenylacetate **11** (14 %) and the 6-*O*-diphenylacetate **10** (41 %).

Table 1. Regioselective Diphenylacylation of **1**, **9** and **19**

Substrate	DPA-Cl (Equiv)	Time (h)	Solvent[a]	Product	Yield (%)	mp (°C)	$[\alpha]_D^{25}$ (*c*, solvent)	MS (*m*/*z*, %)
1	1.5	12	A	**2**	40	130–131	+73° (1, MeOH)	389 ($M^+ + 1$), 357 (M^+ CH_3O)
				3	6	137–140	+72° (1, MeOH)	389 ($M^+ + 1$), 357 (M^+ CH_3O)
				4	25	50–52	+29° (1, MeOH)	583 ($M^+ + 1$), 551 (M^+ CH_3O)
1	2.2	24	B	**4**	83			
9	1.5	3	C	**10**	41	foam	+12° (1, MeOH)	389 ($M^+ + 1$), 357 (M^+ CH_3O), 339 (M^+ CH_3OH_2O)
				11	14	foam	−11° (1, $CHCl_3$)	583 ($M^+ + 1$), 551 (M^+ CH_3O)
				12	14	foam	+52° (0.5, $CHCl_3$)	357 ($M^+ + 1$ CH_3OPh_2CHCHO)
9	2.2	2	D	**13**	38	syrup	−15° (1, $CHCl_3$)	777 ($M^+ + 1$), 745 (M^+ CH_3O)
19	1.5	12	D	**20**	23	145–146	+110° (1, $CHCl_3$)	753 ($M^+ + Na$)[c]
				21	43	148–151	+86° (1, MeOH)	559 ($M^+ + Na$)[c]
19	2.5	12	D	**20**	69			
				21	27			

[a] Solvent for chromatography, see experimental section.
[b] Satisfactory microanalyses obtained: C ± 0.4, H ± 0.2.
[c] FAB spectra.

Repetition of the above reactions with 2.2 equivalents of DPA-Cl in case of substrate **1** gave 2,6-di-*O*-diphenylacetate **4** (83 %) and in case of starting material **9**, 2,3,6-tri-*O*-diphenylacetate **13** (38 %), respectively, after purification of the crude products by column chromatography.

The results of these reactions indicate the order of reactivity to be 6-HO > 2-HO > 3-HO > 4-HO for methyl α-D-glucopyranoside **(1)** and 6-HO > 2-HO ≈ ≈ 3-HO > > 4-HO for methyl α-D-mannopyranoside **(9)**. This reactivity is similar to that observed for benzoylation of **1**,[15] but quite different to that shown for **9** in this reaction.[16]

Methyl 2,6-di-*O*-diphenylacetyl-α-D-glucopyranoside **(4)** and methyl 2,3,6-tri-*O*-diphenylacetyl-α-D-mannopyranoside **(13)** are appropriate starting materials to be used as building-blocks in oligosaccharides synthesis. Compound **4** may also be an useful intermediate in natural product synthesis.[17]

Treatment of α,α-trehalose **(19)** with 1.5 equivalents of DPA-Cl gave a mixture of two products which were readily fractioned by column chromatography to give the 6,6′-di-*O*-diphenylacetate **20** (23 %) and the 6-*O*-diphenylacetate **21** (43 %). When this reaction was carried out using 2.5 equivalents of DPA-Cl the major product was **21** (69 %) and the minor one was **22** (27 %).

The structures of **2–4**, **10–13**, **20** and **21** were readily determined by ^1H NMR spectroscopy based on the strong deshielding effected by the diphenylacetyl group and by formation of the corresponding peracetylated (**5–7**, **14–17**, **22** and **24**), and the perbenzoylated derivatives (**23**, **25**) obtained by conventional acetylation and benzoylation (see Tables 2, 3, 4 and 5).

The removal of the diphenylacetyl groups from **5**, **14**, **22**, **23**, and **25** was accomplished in a convenient one-pot procedure by reaction of these compounds with NBS followed by treatment with thiourea.[9–12] In this way, compounds **8**,[19] **18**,[20] **26**,[21,22] **27**[23] and **28** were obtained with moderate to good yields (40–86 %). The reaction

Table 2. Physical Data of Acetylated and/or Benzoylated Derivatives **5–7**, **14–17**, **22–25**, **27** and **28**

