84. Selective Monoderivatization of Propane-1,3-diamine with Acid Chlorides: 'Hexahydropyrimidine Method' *vs.* Statistic Methods

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The selective *N*-monoderivatization of propane-1,3-diamine (**5**) with carbonyl and sulfonyl chlorides *via* 2-phenylhexahydropyrimidine (**6**) was compared with the direct statistic monoderivatization. It was found that, under optimized conditions, both methods are competitive to one another, depending, however, strongly on the reactivity of the electrophile used. The 'hexahydropyrimidine method' is more reliable with respect to yields, which are moderate but invariably between 54 and 69%, whereas the 'statistic method' leads in certain cases to exceptionally high yields (up to 96%), in others, however, almost none.

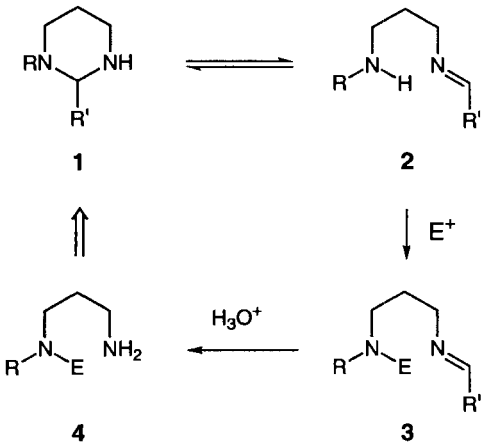
Introduction. – Naturally occurring polyamines have been shown to be important in living cells. For instance, they show high affinity towards nucleic acids and provide numerous effects on nucleic-acid biosynthesis and metabolism [1]. Not only the polyamines but also natural and artificial polyamine derivatives display [2–5] various physiological activities. Polyamines are also used as spacer elements for the interconnection of receptor pharmacophores to form unsymmetrical bivalent ligands [6] or for the linkage of pharmacophores with alkylating or photolabile groups to generate affinity labels [7]. For the chemical synthesis of such physiologically interesting derivatives, polyamines in their terminally *N*-monoprotected form represent the starting material of choice [8–14]. Preparation of these compounds, however, is not facile [3] [15], not even in the simplest cases of the synthesis of *N*-monoderivatized alkane-α,ω-diamines.

In [16], we have reported that *N*-substituted propane-1,3-diamines can efficiently be monoderivatized at the secondary N-atom using a hexahydropyrimidine intermediate of type **1**. We have proposed that heterocycles of type **1** rapidly undergo ring opening to imino-amino species of the type **2**, which, in turn, react with eletrophiles to compounds of type **3**. These gave, after hydrolysis, rise to the corresponding diamine derivatives of type **4** (*Scheme 1*). The hexahydropyrimidine moieties acted in this reaction sequence as the precursors of the protecting imino groups for the aliphatic primary amines. Since this procedure should invariantly lead to analogous products starting from hexahydropyrimidines that are not substituted at the N-atoms, we expected the hexahydropyrimidine protocol for monoderivatization of propane-1,3-diamine (**5**) to be a competitive alternative to the statistic methods used so far [17–22].

We describe in this paper our results obtained with 2-phenylhexahydropyrimidine as the precursor of *N*-monofunctionalized propane-1,3-diamines **12a–d** (*Scheme 2*) and compare our findings to results of an optimized statistic derivatization method.

[1]) Part of the planned Ph.D. thesis of *C. J.*

Scheme 1



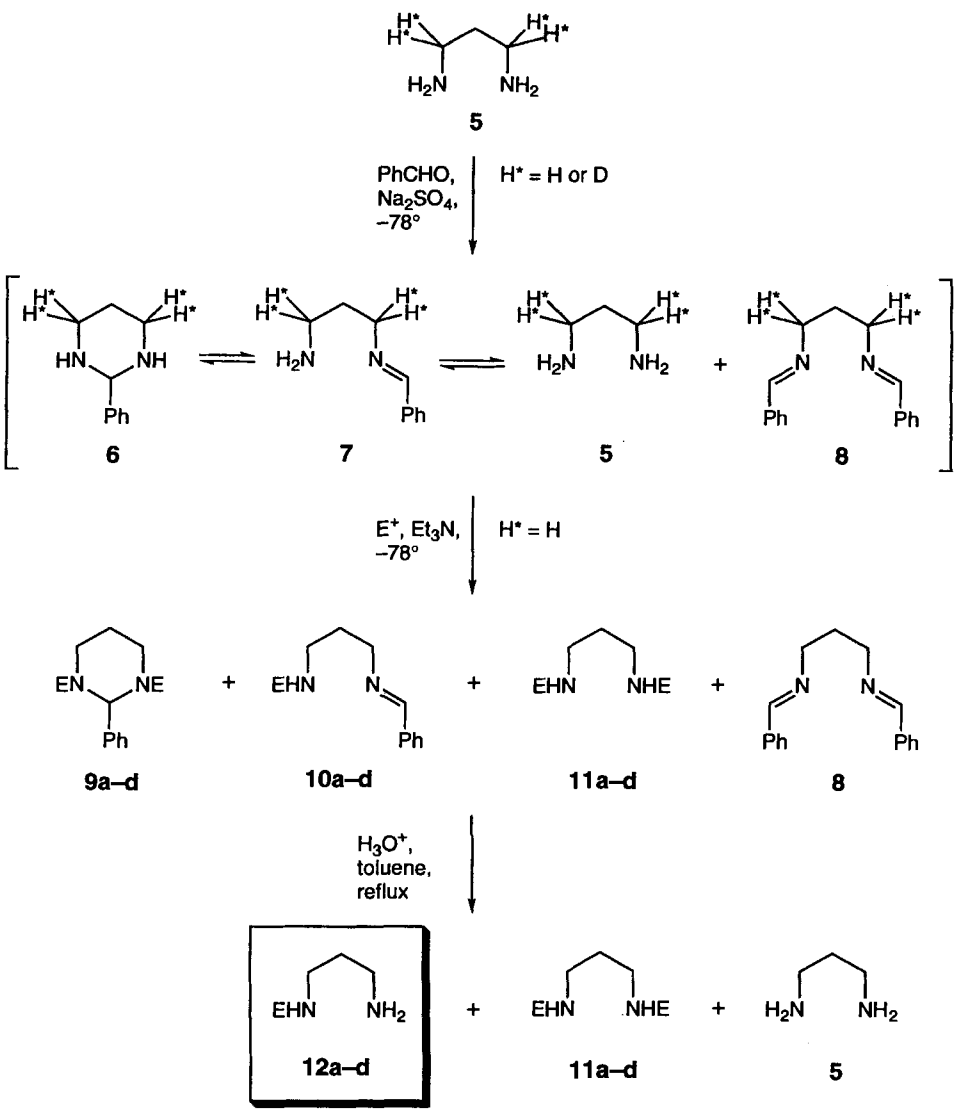
Results and Discussion. – *Derivatization* via *2-Phenylhexahydropyrimidine*. 2-Phenylhexahydropyrimidine (**6**) was prepared by condensation of propane-1,3-diamine (**5**) with PhCHO. In contrast to the previously described synthesis of hexahydropyrimidines **1** starting with *N*-substituted propane-1,3-diamines, however, the reaction with **5** led to a mixture of products (*Scheme 2* and *Fig.*). Along with the desired hexahydropyrimidine **6**, the *N*-benzylidenediamine **7**, *N*,*N'*-dibenzylidenediamine **8**, and unreacted **5** were obtained. This mixture could not be separated into the four components, due to the equilibrium of the involved species with one another[2]). In fact, the reaction of tetradeuterated dibenzylidene derivative [D_4]-**8** with **5** gave rather rapidly (< 5 min at 23°) rise to the four compounds of the type **5**/[D_4]-**5**, **6**/[D_4]-**6**, **7**/[D_4]-**7**, and **8**/[D_4]-**8**, each as an approximately equimolar mixture of the isotopomers (*Scheme 2*).

