Ring Cleavage of *N*-Acyl- and *N*-(Arylsulfonyl)histamines with Di-*tert*-butyl Dicarbonate. A One-Pot Synthesis of 4-Acylamino- and 4-Arylsulfonylamino-1,2-diaminobutanes

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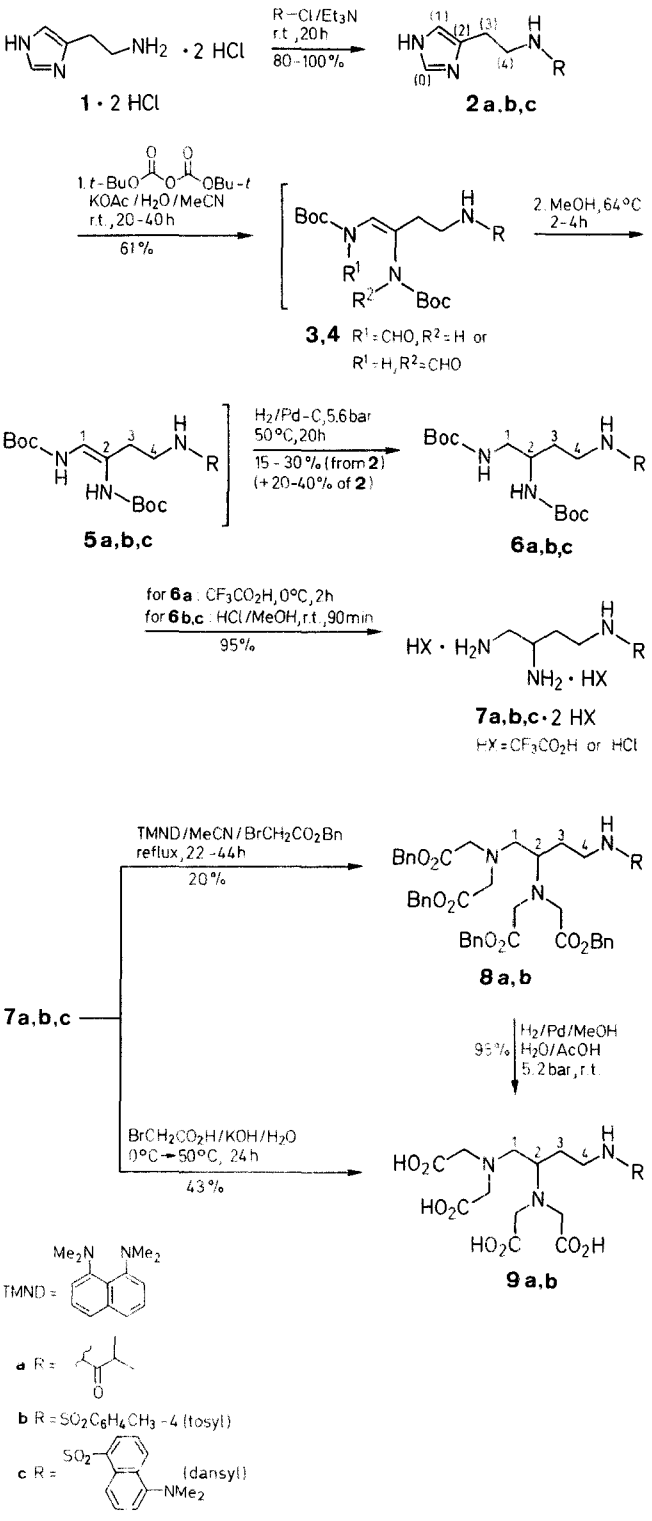
The ring cleavage of *N*-acyl- and *N*-(arylsulfonyl)histamines with di-*tert*-butyl dicarbonate in aqueous acetonitrile containing KOAc provides a one-pot synthesis of 4-acylamino- or 4-arylsulfonylamino-1,2-bis(*tert*-butoxycarbonylamino)butanes. Removal of the Boc groups in these protected triamines with trifluoroacetic acid or dry HCl in MeOH, followed by alkylation with benzyl bromoacetate, and then hydrogenation leads to N^4-acyl-1,2,4-butanetriamine-N^1,N^1,N^2,N^2-tetraacetic acids and the N^4-arylsulfonyl analogs, respectively.

