Synthesis of 3-Alkylated Triacetonamine Derivatives

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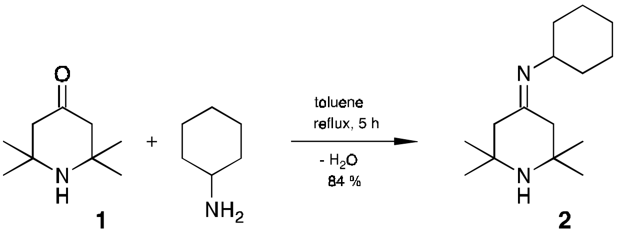
Abstract. Reaction of a lithiated imine derivative of 2,2,6,6-tetramethyl-4-piperidone (triacetonamine, **1**) with activated or less reactive alkyl halides or styrene oxide and subsequent hydrolysis afforded 3-alkylated triacetonamine derivatives. Thus, 3-benzyl-2,2,6,6-tetramethyl-4-piperidone (**3**), 3-(*n*-butyl)-2,2,6,6-tetramethyl-4-piperidone (**4**), 3-(3-chloropropyl)-2,2,6,6-tetramethyl-4-piperidone (**5**), 2,2,3,6,6-pentamethyl-4-piperidone (**6**) and two diastereomers of 3-(2-hydroxy-2-phenylethyl)-2,2,6,6-tetramethyl-4-piperidone (**7**) were prepared in 26–53 % yield. Reaction of the imine anion derived from **1** with benzyl bromide to give **3** has to be performed at low temperatures in order to avoid a competing proton transfer. No reaction at the unprotected piperidine nitrogen was observed.

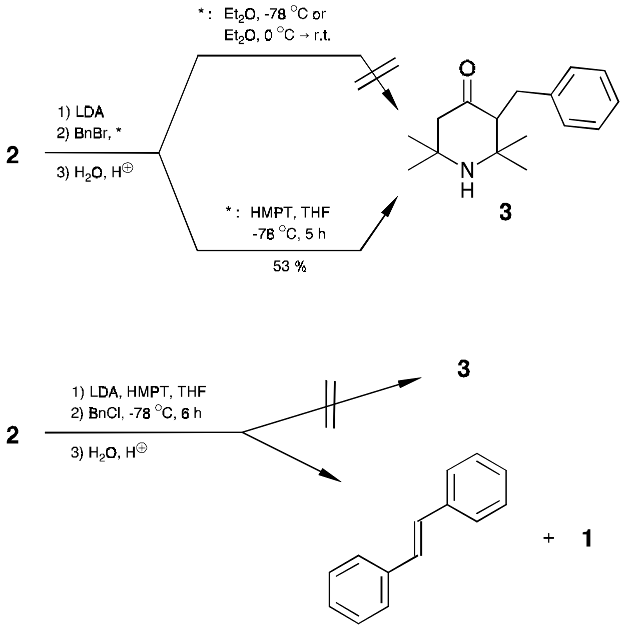
Sterically hindered amines derived from 2,2,6,6-tetramethylpiperidine are widely used in several fields. Some compounds of this type have physiological effects such as antitumor activity, analgesic, antipyretic and anticholinergic activity [1, 2]. Based on their capability to form stable, isolable nitroxyl radicals [3], sterically hindered amines of this type are used as precursors for spin labels [4] and for highly efficient light stabilizers [5], in "living" free radical polymerizations [6] and as an auxiliary for various preparatively useful oxidations of organic compounds [7]. Consequently, there is a considerable interest in obtaining new compounds bearing a sterically crowded piperidine function. Triacetonamine (2,2,6,6-tetramethyl-4-piperidone, **1**) is the most common starting material for 2,2,6,6-tetramethylpiperidine derivatives. Usually, **1** can be modified at the carbonyl group without special difficulties. However, there are comparatively few examples of reactions of **1** at the carbon C-3, presumably due to steric hindrance [2]. For example, there is no satisfying procedure for the 3-alkylation of triacetonamine enamines or enolates with simple alkyl halides. We wish to report here a convenient method for the 3-alkylation of **1** with primary alkyl halides.