The synthesis of [D_4]-**8** was performed as shown in *Scheme 3*: dimethyl glutarate (**13**) was treated with MeONa in MeOD under reflux for several hours to yield the tetradeuterated diester [D_4]-**13** (89% D content). This compound was hydrolyzed with DCl in D_2O to the corresponding diacid [D_4]-**14** (92% D content), which was subsequently subjected to the *Curtius* rearrangement. The deuterated diamine [D_4]-**5** (92% D content) that was obtained after hydrolysis was reacted with 2 equiv. of PhCHO to afford the desired product [D_4]-**8** (92% D content) in 68% overall yield (from [D_4]-**14**).

The equilibrium composition of the mixture of **5**–**8** is strongly dependent on the temperature of the solution and less so on the type of the solvent. The hexahydropyrimidine **6** is markedly dominant at low temperature (86% at −78°, determined by ^{1}H-NMR in $CDCl_3$); at higher temperatures, the equilibrium is shifted towards the other species (*Fig.*). The relevant component of the mixture **5**–**8** for attaining the desired

[2]) Compounds **6** and **7** can interconvert into each other, or they can alternatively form **5** and **8** by an intermolecular benzylidene transfer. Contrary, compounds **5** and **8** cannot lead to any of the other species in the mixture *per se*. Consequently, **5** and **8**, but not **6** and **7**, can be prepared and isolated as pure compounds.

Scheme 2



a E = MeCO (Ac) **c** E = $C_6H_5CH_2OCO$ (Z)

b E = C_6H_5CH=CHCO (Cin) **d** E = 4-$MeC_6H_4SO_2$ (Ts)

N-monoderivatization of diamine **5** is *N*-benzylidene derivative **7**. Since this compound is expected to be formed quite rapidly from hexahydropyrimidine **6** (analogously to the formation of **2** from **1**; see above), high concentration of the latter was anticipated to be advantageous for our aim. In fact, the best results in the attempts to monoderivatize

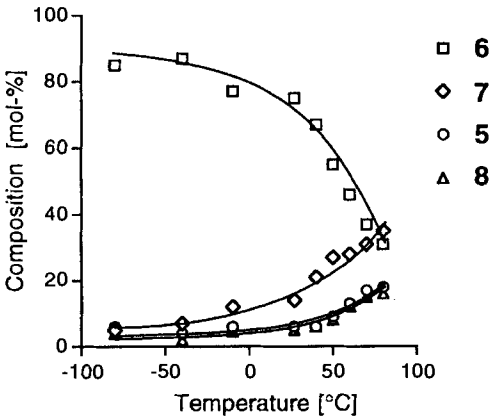
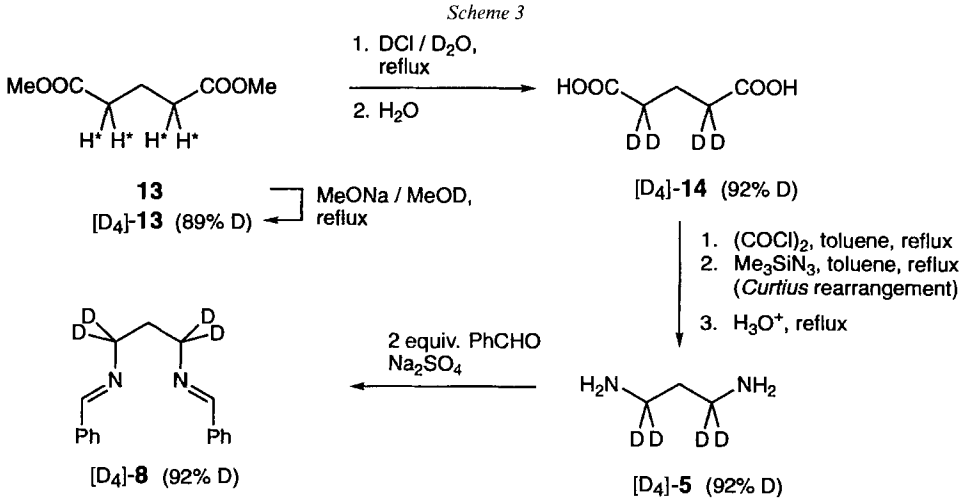


Figure. *Equilibrium composition of the mixture* **5**–**8** *in* $CDCl_3$ *solution as a function of the temperature* (ratios determined by ^{1}H-NMR)

Scheme 3



propane-1,3-diamine (**5**) *via* **6** were obtained, when the mixture of **5**–**8** was treated with electrophiles at −78°. The reaction of **5**–**8** with 2.5–5 equiv. of AcCl, cinnamoyl chloride (CinCl), benzyl chloroformate (ZCl), or TsCl in CH_2Cl_2 at this temperature, followed by acidic hydrolysis, afforded the corresponding *N*-monofunctionalized diamines **12a**–**d** in 54–69% overall yields, determined with respect to **5** (*Table 1*). As expected, *N*,*N*′-dibenzylidene derivative **8** and **11a**–**d** were obtained as side products. Compounds **11a**–**d** were formed from **5** by the reaction with the electrophile, or, in the case of the treatment of **5**–**8** with AcCl, additionally from diacetylated hexahydropyrimidine **9a** by its hydrolysis.