Strong metal chelators, carrying a second functionality that allows attachment to a biomacromolecule, are of considerable interest in diagnostic and therapeutic applications.[1-6] Simple carboxymethylated amines, such as diethylenetriaminepentaacetic acid (DTPA) or various bifunctional ethylenediamine tetraacetic acid (EDTA) derivatives have been exploited for coupling of radioactive,[1-3,5] fluorescent,[4] or NMR-contrasting[6] metal ions. EDTA-type molecules form very strong metal complexes, and consequently bifunctional EDTA derivatives with the EDTA center well separated from the functional group intended for binding the proteins, are very desirable. However, not many vicinal diamines with a third functionality are available. Vicinal diamines may be prepared, for example, from amides of tyrosine, alanine, and phenylalanine by reduction with diborane[7] or by the reductive C–C coupling of *N*-alkylaldimines using low-valent titanium species.[8] The ring-cleaving benzoylation of ethyl imidazole-4-propanoate, followed by hydrogenation and hydrolysis affords 4,5-diaminopentanoic acid;[9] subsequent blocking of the vicinal diamine functions as the N^1,N^2-di-Boc derivative, amidation with N^1-benzyloxycarbonyl-1,3-propanediamine, removal of the Boc groups, *N*-carboxymethylation, and removal of the benzyloxycarbonyl group leads to *N*-(3-aminopropyl)-4,5-bis[bis(carboxymethyl)amino]pentanamide, an EDTA derivative with an extra amine functionality and amide-type linker arm.[10]

An already known[11] direct and facile route to vicinal diamines having a third amine functionality from *N*-tosylhistamine via ring cleavage with di-*tert*-butyl dicarbonate leads to the *vic*-bis(Boc-amino) compounds via dibenzoyl intermediates and then to the free vicinal diamines. The reaction conditions (8 fold molecular excess of di-*tert*-butyl dicarbonate; 10 days) are a limiting factor in the practical application of this procedure to the synthesis of 5-amino-1,2-bis(Boc-amino)alkanes; a further inconvenience is the interim chromatographic purification. We now report a one-pot method for converting *N*-acyl- and *N*-(arylsulfonyl)histamines into 4-acylamino- or 4-(arylsulfonylamino)-1,2-bis(*tert*-butoxycarbonylamino)butanes, respectively.

N^4-(2-Methylpropanoyl)-1,2,4-butanetriamine (**7a**) was synthesized by amidation of histamine (**1**) with 2-methylpropanoyl chloride/triethylamine in chloroform to give N,N^{im}-bis(2-methylpropanoyl)histamine, the N^{im}-acyl group of which was removed selectively by heating with methanol to give *N*-(2-methylpropanoyl)histamine (**2a**) in 82% yield. Ring cleavage under the conditions described for *N*-tosylhistamine[11] (0.23 mol di-*tert*-butyl dicarbonate per 0.05 mol of **2a** in acetonitrile; 10 days) gave a mixture of N^1- and N^2-formyl-N^1,N^2-di-Boc-N^4-(2-methylpropanoyl)-1-butene-1,2,4-triamines **3a** and **4a**. The formyl group was removed by heating **3a/4a** in methanol[12] and the resultant product was hydrogenated to N^1,N^2-di-Boc-N^4-(2-



methylpropanoyl)-1,2,4-butanetriamine (**6a**), which was then chromatographed to remove polar impurities and traces of the unsaturated analog **5a**. The yields obtained from ring cleavage of *N*-tosylhistamine (**2b**) and *N*-(2-methylpropanoylhistamine (**2a**) are similar.