The only reported example of a triacetonamine enolate alkylation with an alkyl halide was performed by treating the *N*-methyl-3-methylene derivative of triacetonamine with methyl iodide in liquid ammonia in presence of lithium/*tert*-butanol to give a mixture of *C*- and *O*-methylated products [8]. Reaction of triacetonamine lithium enolate with larger and harder alkyl halides than methyl iodide in a non-protic solvent would presumably yield even more *O*-alkylated product. In addition, the hindered piperidine nitrogen of **1** can act as a competing nucleophilic site in some cases [2]. The solution of this problem by using a protecting group is not trivial because *N*-acylations of **1** result in a dramatic promotion of piperidine ring cleavage [2, 9]. For those reasons, the ideal triacetonamine derivative for the reaction with alkyl halides and other electrophiles at 3-position should have maximum nucleophilicity at the carbon C-3 in order to avoid both *N*-protection and *O*-alkylation. According to Stork *et al.* [10] and others [11], alkylation of metalated imines is a useful method of preparing α-alkylated carbonyl compounds. In comparison with the corresponding enolates, metalated imines are more reactive at the deprotonated α-carbon, and they tend considerably less towards undesired proton transfers and towards alkylations at the heteroatom [11]. Therefore, we investigated the reaction of the lithiated cyclohexylimine **2** with alkyl halides.



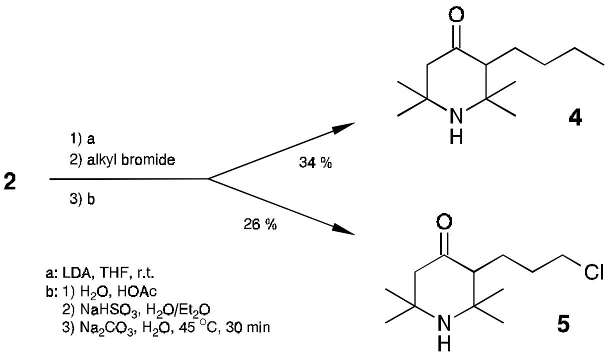
Scheme 1

For the benzylation, imine **2** was metalated with LDA in THF and, after addition of one equivalent of hexamethylphosphoric triamide (HMPT), the anion of **2** reacted readily with benzyl bromide at –78 °C, which was accompanied by a color change from reddish-brown to yellow. Acidic hydrolysis and work-up afforded 3-benzyl triacetonamine (**3**) in 53% yield. The choice of a proper solvent system is essential for this benzylation. Thus, lithiated imine **2** was treated with benzyl bromide in diethyl ether, without addition of HMPT, at –78 °C. After aqueous acidic work-up, no benzyl ketone **3** was obtained. When lithiated imine **2** dissolved in diethyl ether was treated with benzyl bromide at 0 °C, no reaction was observed whereas warming-up to room temperature caused a color change towards reddish-black. After work-up, no benzyl ketone **3** was obtained but *trans*-stilbene was detected by GC-MS and NMR, thus indicating a proton transfer from benzyl chloride to the imine anion. The same proton transfer was observed when benzyl chloride was added at –78 °C to a solution of lithiated **2** in THF in presence of one equivalent of HMPT (Scheme 2).