Even though the relative concentrations of the starting compounds **5**–**8** are also relevant for the outcome of the reaction, the composition of the product mixture depends

Table 1. *Product Distribution after Treatment of the Mixture of* **5**–**8** *with Various Electrophiles, and Overall Yields of* **12a**–**d** *after Hydrolysis*

Entry	Electrophile			Products (Yield [%])				
	E^+	[equiv.]	Addition	Derivatization[a])				Hydrolysis[b])
1	Ac	1.1	slow	**8**(<1)	**9a**(12)	**10a**(57)	**11a**(–)[c])	**12a**(54)
2	Ac	1.1	fast	**8**(9)	**9a**(13)	**10a**(49)	**11a**(–)[c])	**12a**(46)
3	Ac	2.5	fast	**8**(18)	**9a**(35)	**10a**(27)	**11a**(–)[c])	**12a**(25)
4	Cin	1.1	fast	**8**(8)	**9b**(0)	**10b**(56)	**11b**(5)	**12b**(50)
5	Cin	2.5	fast	**8**(6)	**9b**(0)	**10b**(67)	**11b**(11)	**12b**(60)
6	Cin	5.0	fast	**8**(<1)	**9b**(0)	**10b**(75)	**11b**(16)	**12b**(68)
7	Z	1.1	fast	**8**(8)	**9c**(0)	**10c**(64)	**11c**(3)	**12c**(59)
8	Z	2.5	fast	**8**(5)	**9c**(0)	**10c**(70)	**11c**(18)	**12c**(64)
9	Ts	1.1	fast	**8**(12)	**9d**(0)	**10d**(56)	**11d**(9)	**12d**(49)
10	Ts	2.5	fast	**8**(4)	**9d**(0)	**10d**(78)	**11d**(17)	**12d**(69)

[a]) Relative amounts of the components of the mixtures **8**–**11** determined by ^{1}H-NMR.
[b]) Yields of isolated products with respect to the diamine **5**.
[c]) The compound **11a** has been detected in the ^{1}H-NMR spectra of the crude mixtures prior to aqueous workup. Since it is highly soluble in H_2O it was not quantified later.

strongly on the type and the amount of the electrophile used. Particularly striking is the remarkably different product distribution that was obtained with AcCl. As already mentioned above, the reaction of AcCl with **5**–**8** led to all four types of compounds **8**–**11**, while the transformations with CinCl, ZCl, or TsCl as the derivatizing agents afforded only compounds of type **8**, **10**, and **11**, but none of type **9**. This finding is in agreement with earlier observations in connection with the reactions of *N*-monosubstituted hexahydropyrimidines of type **1**. With these compounds it was found that the secondary N-atom of the hexahydropyrimidines **1** is derivatized readily when it is freely accessible. Increased steric shielding of the amino moiety by introduction of a bulky group at C(2) resulted in reduced reactivity of this group, and thus more reaction *via* ring-opened structures of type **2** was effected. Hence, the product distributions of the acylation reactions of hexahydropyrimidines was controlled by the reactivity of the N-atoms in the hexahydropyrimidine precursors. Analogously, the product formation should be influenced by the reactivity of the electrophile, keeping the structure of the hexahydropyrimidine derivative unchanged. This is in fact observed. The treatment of **6** (as the major component of the mixture **5**–**8**) with the moderately reactive CinCl, ZCl, or TsCl afforded compounds **10b**–**d** *via* ring-opened *N*-benzylidene derivative **7** by amidation. The reaction with the more reactive AcCl, however, gave, in addition to **10a** (resulting from acetylation of **7**), also considerable amounts of **9a** (resulting from diacetylation of hexahydropyrimidine **6**). Thus, the introduction of the sterically demanding Ph group at C(2) of **6** to drive the derivatization reaction mainly *via* ring-opened **7** was only effective in cases of CinCl, ZCl, and TsCl but not of AcCl. Evidently, AcCl is sufficiently reactive to attack the N-atoms of **6** rapidly. The direct acylation of **6** with AcCl competes with the reaction path involving formation and derivatization of **7**, since the reaction rate of the direct derivatization of **6** becomes comparable to the reaction rate of formation of **7** from **6**. Increasing the concentration of AcCl by fast addition of the

electrophile to the mixture of **5**–**8** or by increasing the molar ratio in favor of the derivatizing agent accordingly results in increased formation of **9a** and, consequently, in decreased formation of **10a** (*Table 1, Entries 1–3*).

Interestingly, fast addition of the electrophiles is superior to slow addition for optimized formation of *N*-monosubstituted diamines **12b**–**d** (*Table 1, Entries 4–10*). Since direct derivatization of the hexahydropyrimidine **6** with less reactive acyl chlorides does not represent a problem – the transformation and refurnishing of ring-opened **7** is obviously considerably faster than the reaction of **6** with the electrophiles – high concentrations of the derivatizing agents ensure most efficiently the trapping of the ring-opened compound **7**. In that way, the formation of diamine **5** and its *N*,*N*′-dibenzylidene derivative **8** by disproportionation of two molecules of **7** is suppressed. Too high concentrations of the electrophiles, however, may again favor the formation of the doubly derivatized diamine.

Derivatization under Statistic Conditions. The *N*-monoderivatization of alkane-α,ω-diamines under statistic conditions was investigated by several groups and was shown to give generally low yields of the desired products [17–19] [22]. In addition to the monosubstituted diamines, considerable amounts of disubstituted products and starting diamines were found in the resultant product mixtures. Even the use of higher stoichiometric amounts of diamines with respect to the acylating reagents – which should statistically disfavor the formation of doubly derivatized diamines – did initially not result in the desired product ratios: diacylated diamines were still predominant. An explanation for this behavior was offered with the so-called 'diacyl-effect', *i.e.*, the increased reactivity of the free amino moiety of *N*-monoacyl-substituted alkane-α,ω-diamines compared to the NH_2 groups of the non-derivatized starting diamines. According to *Jacobson et al.*, however, the selectivity in favor of doubly derivatized diamines is indeed related to a mixing problem rather than to different reactivities of amino groups [20]. In fact, when the reactants were more efficiently mixed by using a 'high dilution technique', good-to-excellent yields of monoacylated α,ω-diamines were obtained: the slow addition of a highly diluted solution of $(Boc)_2O$ to a well-stirred solution of several alkane-α,ω-diamines ($(Boc)_2O$/diamine 1:8), *e.g.*, afforded the corresponding mono-Boc-alkane-α,ω-diamines in 75–90% yields [21]. An alternative approach to enhance monoderivatization of diamines under 'statistic' conditions is the use of dynamic monoprotection of one amino group with 18-crown-6 [23].