Product[a]	mp (°C)	$[\alpha]_D^{25}$ (*c*, $CHCl_3$)	MS (*m*/*z*, %)
5	130–132	+94° (1)	515 ($M^+ + 1$), 483 ($M^+ - CH_3O$)
6	syrup	+130° (0.5)	515 ($M^+ + 1$), 483 ($M^+ - CH_3O$)
7	116–118	+111° (0.8)	635 ($M^+ - CH_3O$)
14	syrup	+30° (1)	515 ($M^+ + 1$), 483 ($M^+ - CH_3O$)
15	syrup	+19° (1)	635 ($M^+ - CH_3O$)
16	syrup	+1° (0.7)	667 ($M^+ + 1$), 635 ($M^+ - CH_3O$)
17	syrup	−8° (1)	–
22	65–67	+83° (0.6)	1005 ($M^+ + Na$)
23	87–89	+182° (1)	1377 ($M^+ + Na$)
24	foam	+124° (1)	853 ($M^+ + Na$)
25	68–71	+172° (1)	1262.35719 (M^+)[b]
26	syrup	+163° (1.2)	989 ($M^+ + Na$)[c]
27	100–102	+151° (1.1)	1068.28403 (M^+)[b]

[a] Satisfactory microanalyses obtained: C ± 0.40, H ± 0.20.
[b] High resolution mass spectra.
[c] FAB spectrum.

Table 3. Characteristic ^{1}H NMR Data for **2–7**, **10–17**, **20–25**, **27** and **28**

Compound	$(C_6H_5)_2CH$	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	OCH_3
2	s, 5.19	d, 4.46	dd, 3.15	t, 3.35	dd, 3.00	ddd, 3.47	dd, 4.44	dd, 4.11	s, 3.04
3	s, 5.20	d, 4.74	dd, 4.54			m, 3.20–3.65			s, 3.16
4	s, 5.24	d, 4.74	dd, 4.58	t, 3.61	t, 3.19	m, 3.55	dd, 4.52	dd, 4.19	s, 2.98
	s, 5.23								
5	s, 5.06	d, 4.83	dd, 4.77	dd, 5.42	dd, 4.93	ddd, 3.93	dd, 4.31	dd, 4.20	s, 3.17
6	s, 5.03	d, 4.97	dd, 4.89	t, 5.48	t, 5.01	ddd, 4.14	dd, 4.25	dd, 4.08	s, 3.33
7	s, 5.06	d, 4.88	dd, 4.78	t, 5.44	t, 4.89	ddd, 3.94	dd, 4.31	dd, 4.20	s, 3.13
	s, 5.02								
10	s, 5.09	d, 4.55	dd, 3.83	dd, 3.71	t, 3.56	m, 3.62	m, 4.50	dd, 4.35	s, 3.02
11	s, 5.06	d, 4.66	dd, 5.10	dd, 3.91	t, 3.39	m, 3.69	m, 4.35–4.47		s, 3.15
	s, 5.05								
12	s, 5.12	d, 4.06	s, 3.92	dd, 5.08	br t, 3.67	ddd, 3.74	dd, 4.49	dd, 4.42	s, 3.20
	s, 5.09								
13	s, 5.03	d, 4.61	dd, 5.27	dd, 5.20	t, 3.55	ddd, 3.76	dd, 4.42	dd, 4.35	s, 3.16
	s, 4.95								
	s, 4.70								
14	s, 5.06	s, 4.61	dd, 5.18	dd, 5.29	t, 5.18	ddd, 3.92	dd, 4.32	dd, 4.24	s, 3.14
15	s, 5.07	d, 4.60	dd, 5.26	dd, 5.27	t, 5.13	ddd, 3.90	dd, 4.28	dd, 4.19	s, 3.13
	s, 4.97								
16	s, 5.05	d, 4.60	dd, 5.22	dd, 5.35	t, 5.19	ddd, 3.89	dd, 4.28	dd, 4.20	s, 3.12
	s, 4.94								
17	s, 5.07	d, 4.61	dd, 5.36	dd, 5.35	t, 5.13	ddd, 3.87	dd, 4.24	dd, 4.15	s, 3.11
	s, 5.02								
	s, 4.52								
20	s, 5.18	d, 4.71	m, 3.18	dt, 3.54	dt, 3.06	m, 4.14	br d, 4.36	dd, 4.14	–
21	s, 5.17	d, 4.84		m, 3.00–3.60		m, 3.91	dd, 4.38	dd, 4.11	–
		d, 4.83				m, 3.63	3.00–3.60		
22	s, 5.05	d, 4.85	dd, 4.88	t, 5.41	t, 4.94	m, 4.00–4.08		dd, 4.33	–
23	s, 5.05	d, 5.30	dd, 5.25	t, 6.15	t, 5.41	ddd, 4.09	dd, 3.89	dd, 3.70	–
24	s, 5.04	d, 5.18	m, 4.88–5.05	t, 5.44	m, 4.88–5.05		m, 4.17–4.31		–
		d, 5.03					m, 3.95–4.12		
25	s, 5.45	d, 5.60	dd, 5.43	t, 6.25	t, 5.65	ddd, 4.24	dd, 4.04	dd, 3.91	–
		d, 5.47	dd, 5.31	t, 6.20	t, 5.42	ddd, 4.14	dd, 3.87	dd, 3.71	–
27	–	d, 5.74	dd, 5.41	t, 6.30	t, 5.51	dt, 3.91	dd, 3.18	dd, 2.98	–
28	–	d, 5.74	dd, 5.48	t, 6.33	t, 5.68	ddd, 4.33	dd, 3.96	dd, 2.95	–
		d, 5.73	dd, 5.43	t, 6.28	t, 5.48	dt, ~3.88	dd, 3.85	dd, 3.18	–