Based on reported[13] observations on the ring cleavage of imidazole with diethyl dicarbonate in phosphate buffer, we modified our experimental procedure by increasing the concentration of the *N*-acylhistamine **2a** and of di-*tert*-butyl dicarbonate and decreasing the amount of potassium acetate. In the one-pot synthesis, the ring cleavage is performed under two-phase conditions (acetonitrile/aqueous potassium acetate) with vigorous stirring for 24–48 hours to afford **6a** in 15–20% overall yield from **2a**. Product **6a** can be separated from starting material **2a** (recovered in 25–40% yield) due to the insolubility of **2a** in ethyl acetate, and because in the partition between aqueous hydrochloric acid and chloroform, product **6a** readily goes into the chloroform phase. The hydrogenation of **5a** to **6a** is performed with the crude reaction mixture obtained from the conversion **2a** → **5a**; however, for batches larger than 10 g, hydrogenation remains incomplete and must be repeated after washing the reaction mixture with aqueous hydrochloric acid. The R_f value of compounds **5a** and **6a** are almost identical (silica, EtOAc or EtOAc/hexane); the reduction of **5a** → **6a** is complete when the TLC spot of **6a** invisible under UV light, but becomes visible upon development with ninhydrin. Removal of the Boc groups from **6a** with trifluoroacetic acid leads to **7a** (as the trifluoroacetic acid salt).

The analogous one-pot synthesis of the previously described N^1,N^2-di-Boc-N^4-tosyl-1,2,4-butanetriamine (**6b**)[11] proceeds in 19% overall yield and with 41% recovery of *N*-tosylhistamine (**2b**). Similarly, the one-pot synthesis of N^1,N^2-di-Boc-N^4-dansyl-1,2,4-butanetriamine (**6c**) proceeds in 28% overall yield and with 18% recovery of the starting *N*-dansylhistamine (**2c**).

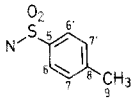
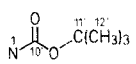
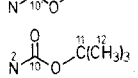
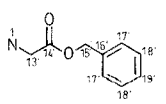
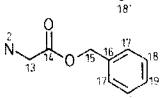
1,2-Diamino-4-(2-methylpropanoylamino)butane (**7a**) may be tetraalkylated with 4 equivalents of bromoacetic acid to give $2N^4$-(2-methylpropanoyl)-1,2,4-butanetriamine-N^1,N^1,N^2,N^2-tetraacetic acid (**9a**). The route requires the isolation of water-soluble products from the aqueous medium and their separation from inorganic salts in excess. For these reasons, the hydrophobic tetrabenzyl esters **8a** and **8b** were prepared and purified by column chromatography or preparative TLC (and characterized by NMR). The benzyl groups were removed by hydrogenation to **9a** and **9b**, respectively.

Structural assignment of the synthesized compounds by ^{1}H-NMR is somewhat limited and usually difficult due to the presence of highly labile protons of the amino and carboxy groups and also of hydration water. ^{13}C-NMR spectrometry was therefore an important tool in the structural assignment. Complete ^{13}C-NMR data for the tosyl series (compounds **2b, 5b, 6b, 8b, 9b**) are given in the Table; these data relate to the ^{13}C assignments via four groups: skeletal, tosyl, *t*-Boc, and benzyloxycarbonylmethyl groups.

In summary, the ring cleavage of *N*-acyl- and *N*-sulfonylhistamines with di-*tert*-butyl dicarbonate in the twophase system KOAc/H_2O/MeCN, followed by deformylation with methanol and hydrogenation, provides a convenient onepot synthesis of N^4-acyl- and N^4-arylsulfonyl-N^1,N^2-di-Boc-1,2,4-butanetriamines **6a, b, c** in 20–30% overall yields and with 10–40% recovery of starting material. The protected triamines **6a, b, c** are useful intermediates for the synthesis of substituted EDTA derivatives. The present method will also be applicable to *N*-acyl and *N*-sulfonyl derivatives of 4-(3- and 4-aminoalkyl)imidazoles.