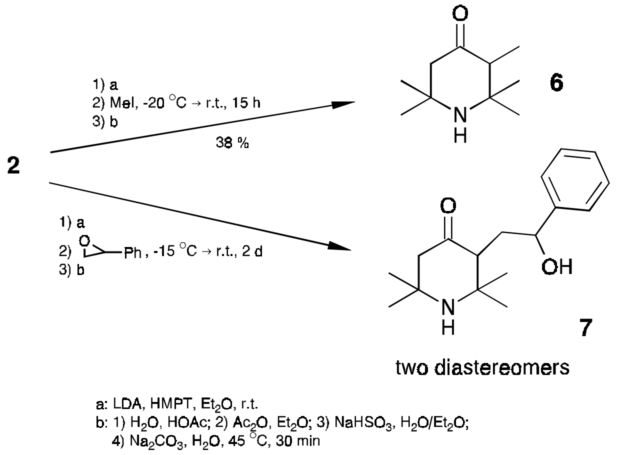
Scheme 2

With simple aliphatic alkyl bromides, no competing side reactions such as piperidine alkylation or proton transfer are to be expected. Thus, alkylations of lithiated imine **2** with *n*-butyl bromide or 1-bromo-3-chloropropane proceeded readily in THF without HMPT at room temperature to give the 3-alkylated ketones **4** and **5**, respectively. Reaction of 1-bromo-3-chloropropane occurred chemoselectively at the brominated carbon as expected [12] (Scheme 3).



Scheme 3

Whereas triacetonamine (**1**) is methylated by methyl iodide in high yields at the piperidine nitrogen at room temperature or elevated temperatures [13], lithiated imine **2** in ether/HMPT solution reacted with methyl iodide exclusively at 3-position. Aqueous acidic work-up afforded 3-methyl triacetonamine (**6**). Similarly, the anion of **2** reacted with racemic styrene oxide to give, after hydrolysis, alcohol **7** as two diastereomers (Scheme 4). In both cases, HMPT was added in order to promote the *C*-alkylation over a competing piperidine alkylation [2] or alkylation of LDA. Both the alkylation with methyl iodide and with styrene oxide were performed in ether/HMPT in order to test the suitability of diethyl ether as solvent, though THF is clearly expected to be the better solvent for a high nucleophilictiy of the imine anion.



Scheme 4

Concerning the work-up procedures, several methods were tested. The partial imine formation from the alkylated piperidone and cyclohexylamine after hydrolysis is a problem because the usual direct separation procedure after acidic hydrolysis is not possible with the basic piperidones. Attempted chromatographic separations of cyclohexylamine and triacetonamine (**1**) and its derivatives were shown to be difficult by TLC. In the case of the crystalline α-benzyl ketone **3**, the ammonium acetate of **3** was separated from the acidic aqueous solution by extraction with methylene chloride, and after dissolving the residue in water and addition of sodium carbonate, the ketone **3** precipitated, but it was contaminated by the oily imine. This could be removed by washing with pentane. Since this method is not suitable for liquid products, we separated the ketones **4**–**6** *via* their hydrogen sulfite adducts. The isolated yields are quite low because the sulfite adducts did not crystallize completely, presumably due to the formation of water-soluble piperidinium sulfites and to imine formation. However, this procedure is advantageous because of its convenience. The cyclohexylamine formed by imine hydrolysis can be separated from the piperidone by treatment with acetic anhydride and subsequent removal of the resulting cyclohexyl acetamide by extraction from the acidic aqueous solution. This method was used for the work-up of compounds **6** and **7**. The comparatively low yields of the alkylated piperidones are clearly due to the work-up procedures. GC-MS analyses of the crude mixtures after acidic hydrolysis, before further work-up, showed the alkylated piperidones to be formed in nearly quantitative yields.

In conclusion, alkylation of lithiated imine **2** is a useful way to obtain 3-alkylated triacetonamine derivatives. With reactive alkylating agents the alkylations were performed in presence of HMPT at lower temperatures, and with aliphatic alkyl bromides in THF at room temperature. The advantage of the method is the high nucleophilicity of the imine anion, thus allowing *C*-alkylations of triacetonamine (**1**) without piperidine protection and even with comparatively weak electrophiles. In the future, it should be possible to extend this synthetic route to a broader variety of electrophiles and to a stereoselective method by using chiral amines instead of cyclohexylamine, according to reported examples [14]. Possibly, the cancerogenic HMPT may be substituted by a less dangerous cosolvent [15].