Accordingly, the monoderivatized diamines **12b**–**d** were prepared from **5** and the corresponding acyl chlorides (ratio 5:1) by application of the 'high dilution technique' proposed by *Jacobson et al.* [20]. The results are summarized in *Table 2*. Interestingly and unexpectedly, the yields of **12a**–**d** vary over a rather broad range. With respect to the formation of the desired monoderivatized diamine of type **12**, the treatment of diamine **5** with TsCl as the electrophile afforded the best result (96%[3]) of **12d**). The reactions with CinCl and ZCl (50 and 75% of **12b** and **12c**, resp.[3])) showed moderate-to-low 'statistic selectivities', and the reaction with AcCl led almost exclusively to the doubly derivatized **11a** (85%[3])) instead of the desired **12a** (8%). The divergence of the results of the reactions with several electrophiles cannot be rationalized. Since the conditions for all

[3]) The yield is determined with respect to the electrophile added in deficiency.

transformations were strictly kept constant, a mixing problem as suggested by *Jacobson et al.* [20] should largely be excluded[4]).

Table 2. *Comparison of the 'Statistic Method' and the 'Hexahydropyrimidine Method' for the Derivatization of Propane-1,3-diamine* (**5**)

Electrophile	Products (Yield [%])		
E^+	'Statistic method'[a])		'Hexahydropyrimidine method'[b])
Ac	**11a**(85)	**12a**(8)	**12a**(54)
Cin	**11b**(44)	**12b**(50)	**12b**(68)
Z	**11c**(20)	**12c**(75)	**12c**(64)
Ts	**11d**(<1)	**12d**(96)	**12d**(69)

[a]) Yields determined with respect to the electrophile.
[b]) Yield determined with respect to diamine **5**.

Conclusion. – The results of this investigation show that both methods, the direct statistic derivatization and the derivatization *via* hexahydropyrimidine **6**, for monoderivatizing propane-1,3-diamine (**5**) have their advantages and are competitive to one another depending strongly on the electrophile used. Whereas the 'hexahydropyrimidine method' gives the desired products in almost invariable yields (54–69%), the 'direct statistic method' produces the corresponding compounds in diverging yields (8–96%), with no structural bias to predict the result. Even though a one-step procedure should generally be preferable to a three-step-synthesis, this is not *a priori* the case for the transformation of **5** into compounds of the type **12**: the three-step reaction sequence *via* hexahydropyrimidine **6** is actually readily performed as a one-pot procedure. Decisive for the choice of either variation to prepare compounds of the type **12** must, therefore, be in the first instance the yield that can be obtained of the respective product. Also considered should be the fact, that the statistic conversion needs an excess of diamine, while the procedure *via* **6** employs an excess of electrophile. Since for specific derivatizations (not simple introduction of a protecting group) the electrophile might be the more valuable component, the direct derivatization method will probably often be preferred. It is also not concealed at this point that the purification of the products is generally more facile when using the 'statistic method'.

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[4]) It is possible, though, that still a mixing problem might arise with highly reactive electrophiles: whereas dispersal of less reactive reagents in the reaction mixture is possibly faster than the reaction with the electrophile itself, this might be different for highly reactive reagents. Since local concentration peaks cannot be avoided independent of the method of addition (unless the reagent is already sufficiently diluted prior to addition), reaction might occur in a local 'high concentration' environment.

Experimental Part

1. *General.* Unless stated otherwise: all org. solvents were distilled prior to use. For the reactions, CH_2Cl_2 was dried over molecular sieves (3 Å). All reactions were carried out under Ar. Soln. of salts and acids for workup procedures were prepared in de-ionized H_2O. Extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography: silica gel *Merck 60* (40–63 μm). M.p.: *Mettler FP-5/FP-52*. IR Spectra (neat): *Perkin-Elmer 781*; in cm^{-1}. ^{1}H-NMR: at 300 MHz in $CDCl_3$; *Bruker AC-300* or *Bruker ARX-300*, δ in ppm rel. to $CHCl_3$ ($\delta = 7.26$), J in Hz. ^{13}C-NMR: at 75.6 MHz in $CDCl_3$; *Bruker ARX-300*; δ in ppm rel. to $CDCl_3$ ($\delta = 77.0$); multiplicities from DEPT experiments. CI-MS: with NH_3 as the reactant gas; *Finnigan SSQ 700* or *Finnigan MAT 90*, data in *m/z*.

2. *Starting Compounds* **5**–**8**. 2.1. *Propane-1,3-diamine* (**5**), *2-Phenylhexahydropyrimidine* (**6**), N-*Benzylidenepropane-1,3-diamine* (**7**), N,N′-*Dibenzylidenepropane-1,3-diamine* (**8**). A soln. of PhCHO (10.5 g, 100.0 mmol) in CH_2Cl_2 (25 ml) was added dropwise at −78° to a soln. of **5** (8.87 g, 120.0 mmol) in CH_2Cl_2 (50 ml). It was slowly warmed to 23°, Na_2SO_4 (5.6 g, 56.8 mmol) was added, and it was stirred for 1 h. Filtration and evaporation gave a mixture **5**/**6**/**7**/**8** (together 16.1 g, quant., ratio (23°): *ca.* 5:75:15:5) as a colorless oil. Compounds **8** and [D_4]-**8** were independently prepared (see *2.3*). The ratio of the four components were determined by ^{1}H-NMR at different temp. (see *Fig.*). CI-MS (of the mixture **5**–**8**): 251 (100, [**8** + H]$^+$), 163 (74, [**6** + H]$^+$) and/or [**7** + H]$^+$), 75 (0.3 [**5** + H]$^+$).

Data of **6** (obtained from the mixture **5**–**8**): ^{1}H-NMR: 7.45–7.23 (*m*, 5 arom. H); 4.52 (*s*, H–C(2)); 3.27–3.20 (*m*, H_{eq}–C(4), H_{eq}–C(6)); 3.00–2.91 (*m*, H_{ax}–C(4), H_{ax}–C(6)); 1.68–1.44 (*m*, CH_2(5)). ^{13}C-NMR (signals of arom. C omitted): 74.3 (*d*, C(2)); 45.8 (*t*, C(4), C(6)); 26.8 (*t*, C(5)).