[a] Solvent: DMSO-d_6 + D_2O for **2–4** and **21**; $CDCl_3$ for **5–7,10,12–17** and **22–28**; DMSO-d_6 for **11** and **20**.
[b] For J values, please see Table 4.

conditions used are summarized in Table 6, and physical data of **26** and **27** are given in Tables 3 and 4. The moderate yield observed in the deprotection of compound **22** can presumably be ascribed to photobromination of the acetoxy groups in the treatment with NBS owing to the long reaction time used in this case. Blattner et al.[24] have observed in photobromination reactions transformation of acetoxy groups in bromoacetyl and dibromoacetyl derivatives as side products.

The results detailed above prove the utility of DPA-Cl in acylations of carbohydrates with a good regioselectivity. Diphenylacetyl groups can be readily removed under mild and neutral conditions in the presence of other acyl groups such as acetyl or benzoyl.

Application of this reagent in cyclomaltooligosaccharides is underway, and will be reported soon.

Melting points were determinated with a Reichert hotplate microscope and are uncorrected. Solutions were dried (Na_2SO_4) before concentration under diminished pressure. NMR spectra were obtained with a Bruker AM-300 spectrometer. Elemental analyses were performed with a Perkin-Elmer analyzer 240C. MS data (m/z) were obtained by the chemical ionization mode using methane as the ionizing gas with a Hewlett-Packard 5988A instrument and molecular weights were obtained was a Kratos MS-80-RFA instrument. Specific optical rotations were measured with a Perkin-Elmer Polarimeter 141. TLC and column chromatography were performed on precoated silica gel plates (Merck 60 F_{245}) and on Kieselgel 60 (Merck 230–400 mesh), respectively, with the following solvent systems: (A) hexane/EtOAc (1:1); (B) hexane/Et_2O (1:1); (C) $CHCl_3$/MeOH (5:1); (D) $CHCl_3$/MeOH (10:1). All the evaporations were carried out under diminished pressure at 40 °C. Diphenylacetyl chloride (tech., 90%) was purchased from Aldrich Co.

Acylation of 1, 9 and 19 with Diphenylacetyl Chloride; General Procedure:

A solution of diphenylacetyl chloride in anhydr. pyridine (ratio, 1 g:25 mL) was added dropwise to a stirred and chilled (~ −10 °C) solution of the corresponding sugar in anhydr. pyridine (ratio, 1 g:30 mL). The mixture was kept at this temperature for the period indicated in Table 1. MeOH (25 mL) was added and the mixture evaporated and coevaporated with toluene. The residue was purified by column chromatography using eluents as indicated in Table 1.

Table 4. J Values (Hz) for the ^{1}H NMR Data of **2–7, 10–17, 20–25, 27** and **28**

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
2	3.6	9.6	~9.0	~10.0	2.0	7.0	11.7
3	3.6	10.0	–	–	–	–	–
4	3.6	10.0	~9.3	~9.3	1.6	6.7	11.8
5	3.6	10.0	9.4	10.0	2.4	5.7	12.1
6	3.7	10.2	~9.5	~10.0	2.4	4.6	12.3
7	3.6	10.3	~9.2	~10.0	2.4	5.7	12.1
10	0.8	3.1	9.2	~9.7	–	7.7	11.7
11	1.7	3.3	9.0	~10.3	–	–	–
12	1.8	3.2	10.0	~9.5	2.4	4.8	12.0
13	1.8	3.4	9.6	~9.5	2.5	5.8	11.9
14	1.7	3.4	10.0	~10.0	2.8	6.5	12.0
15	1.2	3.5	9.9	~9.8	2.7	6.6	12.0
16	1.7	3.4	10.1	~10.5	2.8	6.8	12.0
17	1.6	3.4	8.1	~10.5	2.6	6.9	12.0
20	3.6	9.1	~9.1	~9.5	–	5.1	11.5
21	3.7	–	–	–	2.0	5.3	11.8
	3.2						
22	3.8	9.5	~9.5	~9.8	–	6.9	12.4
23	3.9	10.0	~9.5	~9.5	2.2	5.2	12.3
24	3.8	–	~9.5	~9.5	–	–	–
	4.0						
25	3.8	9.8	~9.9	~9.6	2.2	4.7	12.4
	3.8	10.1	~9.9	~9.8	2.7	5.1	
27	3.9	10.2	~9.9	~9.9	2.0	2.8	13.2
28	4.0	10.1	~9.9	~9.9	2.7	4.5	12.4
	3.9	10.1	~9.9	~9.9	2.0	2.6	13.4