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Experimental

NMR spectra were recorded in $CDCl_3$ with $CHCl_3$ or TMS as internal standard on Bruker AC-300 P (300 MHz for ^1H and 75 MHz for ^{13}C). ^{13}C peaks were assigned by means of DEPT spectra. MS were recorded on a Hewlett Packard GC-MS device (5890 Series II, EI, 70 eV, quadrupole). Elemental analyses were performed on a Carlo Erba CHN-S Elemental Analyzer 1108. LDA solutions were prepared according to the literature [16] by using BuLi hexane solutions (1.5 to 2.5 M). BuLi concentrations were determined according to reference [17]. Lithiations and alkylations were performed in flasks closed by rubber septa and filled with Ar, by using syringes for reagent additions and needles for flushing with the inert gas. The solvents for the lithiations and alkylations were dried by standard methods.

N-Cyclohexyl-N-(2,2,6,6-tetramethyl-4-piperidinyliden) amine (2)

A mixture of **1**·H_2O (13.8 g, 80 mmol) and cyclohexylamine (27.4 ml, 240 mmol) in toluene (200 ml) was refluxed for 5 h with using a water collector. After evaporating the solvent, the resulting red oil was distilled *in vacuo*. Excess cyclohexylamine was removed at *r.t.*/2.5 torr, and a first distillate fraction (about 1 ml, partly crystallizing in the condenser) at 90 °C/0.8 torr was observed. The second fraction (completely liquid) at 98–100 °C/0.65 torr was collected to give 15.8 g (84%) of imine **2** as a yellowish oil that was stored under Ar. ^1H NMR: δ/ppm = 1.06/1.07 (2s, 12H, 2-/6-Me), 1.10–1.72 (m, 10H, cyclohexyl CH_2), 2.06/2.10 (2s, 4H, 3-/5-H), 3.22 (m, 1H, =N–CH). – ^{13}C NMR: δ/ppm = 24.6 (cyclohexyl C-3/C-5), 25.2 (cyclohexyl C-4), 31.0/31.4 (2-/6-Me), 33.7 (cyclohexyl C-2/C-6), 41.3 (C-3 *cis* to cyclohexyl), 51.7 (C-5 *trans* to cyclohexyl), 53.0/53.4 (C-2/C-6), 58.2 (cyclohexyl C-1), 166.5 (C=N). – MS: *m/z* (%) = 236 (17) [M^+], 235 (100), 138 (27), 82 (28), 55 (22), 42 (15), 41 (25), 39 (11), 32 (77), 29 (11).

$C_{15}H_{28}N_2$	Calcd.:	C 76.21	H 11.94	N 11.86
(236.39)	Found:	C 75.95	H 11.86	N 11.93.

3-Benzyl-2,2,6,6-tetramethyl-4-piperidone (3)