Data of **7** (obtained from the mixture **5**–**8**): ^{1}H-NMR: 8.26 (*s*, N=CH); 7.45–7.23 (*m*, 5 arom. H); 3.66 (*t*, $J = 6.8$, $=NCH_2$); 2.79 (*t*, $J = 6.7$, H_2NCH_2); 1.83 (*quint.*, $J = 6.8$, NCH_2CH_2). ^{13}C-NMR (signals of arom. C omitted): 160.2 (*d*, N=CH); 58.7 (*t*, $=NCH_2$); 39.7 (*t*, H_2NCH_2); 34.3 (*t*, NCH_2CH_2).

2.2. *Equilibrium Experiment.* The equilibrium mixture **5**/[D_4]-**5**/**6**/[D_4]-**6**/**7**/[D_4]-**7**/**8**/[D_4]-**8** was prepared by addition of **5** (28 mg, 0.38 mmol) to a soln. of [D_4]-**8** (95 mg, 0.38 mmol) in $CDCl_3$ (0.6 ml) in a NMR tube and shaking for 5 s. After 5 min, ^{1}H-NMR of the labeled sample showed the same product ratio as the above-mentioned colorless oil, with the signals of the protons at the labeled positions of the four components integrating *ca.* 50% of the signals of an unlabeled sample.

2.3. N,N′-*Dibenzylidenepropane-1,3-diamine* (**8**) *and* N,N′-*Dibenzylidene[1,1,3,3-*$^2H_4$*]propane-1,3-diamine* ([D_4]-**8**). Diamine **5** (1.85 g, 25.0 mmol) was added to a soln. of PhCHO (5.03 g, 50.0 mmol) in toluene (25 ml), and the mixture was heated to reflux for 3 h. It was cooled to 23°, and anh. Na_2SO_4 was added. Filtration and evaporation gave **8** (5.56 g, 22.2 mmol, 89%) as a colorless oil. Likewise, [D_4]-**5** · 2 HCl (77 mg, 0.50 mmol) with PhCHO (106 mg, 1.0 mmol) in presence of Et_3N (506 mg, 5.0 mmol) gave [D_4]-**8** (95 mg, 0.38 mmol, 76%, D-content in α-position to the N-atoms: 92%).

Data of **8**: IR: 2920*w*, 2840*m*, 1640*s*, 1580*m*, 1450*m*, 1375*w*, 1310*w*, 1220*w*, 970*w*, 755*m*, 690*s*. ^{1}H-NMR: 8.31 (*s*, 2 N=CH); 7.76–7.71 (*m*, 4 arom. H); 7.45–7.38 (*m*, 6 arom. H); 3.57 (*t*, $J = 6.8$, $2NCH_2$); 1.98 (*quint.*, $J = 6.8$, NCH_2CH_2). ^{13}C-NMR: 160.5 (*d*, 2 N=CH); 136.6 (*s*, 2 arom. C); 130.0 (*d*, 2 arom. C); 128.7, 128.6 (*2d*, 2 × 4 arom. C); 58.6 (*t*, $2NCH_2$); 31.5 (*t*, NCH_2CH_2). CI-MS: 251 ([*M* + H]$^+$).

Data of [D_4]-**8**: IR: similar to that of **8** but showing additional signals at 2210*m*, 2080*m* (ν(C–D)). ^{1}H-NMR: identical to that of **8**, except: 3.62–3.52 (*m*, 0.32 H). ^{13}C-NMR: identical to that of **8**, except 58.6 (*quint.*, $2NCD_2$). CI-MS: 255 (100, [[D_4]-**8** + H]$^+$), 254 (8, [[D_3]-**8** + H]$^+$).

3. *Derivatization of Propane-1,3-diamine* (**5**). 3.1. *Reactions of* **5**–**8** *with Electrophiles, Followed by Hydrolysis: General Procedure.* A soln. of the electrophile (1.1–5.0 equiv., see *Table 1*) in CH_2Cl_2 (0.2–0.6M) was added in one batch or dropwise at −78° (*cf. Table 1*) to a soln. of **5**–**8** (1.0 equiv.) and Et_3N (1–2-fold excess to the electrophile) in CH_2Cl_2 (0.2–0.6M). It was warmed to 23° and stirred for 1 h. An aq. soln. of NaOH (1N, equal volume of org. solute) was added, the org. phase was separated, washed with brine until neutral, and evaporated to give a colorless oil consisting of the compounds of the type **8**–**11** in the amounts given in *Table 1*. (The compound **9a** and the compounds of the type **10** were spectroscopically characterized within this mixtures.) The mixtures of **8**–**11** were heated to reflux for 1 h in toluene/aq. HCl soln. (1N) 1:1, or, in the case of the tosylated compounds, stirred in MeOH/aq. sat. NH_4Cl soln. 1:4 for 24 h. The aq. phase was extracted with CH_2Cl_2, and the combined org. phases afforded products **11** after evaporation. Basification of the aq. soln. with NaOH and extraction with CH_2Cl_2 provided amines **12**. The products were obtained as pure compounds, except for **12a**, which was purified by chromatography ($MeOH/CH_2Cl_2/NH_4OH$ 7:3:1).

3.2. *Direct Acylation of* **5** *under Statistic Conditions: General Procedure.* A soln. of the electrophile in CH_2Cl_2 (1 equiv., *ca.* 0.05M) was added within 4 h *via* a syringe-pump at 23° to a vigorously stirred soln. of **5** in CH_2Cl_2 (5 equiv., *ca.* 0.1M). After complete addition, aq. HCl soln. (1N) was added. The solvents were then either directly

evaporated and the residue was chromatographed (for **11a**/**12a**; $MeOH/CH_2Cl_2/NH_4OH$ 7:3:1), or the org. layer was separated, and the volatiles were evaporated to yield products of the type **11**, and the aq. layer was basified with aq. NaOH (1N) and extracted with CH_2Cl_2 to give the compounds of the type **12**. For yields of the compounds **11a–d** and **12a–d**, see *Table 2*.