Removal of Diphenylacetyl Chloride Group from 5, 14, 22, 23, and 25; General Procedure:

To a solution of the corresponding sugar in freshly destilled CCl_4 (ratio, 1 g: 50 mL) was added NBS and $Ba(CO_3)_2$ (2 equiv./1 equiv. NBS). The suspension was heated at the reflux temperature with efficient stirring and the mixture was irradiated directly with a 60-W incandescent bulb for a period indicated in Table 6. The reaction mixture was filtered and washed with CCl_4 (25 mL). The filtrate and washings were evaporated under diminished pressure. The crude product was dissolved in anhydr. MeCN and thiourea was added. After heating at the reflux temperature with stirring for the time indicated in Table 6 and evaporation of the reaction mixture, EtOAc was added, and washed with water. The organic layer was dried, filtered and evaporated. The resulting crude product was purified by column chromatography.

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Table 5. Characteristic ^{13}C NMR Data for **2–7, 10–17, 20–25, 27** and **28** ($CDCl_3$/TMS, δ)

Compound	C-1	C-2, C-3, C-4, C-5	C-6	OCH_3, $(C_6H_5)_2\underline{C}H$
2[a]	99.5	73.0, 71.6, 70.2, 69.5	64.3	55.9, 54.0
3[a]	96.0	74.1, 72.5, 70.2, 70.2	60.4	56.1, 55.5
4[a]	96.1	73.7, 70.3, 70.0, 69.6	63.8	56.2, 54.2, 55.9
5[a]	96.4	70.9, 70.0, 68.9, 67.2	62.8	56.9, 55.5
6[a]	96.8	71.5, 69.6, 68.6, 67.3	62.0	56.9, 55.1
7	96.4	71.4, 69.5, 68.9, 67.3	62.8	57.0, 56.9, 55.2
10	100.6	71.5, 70.4, 70.2, 67.8	64.8	57.1, 54.5
11	98.2	72.6, 70.1, 70.1, 68.2	64.4	57.0, 54.9, 57.0
12	100.5	75.1, 70.8, 69.1, 65.6	63.8	57.2, 55.0
13	98.4	72.7, 70.6, 70.5, 66.3	64.2	57.2, 57.1, 56.8, 55.1
14	98.2	69.5, 69.2, 68.3, 66.0	63.4	56.8, 56.8, 54.8
15	98.3	70.0, 69.2, 68.5, 66.5	63.7	57.0, 55.0
16	98.0	69.5, 69.2, 68.3, 66.0	63.4	56.8, 56.8, 54.8
17	98.2	70.1, 69.7, 68.7, 66.0	63.7	57.0, 56.9, 56.3, 55.0
20[a]	93.3	72.5, 71.2, 69.9, 69.6	63.7	55.9
21[a]	93.2	72.7, 72.5, 72.4, 71.5	63.7	–, 55.9
	93.1	71.2, 70.0, 69.9, 69.6	60.6	–
22	91.9	70.1, 69.6, 68.9, 67.9	62.6	56.6
23	91.6	70.9, 70.1, 68.3, 68.1	61.5	56.5
24	92.2	70.2, 70.0, 69.9, 69.8	62.6	–, 56.7
	92.1	68.9, 68.6, 68.2, 68.0	61.8	–
25	92.1	71.2, 70.4, 68.8, 68.6	62.0	56.7
			61.8	
27	93.0	71.5, 70.6, 70.1, 68.8	59.8	–
28	93.0	71.5, 70.6, 70.3, 70.0	61.9	–
	92.7	71.3, 68.9, 68.7, 68.5	59.8	–

[a] Measured in DMSO-d_6.

Table 6. Cleavage of Diphenylacetate Derivatives **5, 14, 22, 23** and **25**

Substrate	NBS (Equiv)	Time (h)	Thiourea (Equiv)	Time (h)	Product	Yield (%)	mp (°C)		$[\alpha]_D^{25}$ (*c*, solvent)	
							found	reported		
5	1.5	7	6	5	**8**	88	110–112	111[19]	+127° (1, $CHCl_3$)	149°[19]
14	3.3	24	10	6	**18**	81	100	97–98[20]	+50° (1, $CHCl_3$)	55°[20]
22	4.0	48	10	24	**26**	40	84–86	82–86[21,22]	–	–
23	6.6	24	20	24	**27**	59	syrup	syrup[21]	+163° (1.2, $CHCl_3$)	–
25	4.0	24	8	16	**28**[a]	59	100–102	–	+151 (1.1, $CHCl_3$)	–

[a] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.2.

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