To a freshly prepared solution of LDA (2.1 mmol) in THF (3 ml), a solution of HMPT (0.36 g, 2.0 mmol) in THF (1 ml) was added. A solution of imine **2** (0.472 g, 2.00 mmol) in THF (1 ml) was added dropwise at 0 °C. After being stirred at 0 °C for 20 min, the reddish-brown solution was cooled to –78 °C under Ar flushing, and a solution of BnBr (0.359 g, 2.10 mmol) in THF (1 ml) was added dropwise over 10 min. The mixture was stirred at –78 °C for 5 h, and H_2O (1 ml) was added. After removing the dry-ice bath, the mixture was stirred with a solution of HOAc (0.7 ml, 12 mmol) in H_2O (15 ml) for 15 min. After being washed with *n*-pentane (1× 20 ml), the acidic aqueous layer was extracted with CH_2Cl_2 until it turned colorless. The CH_2Cl_2 was removed by evaporation, and the resulting oil was dissolved in H_2O (20 ml). Under vigorous stirring, solid Na_2CO_3 was added to give a solid precipitate. This was collected, washed with H_2O and dried. The crude product was suspended in *n*-pentane (2 ml), filtered and washed with *n*-pentane to give 0.261 g (53%) of pure ketone **3** as a white solid, *m.p.* 99–100 °C. – ^1H NMR: δ/ppm = 1.12 (s, 3H)/1.18 (s, 3H)/1.24 (s, 3H)/1.37 (s, 3H) (2-/6-Me), 2.23–2.32 (AB system, 2H, *J* = 12.0 Hz, 5-H), 2.50 (dd, 1H, *J* = 13.6 Hz and 2.3 Hz, Ph-$C\underline{H}_a$), 2.59 (dd, 1H, *J* = 9.8 Hz and 2.3 Hz, 3-H), 3.13 (dd, 1H, *J* = 13.6 Hz and 9.8 Hz, Ph-$C\underline{H}_b$), 7.12–7.32 (m, overlapped with $CHCl_3$ signal, Ph). – ^{13}C NMR: δ/ppm = 24.0 (2-Me), 28.1/30.9/32.8 (2-/6-Me), 30.2 (Ph-$\underline{C}H_2$), 54.1 (C-5), 57.6 (C-6), 61.4 (C-2), 62.1 (C-3), 126.0 (Ph C-4), 128.3/128.9 (Ph C-2/C-3), 140.6 (Ph C-1), 208.3 (C=O). – MS: *m/z* (%) = 245 (22) [M^+], 230 (18) [$M^+ - CH_3$], 136 (15), 131 (26), 104 (21), 98 (43), 91 (94) [$PhCH_2^+$], 83 (26), 77 (14), 65 (14), 58 (100), 55 (15), 42 (49), 39 (14), 32 (16).

$C_{16}H_{23}NO$	Calcd.:	C 78.32	H 9.45	N 5.71
(245.35)	Found:	C 78.24	H 9.54	N 5.70.

3-(n-Butyl)-2,2,6,6-tetramethyl-4-piperidone (4)

To a freshly prepared solution of LDA (2.1 mmol) in THF (3 ml), a solution of imine **2** (0.472 g, 2.00 mmol) in THF (1 ml) was added dropwise. After stirring for 15 min, *n*-butyl bromide (0.22 ml, 2.0 mmol) was added. After being stirred for 14 h at *r.t.*, the resulting yellowish suspension was treated subsequently with H_2O (1 ml) and with HOAc (0.8 ml, 14 mmol) in H_2O (8 ml). After 15 min of stirring, aqueous NaOH was added till pH~12, and the mixture was extracted with Et_2O. In a beaker, the Et_2O extract was treated with saturated aqueous $NaHSO_3$ (5 ml) under intensive stirring for 5 min. After further 15 min, filtration and washing with Et_2O afforded white crystals. These were dissolved in a solution of Na_2CO_3 (0.7 g, 7 mmol) in H_2O (15 ml) and stirred for 30 min at 45 °C. The resulting emulsion was extracted with Et_2O and dryed ($NaSO_4$), and removal of the solvent gave 0.144 g (34%) of ketone **4** as a yellow oil. – ^1H NMR: δ/ppm = 0.82 (t, 3H, *J* = 7.1 Hz, butyl Me), 0.97 (s, 3H, 2-Me_a), 0.99–1.29 (m, butyl 1-H_a/2-/3-H) overlapped with 1.12 (s, 2-Me_b) and 1.20 (s, 6-Me) (together 14H), 1.57 (br s, NH) overlapped with 1.60–1.71 (m, butyl 1-H_b) (together 2H), 2.12 (dd, 1H, *J* = 10.9 Hz and 2.1 Hz, 3-H), 2.20–2.29 (AB system, 2H, *J* = 12.1 Hz, 5-H). – ^{13}C NMR: δ/ppm = 13.8 (butyl Me), 22.8 (butyl C-3), 24.9 (butyl C-1), 25.6 (2-Me), 30.1/32.0/33.7 (2-/6-Me), 30.9 (butyl C-2), 54.5 (C-5), 55.8 (C-6), 59.1 (C-2), 61.3 (C-3), 211.9 (C=O). – MS: *m/z* (%) = 211 (13) [M^+], 196 (25) [M^+ – CH_3], 168 (35), 121 (28), 112 (16), 98 (30), 83 (45), 69 (17), 58 (100), 55 (44), 43 (20), 42 (54).