3.3. *1,3-Diacetyl-2-phenylhexahydropyrimidine* (**9a**, mixture of 2 stereoisomers 1:1): ^{1}H-NMR (from mixture of **8**/**9a–11a**, see above). 7.60 (*s*, H–C(2)); 4.58–4.48, 3.69–3.59 (2*m*, H_{eq}–C(4), H_{eq}–C(6)); 3.24–3.12, 2.85–2.72 (2*m*, H_{ax}–C(4), H_{ax}–C(6)); 2.22, 2.18 (2*s*, 2 Me); 1.72–1.54, 1.51–1.41 (2*m*, CH_2(5)). ^{13}C-NMR: 170.6, 170.1 (2*s*, 2 CO); 137.8, 135.3 (*s*, 1 arom. C); 133.4, 130.0, 129.6, 129.3, 129.0, 128.3, 128.1, 125.9, 125.2 (9*d*, 5 arom. C); 64.6 (*d*, C(2)); 41.6, 36.5 (2*t*, C(4)); C(6), 25.0 (*t*, C(5)); 21.5, 21.3 (2*q*, 2 Me). CI-MS: 247 ($[M + H]^+$).

3.4. *Products of the Type* **10**. Spectroscopic data from mixtures of compounds **8–11**: see above.

N-*[3-(Benzylidenamino)propyl]acetamide* (**10a**). ^{1}H-NMR: 8.26 (*s*, N=CH); 7.70–7.67 (*m*, 2 arom. H); 7.42–7.39 (*m*, 3 arom. H); 6.38 (br., CONH, exchangeable with D_2O); 3.68 (*t*, J = 6.0, $=NCH_2$), 3.40 (*q*, J = 6.0, $CONHCH_2$); 1.92 (*s*, Me); 1.88 (*quint.*, J = 6.2, NCH_2CH_2). ^{13}C-NMR: 170.0 (*s*, CO); 161.4 (*d*, N=CH); 136.3 (*s*, 1 arom. C); 130.7 (*d*, 1 arom. C); 128.5, 127.8 (2*d*, 2 × 2 arom. C); 59.7 (*t*, $=NCH_2$); 38.4 (*t*, $CONHCH_2$); 30.3 (*t*, NCH_2CH_2); 23.2 (*q*, Me).

(E)-N-[3-(Benzylidenamino)propyl]-3-phenylprop-2-enamide (**10b**). ^{1}H-NMR: 8.17 (*s*, N=CH); 7.48 (*d*, J = 15.7, PhC*H*=); 7.67–7.17 (*m*, 10 arom. H); 6.94 (br., CONH, exchangeable with D_2O); 6.34 (*d*, J = 15.7, COCH=); 3.62 (*t*, J = 6.5, $=NCH_2$); 3.46 (*q*, J = 6.1, $CONHCH_2$); 1.87 (*quint.*, J = 6.1, NCH_2CH_2). ^{13}C-NMR: 165.9 (*s*, CO); 161.4 (*d*, N=CH); 140.0 (*d*, PhCH=); 135.9, 134.9 (2*s*, 2 arom. C); 130.7, 129.3 (2*d*, 2 × 1 arom. C); 128.7, 128.6, 127.9, 127.6 (4*d*, 4 × 2 arom. C); 127.9, 127.6; 121.4 (*d*, COCH=); 59.9 (*t*, $=NCH_2$); 38.8 (*t*, $CONHCH_2$); 30.4 (*t*, NCH_2CH_2).

Benzyl N-[3-(Benzylidenamino)propyl]carbamate (**10c**). ^{1}H-NMR: 8.12 (*s*, N=CH); 7.63–7.54 (*m*, 2 arom. H); 7.32–7.09 (*m*, 8 arom. H); 5.47 (br., CONH, exchangeable with D_2O); 4.97 (*s*, CH_2O); 3.54 (*t*, J = 6.4, $=NCH_2$); 3.23 (*q*, J = 6.2, $CONHCH_2$); 1.77 (*quint.*, J = 6.4, NCH_2CH_2). ^{13}C-NMR: 161.4 (*d*, N=CH); 156.4 (*s*, CO); 136.7, 135.9 (2*s*, 2 arom. C); 130.6 (*d*, 1 arom. C); 128.4, 128.3 (2*d*, 2 × 2 arom. C); 128.0 (*d*, 3 arom. C); 127.8 (*d*, 2 arom. C); 67.5 (*t*, CH_2O), 59.4 (*t*, $=NCH_2$); 39.8 (*t*, $CONHCH_2$); 30.8 (*t*, NCH_2CH_2).

N-*[3-(Benzylidenamino)propyl]*-p-*toluenesulfonamide* (**10d**). ^{1}H-NMR: 8.11 (*s*, N=CH); 7.67–7.14 (*m*, 9 arom. H); 5.80 (br. *t*, J = 5.5, $NCHSO_2$, exchangeable with D_2O); 3.55 (*t*, J = 5.9, $=NCH_2$); 3.09 (*q*, J = 5.8, SO_2NHCH_2); 2.36 (*s*, Me); 1.75 (*quint.*, J = 6.0, NCH_2CH_2). ^{13}C-NMR: 161.7 (*d*, N=CH); 143.0, 137.0, 135.5 (3*s*, 3 arom. C); 130.9 (*d*, 1 arom. C); 130.4, 129.5, 128.7, 128.0 (4*d*, 4 × 2 arom. C); 59.7 (*t*, $=NCH_2$); 42.7 (*t*, SO_2NHCH_2); 29.8 (*t*, NCH_2CH_2); 21.4 (*q*, Me).

3.5. *Products of the Type* **11**. N,N′-*(Propane-1,3-diyl)bis[acetamide]* (**11a**). IR ($CHCl_3$): 3440*m*, 3320*m*, 2940*m*, 1665*s*, 1525*s*, 1430*m*, 1370*s*, 1280*m*, 1095*w*, 1040*w*. ^{1}H-NMR: 6.87 (br., 2 CONH, exchangeable with D_2O); 3.19 (*q*, J = 6.2, $2NCH_2$); 1.92 (*s*, 2 Me); 1.56 (*quint.*, J = 6.2, NCH_2CH_2). ^{13}C-NMR: 170.9 (*s*, 2 CO); 35.9 (*t*, $2NCH_2$); 29.4 (*t*, NCH_2CH_2); 23.1 (*q*, 2 Me). CI-MS: 159 ($[M + H]^+$).

*(E,E)-3,3′-Diphenyl-*N,N′-*(propane-1,3-diyl)bis[prop-2-enamide]* (**11b**). IR (KBr): 3290*s*, 3060*w*, 2950*w*, 1655*s*, 1620*s*, 1545*s*, 1450*m*, 1340*m*, 1225*m*, 975*m*, 765*m*, 730*m*, 695*m*, 675*m*. ^{1}H-NMR: 7.57 (*d*, J = 15.7, 2PhC*H*=); 7.44–7.41 (*m*, 4 arom. H); 7.28–7.26 (*m*, 6 arom. H); 6.68 (br. *t*, 2CONH, exchangeable with D_2O); 6.42 (*d*, J = 15.7, 2COCH=); 3.39 (*q*, J = 6.2, $2NCH_2$); 1.69 (*quint.*, J = 6.2, NCH_2CH_2). ^{13}C-NMR: 166.7 (*s*, 2 CO); 141.1 (*d*, 2PhCH=); 134.8, 129.7 (2*d*, 2 × 2 arom. C); 128.8, 127.8 (2*d*, 2 × 4 arom. C); 120.8 (*d*, 2COCH=); 36.1 (*t*, $2NCH_2$); 29.9 (*t*, NCH_2CH_2). CI-MS: 335 ($[M + H]^+$).

Benzyl N-{3-[(Benzyloxycarbonyl)amino]propyl}carbamate (**11c**). Colorless solid. M.p. (CH_2Cl_2/hexane) 112–113°. IR ($CHCl_3$): 3450*s*, 3060*w*, 3030*m*, 2950*m*, 1720*s*, 1520*s*, 1450*m*, 1240*s*, 1140*s*, 1070*m*, 1025*s*. ^{1}H-NMR: 7.33–7.19 (*m*, 10 arom. H); 5.01 (*s*, $2CH_2O$); 3.15 (*q*, J = 6.2, $2NCH_2$); 1.56 (*quint.*, J = 6.2, NCH_2CH_2). ^{13}C-NMR: 156.8 (*s*, 2 CO); 136.5 (*s*, 2 arom. C); 128.3 (*d*, 4 arom. C); 128.2 (*d*, 2 arom. C); 128.0 (*d*, 4 arom. C); 66.7 (*t*, 2 CH_2O); 37.6 (*t*, 2 NCH_2); 30.4 (*t*, NCH_2CH_2). CI-MS: 360 (83, $[M + NH_4]^+$), 343 (100, $[M + H]^+$), 299 (28, $[M + H - CO_2]^+$).

N-*{3-[[(4-Methylphenyl)sulfonyl]amino}propyl}*-p-*toluenesulfonamide* (**11d**). IR ($CHCl_3$): 3380*w*, 2969*w*, 1590*w*, 1405*w*, 1330*m*, 1260*s*, 1160*s*, 1090*s*, 1015*s*, 810*s*, 640*m*. ^{1}H-NMR: 7.71 (*d*, J = 8.3, 4 arom. H (*o* to SO_2)); 7.28 (*d*, J = 8.1, 4 arom. H (*m* to SO_2)); 4.92 (br. *s*, $2NHSO_2$, exchangeable with D_2O); 3.00 (*q*, J = 4.5, $2SO_2NHCH_2$); 2.41 (*s*, 2 Me); 1.65 (*quint.*, J = 6.2, 2H, NCH_2CH_2). ^{13}C-NMR: 143.5 (*s*, 2 arom. C, CSO_2); 136.8 (*s*, 2 arom. C, *C*Me); 129.8 (*d*, 4 arom. C, *o* to SO_2); 127.0 (*d*, 4 arom. C, *m* to SO_2); 39.8 (*t*, $2SO_2NHCH_2$); 29.9 (*t*, NCH_2CH_2); 21.5 (*q*, 2 Me). CI-MS: 400 ($[M + NH_4]^+$).

3.6. *Products of the Type* **12**. N-*(3-Aminopropyl)acetamide* (**12a**). IR (of **12a** · HCl in KBr): 3450 (br.), 3250*s*, 3040*m*, 2750*m*, 1645*s*, 1555*s*, 1485*s*, 1475*m*, 1440*m*, 1370*s*, 1305*m*, 1290*m*, 1275*m*, 1165*m*, 1015*s*, 830*m*. ^{1}H-NMR: 6.08 (br. *s*, 1 CONH, exchangeable with D_2O); 3.27 (*q*, J = 6.2, $CONHCH_2$); 2.73 (*t*, J = 6.2, H_2NCH_2);

1.90 (*s*, Me); 1.56 (*quint.* $J = 6.5$, NCH_2CH_2); 1.49 (br. *s*, NH_2, exchangeable with D_2O). ^{13}C-NMR: 170.1; (*s*, CO); 40.1 (*t*, $CONHCH_2$); 37.9 (*t*, H_2NCH_2); 32.2 (*t*, NCH_2CH_2); 23.2 (*q*, Me). CI-MS: 117 ($[M + H]^+$).

(E)-N-(3-Aminopropyl)-3-phenylprop-2-enamide (**12b**). IR ($CHCl_3$): 3250*m*, 2990*m*, 2940*m*, 2865*m*, 1665*s*, 1625*s*, 1550*m*, 1450*m*, 1335*m*, 1265*m*, 975*m*. ^{1}H-NMR: 7.51 (*d*, $J = 15.7$, PhC*H*=); 7.40 (*s*, CONH, exchangeable with D_2O); 7.39–7.34 (*m*, 2 arom. H); 7.22–7.18 (*m*, 3 arom. H); 6.42 (*d*, $J = 15.6$, COCH=); 3.39 (*q*, $J = 6.2$, $CONHCH_2$); 2.71 (*t*, $J = 6.4$, H_2NCH_2); 1.60 (*quint.*, $J = 6.4$, NCH_2CH_2); 1.39 (*s*, NH_2, exchangeable with D_2O). ^{13}C-NMR: 166.0 (*s*, CO); 140.0 (*d*, PhCH=); 134.8 (*s*, arom. C); 129.3 (*d*, arom. C); 128.5, 127.5 (2*d*, 2 × 2 arom. C); 121.1 (*d*, COCH=); 39.9 (*t*, $CONHCH_2$); 37.8 (*t*, H_2NCH_2); 32.2 (*t*, NCH_2CH_2). CI-MS: 205 ($[M + H]^+$).