$C_{13}H_{25}NO$ Calcd.: C 73.88 H 11.92 N 6.63
(211.34) Found: C 73.53 H 12.07 N 6.50.

3-(3-Chloropropyl)-2,2,6,6-tetramethyl-4-piperidone (**5**)

To a freshly prepared solution of LDA (1.0 mmol) in THF (2 ml), a solution of imine **2** (0.236 g, 1.00 mmol) in THF (1 ml) was added dropwise. After being stirred for 15 min at *r.t.*, the reddish-brown solution was cooled to –78 °C under Ar flushing, and a solution of 1-bromo-3-chloropropane (0.157 g, 1.00 mmol) in THF (1 ml) was added dropwise over 15 min. The mixture was warmed to 0 °C while it turned yellow. After being stirred at 0 °C for 1 h, the mixture was left to stand at *r.t.* for 19 h. Work-up and purification as described for compound **4** afforded 0.061 g (26%) of chloroketone **5** as a yellow oil. – ^{1}H NMR: δ/ppm = 1.02 (s, 3H, 2-Me), 1.15 (s, 3H)/1.24 (s, 3H)/1.26 (s, 3H) (2-Me/6-Me), 1.36–1.94 (m, 5H, $C\underline{H}_2$–$C\underline{H}_2$–CH_2Cl and NH), 2.19 (dd, 1H, *J* = 10.6 Hz and 2.0 Hz, 3-H), 2.30 (“s”, 2H, 5-H), 3.46–3.59 (m, 2H, CH_2Cl). – ^{13}C NMR: δ/ppm = 22.4 (C-1'), 25.3 (2-Me), 29.7/32.2/34.0 (2-/6-Me), 31.4 (C-2'), 45.1 (CH_2Cl), 54.9 (C-5), 56.0 (C-6), 59.3 (C-2), 60.7 (C-3), 211.5 (C=O). – MS: *m/z* (%) = 233 (4)/231 (12) [M^+], 218 (9)/216 (28) [M^+ – CH_3], 168 (37), 112 (14), 98 (28), 84 (18), 83 (29), 58 (100), 55 (40), 42 (50), 41 (29), 39 (12).

$C_{12}H_{22}NOCl$ Calcd.: C 62.19 H 9.57 N 6.04
(231.75) Found: C 62.45 H 9.71 N 6.14.

2,2,3,6,6-Pentamethyl-4-piperidone (**6**)

To a freshly prepared solution of LDA (3.1 mmol) and HMPT (0.57 ml, 3.0 mmol) in Et_2O (6 ml), a solution of imine **2** (0.710 g, 3.00 mmol) in Et_2O (1.5 ml) was added dropwise. After being stirred for 20 min, the reddish-brown solution was cooled to –20 °C under Ar flushing, and MeI (0.19 ml, 3.0 mmol) was added dropwise over 15 min. The mixture was stirred at –20 °C for 30 min and left to stand at *r.t.* for 15 h. After addition of HOAc (1.43 ml, 25 mmol) dissolved in H_2O (20 ml), the mixture was stirred for 10 min, and the Et_2O was removed by evaporation. The resulting solution was treated with NaOH until pH~12 and extracted with Et_2O. To the undried Et_2O extract, Ac_2O (0.46 g, 4.5 mmol) was added, and the solvent was evaporated. The oily residue was treated with H_2O (25 ml) and 37% HCl (2 drops), washed with *n*-pentane/Et_2O 1:1 (2×20 ml), stirred intensively with active charcoal (0.3 g) and filtered. To the clear yellow filtrate, NaOH was added till pH~12. After extraction with Et_2O, the product was purified *via* its $NaHSO_3$ adduct as described for **4**. Thus, 0.199 g (38%) of ketone **6** was obtained as a yellow oil still containing traces of **1** (NMR: 4%). – ^{1}H NMR: δ/ppm = 0.94 (d, 3H, *J* = 6.7 Hz, 3-Me), 0.98 (s, 3H, 2-Me_a), 1.11 (s, 3H)/1.21 (s, 6H) (2-Me_b/6-Me), 2.26 (“s”, 5-H) overlapped with 2.29 (q, *J* = 6.7 Hz, 3-H) (together 3H). – ^{13}C NMR: δ/ppm = 9.7 (3-Me), 24.9 (2-Me), 29.6/32.3/34.2 (2-/6-Me), 54.3 (C-5), 55.0 (C-3), 55.3 (C-2), 58.7 (C-6), 212.3 (C=O). – MS: *m/z* (%) = 169 (36) [M^+], 154 (46) [M^+ – CH_3], 112 (21), 98 (52), 97 (16), 84 (24), 83 (30), 70 (17), 69 (18), 58 (100), 57 (19), 56 (25), 42 (76), 41 (33), 39 (19).