Benzyl N-(3-Aminopropyl)carbamate (**12c**). IR ($CHCl_3$): 3450*m*, 2940*m*, 2865*m*, 1715*s*, 1515*s*, 1455*m*, 1265*s*, 1135*m*, 1065*m*, 1025*m*, 695*s*. ^{1}H-NMR: 7.35–7.22 (*m*, 5 arom. H); 6.09 (br. *s*, CONH, exchangeable with D_2O); 5.05 (*s*, CH_2O); 3.28 (*q*, $J = 6.1$, $CONHCH_2$); 2.66 (*t*, $J = 6.6$, H_2NCH_2); 1.54 (*quint.*, $J = 6.6$, NCH_2CH_2); 1.28 (br. *s*, NH_2, exchangeable with D_2O). ^{13}C-NMR: 156.2 (*s*, CO); 136.3 (*s*, 1 arom. C); 127.9 (*d*, 2 arom. C); 127.4 (*d*, 3 arom. C); 65.8 (*t*, CH_2O); 39.0 (*t*, $CONHCH_2$); 38.2 (*t*, H_2NCH_2); 32.6 (*t*, NCH_2CH_2). CI-MS: 209 ($[M + H]^+$).

N-(3-Aminopropyl)-p-toluenesulfonamide (**12d**). IR (KBr): 3360*m*, 3060*w*, 2920*w*, 2865*m*, 1600*m*, 1495*m*, 1385*m*, 1325*s*, 1300*m*, 1155*s*, 1090*m*, 950*m*, 815*s*, 745*m*, 655*s*. ^{1}H-NMR: 7.67 (*d*, $J = 8.3$, 2 arom. H (*o* to SO_2)); 7.21 (*d*, $J = 8.0$, 2 arom. H (*m* to SO_2)); 2.94 (*t*, $J = 6.3$, SO_2NHCH_2); 2.68 (*t*, $J = 6.2$, H_2NCH_2); 2.34 (*s*, Me); 1.50 (*quint.*, $J = 6.3$, NCH_2CH_2). ^{13}C-NMR: 143.0 (*s*, arom. C, CSO_2); 137.1 (*s*, arom. C, *C*Me); 129.5 (*d*, 2 arom. C, *o* to SO_2); 126.9 (*d*, 2 arom. C, *m* to SO_2); 42.3 (*t*, SO_2NHCH_2); 40.3 (*t*, H_2NCH_2); 31.3 (*t*, NCH_2CH_2); 21.4 (*q*, Me). CI-MS: 229 ($[M + H]^+$).

4. *Labeled Compounds.* 4.1. *Dimethyl [2,2,4,4-$^2H_4$]Butanedioate* ([D_4]-**13**). A soln. of dimethyl butanedioate (**13**, 1.68 g, 10.5 mmol) and MeONa (2.43 g, 45.0 mmol) in MeOD (19.0 ml) was heated to reflux for 72 h. The mixture was allowed to cool to 23° before a soln. of DCl in D_2O (*ca.* 35%, 4.5 ml) was added. Filtration and evaporation gave [D_4]-**13** (1.71 g, 10.4 mmol, 99%, D-content in α-position to the ester groups: 89%). IR: 2975*m*, 1735*s*, 1435*m*, 1365*w*, 1315*w*, 1250*m*, 1200*s*, 1170*s*, 1060*w*, 1020*w*, 995*w*. ^{1}H-NMR: 3.60 (*s*, 2 MeO); 2.33–2.29 (*m*, 0.44 H, $COCH_2$, COCDH); 1.92–1.82 (*m*, $COCD_2CH_2$). ^{13}C-NMR: 173.1 (*s*, 2CO); 51.4 (*q*, 2 MeO); 32.8 (*quint.*, 2 $COCD_2$); 19.9 (*t*, $COCD_2CH_2$). CI-MS: 182 (44, $[M + NH_4]^+$); 165 (100, $[M + H]^+$).

4.2. *[2,2,4,4-$^2H_4$]Butanedioic Acid* ([D_4]-**14**). A soln. of [D_4]-**13** (1.71 g, 10.4 mmol) in DCl/D_2O (*ca.* 18%, 30 ml) was heated to reflux for 16 h. Addition of H_2O and evaporation gave [D_4]-**14** (1.42 g, 10.3 mmol, 99%, D-content in α-position to the C=O groups: 92%). IR: 3010*m*, 1710*m*, 1605*w*, 1490*w*, 1260*w*, 1055*m*, 1030*m*, 730*m*, 695*m*. ^{1}H-NMR (D_2O): 1.92–1.82 (*m*, 0.32 H, $COCH_2$, COCDH); 1.28 (*s*, $COCD_2CH_2$). ^{13}C-NMR (D_2O): 177.8 (*s*, 2 CO); 32.6 (*quint.*, 2$COCD_2$); 19.4 (*t*, $COCD_2CH_2$). CI-MS: 154 (100, $[M + NH_4]^+$); 137 (29, $[M + H]^+$).

4.3. *[1,1,3,3-$^2H_4$]Propane-1,3-diamine Dihydrochloride* ([D_4]-**5** · 2 HCl). A soln. of [D_4]-**14** (1.38 g, 10.0 mmol) and oxalyl chloride (13.0 g, 100 mmol) was heated to reflux for 3 h (control with IR of a sample: absorption at 1710 cm^{-1} (COOH) disappeared and absorptions at 1805 and 1765 cm^{-1} (COCl) appeared). The excess of oxalyl chloride and the solvent were removed *in vacuo* before a soln. of trimethylsilyl azide (3.46 g, 30 mmol) in toluene (30 ml) was added. The mixture was heated to reflux for 16 h (IR: absorption at 2270 cm^{-1} (NCO)), and the solvent was removed *in vacuo*. An aq. soln. of HCl (1N, 30 ml) was added and the mixture heated to reflux for 24 h. Then, the volatiles were evaporated to give [D_4]-**5** · 2 HCl (1.41 g, 9.4 mmol, 94%, D-content in α-position to the NH_2 groups: 92%) as a crystalline, colorless solid. M.p. (MeOH/acetone): > 300°. IR (KBr): 2980*s*, 2280*w*, 2230*w*, 1605*w*, 1480*s*, 1460*s*, 1345*w*, 1170*w*, 1060*w*, 905*w*, 820*m*. ^{1}H-NMR (D_2O): 3.09–2.98 (*m*, 0.32 H, NCH_2, NCDH); 1.98 (*s*, NCD_2CH_2). ^{13}C-NMR (D_2O): 36.0 (*quint.*, 2NCD_2); 24.4 (*t*, NCD_2CH_2). CI-MS: 79 ($[M + H]^+$).

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