Reaction of Lithiated Imine 2 with Styrene Oxide: Synthesis of 3-(2-Hydroxy-2-phenylethyl)-2,2,6,6-tetramethyl-4-piperidone (7)

To a freshly prepared solution of LDA (2.0 mmol) and HMPT (0.38 ml, 2.0 mmol) in Et_2O (6 ml), a solution of imine **2** (0.473 g, 2.00 mmol) in Et_2O (1 ml) was added dropwise. After being stirred for 20 min, the reddish-brown solution was cooled to –15 °C under Ar flushing, and racemic styrene oxide (0.23 ml, 2.0 mmol) dissolved in Et_2O (1 ml) was added dropwise over 15 min. The mixture was stirred at –15 °C for 2 h and at *r.t.* for 2 d. After addition of HOAc (0.86 ml, 15.0 mmol) dissolved in H_2O (15 ml), the mixture was stirred for 10 min, and the Et_2O was removed by evaporation. The resulting solution was treated with 37% HCl (0.1 ml), washed with *n*-pentane (1×20 ml), and NaOH was added till pH ~12. After extraction with Et_2O, the Et_2O extract was treated as described for **6** but with employing 0.22 g (2.1 mmol) of Ac_2O, 20 ml of H_2O, 0.1 ml of 37% HCl, 3×20 ml of *n*-pentane/Et_2O 2:1 and 0.5 g of active charcoal. For the separation of **7** *via* the $NaHSO_3$ adducts, the resulting mixture was dissolved in Et_2O (5 ml), and 3 ml of saturated $NaHSO_3$ and subsequently 0.5 g of Na_2CO_3 in 5 ml of H_2O were used as described above. Thus, 0.106 g of a yellow viscous oil containing mainly the two diastereomers **7**' and **7**'' was obtained (NMR: 50% **7**' : 40 % **7**'' : 5 % **1** : 5% *N*-cyclohexylacetamide). – ^{13}C NMR: diastereomer **7**': δ/ppm = 24.9 (2-Me), 29.1/31.9/34.2 (2-/6-Me), 34.7 ($\underline{C}H_2$–CHOH), 55.3 (C-5), 55.9 (C-6), 57.1 (C-3), 59.3 (C-2), 71.8 (Ph-$\underline{C}$H–OH), 125.3 (Ph C-2/C-6), 127.1 (Ph C-4), 128.2 (Ph C-3/C-5), 145.3 (Ph C-1), 212.6 (C=O); diastereomer **7**'': δ/ppm = 25.1 (2-Me), 29.4/31.8/34.0 (2-/6-Me), 34.4 ($\underline{C}H_2$–CHOH), 55.0 (C-5), 55.8 (C-6), 58.9 (C-3), 59.3 (C-2), 73.8 (Ph-$\underline{C}$H–OH), 126.0 (Ph C-2/C-6), 127.5 (Ph C-4), 128.4 (Ph C-3/C-5), 144.4 (Ph C-1), 212.9 (C=O).

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