Sources of reagents: di-*tert*-butyl dicarbonate (Fluka), *N,N,N',N'*-tetramethyl-1,8-naphthalenediamine (Sigma), palladium black (Fluka), benzyl bromoacetate (Sigma), 5-dimethylaminonaphthalene-1-sulfonyl

Table. ^{13}C-NMR Data of *N*-Tosyl Compounds **2b**, **5b**, **6b**, **8b**, **9b**: Assignments of Chemical Shifts δ

Group	C-Atom	Compound (Solvent/Reference)				
		2b ($CDCl_3$/TMS)	**5b** ($CDCl_3$/TMS)	**6b** ($CDCl_3$/TMS)	**8b** ($CDCl_3$/TMS)	**9b** (D_2O/CH_3OH)
butane skeleton	0	136.01	–	–	–	–
	1	117.55	118.30	44.24	57.74	56.54
	2	135.84	118.87	49.61	58.45	56.38
	3	28.44	33.77	33.42	29.80	27.98
	4	43.99	40.80	39.76	41.22	44.80
	5	138.88	132.08	137.40	137.03	140.41
	6	127.98	127.10	127.03	127.18	127.09
	7	130.65	129.72	129.63	129.37	130.10
	8	144.51	143.35	143.05	142.54	142.71
	9	21.94	21.51	21.49	21.46	21.14
	10	–	152.24	157.12	–	–
	10'	–	152.63	157.12	–	–
	11	–	80.96	79.70	–	–
	11'	–	80.69	79.78	–	–
	12	–	28.25	28.28	–	–
	12'	–	28.19	28.32	–	–
	13 (13')				52.04 (52.25)	55.01 (59.73)
	14 (14')				170.55 (171.65)	180.43 (180.17)
	15 (15')				66.48 (66.70)	
	16 (16')				135.40 (135.52)	
	17 (17')				128.41 (128.41)	
	18 (18')				128.57 (128.70)	
	19 (19')				128.40 (128.40)	

chloride (dansyl chloride) (Sigma). TLC was performed on Merck Kieselgel 60F 254 plates using the eluents $CHCl_3$ and $CHCl_3$/MeOH (95:5); reagents used for visualization were alkaline aqueous 1% $KMnO_4$ solution and ethanolic 0.2% ninhydrin solution. Flash Chromatography was carried out on 40–63 µm silica gel (Merck No. 9385 and EtOAc or $CHCl_3$/1% MeOH as eluents. Melting points were determined on a gallenkamp apparatus and are corrected. IR spectra were obtained on a Matteson CYGNUS 25 FTIR spectrophotometer. ^{1}H-NMR spectra were recorded at 80 MHz on a Varian FT80A spectrometer and ^{13}C-NMR spectra at 75.5 MHz on a Bruker AM-300 spectrometer, using TMS as internal reference for $CDCl_3$ solutions and MeOH (δ = 49.5) for D_2O solutions. The assignments were aided by multiplicities and $^{13}C \times {}^1H$ correlations resulting from off-resonance decoupled spectra.

N-(2-Methylpropanoyl)histamine (2a):

Freshly distilled 2-methylpropanoyl chloride (isobutyryl chloride; 11.7 g, 110 mmol) and histamine · 2HCl (**1** · 2HCl; 7.6 g, 54 mmol) are added to a stirred solution of Et_3N (25.7 g, 250 mmol) in $CHCl_3$ (800 mL) at 0 °C. After 2 h, the temperature is raised to 20 °C. Stirring is continued for 20 h, the Et_3N · HCl then filtered off, the solvent evaporated, the residue dissolved in MeOH (100 mL), and this solution heated to boiling for 2 h to remove the N^{im}-acyl group. The solvent is then evaporated and the residue is crystallized from EtOAc; yield: 16.3 g (82)%; mp 139–140 °C; TLC (silica, EtOAc/MeOH, 10:1): R_f = 0.2.

$C_9H_{15}N_3O$	calc.	C 59.66	H 8.28	N 23.20
(181.2)	found	59.76	8.40	22.90

^{1}H-NMR (CD_3OD/TMS): δ = 0.87 (d, 6H, J = 8 Hz, $2CH_3$); 2.13 (q, 1H, J = 8 Hz, CH); 2.48 (t, 2H, J = 8 Hz, CH_2); 3.12 (t, 2H, J = 8 Hz, CH_2); 6.63 (s, 1H, CHNH); 7.37 (s, 1H, CHNH).

N^1,N^2-Di-Boc-N^4-(2-methylpropanoyl)-1-butene-1,2,4-triamine (5a):

Mixture of N^1- and N^2-Formyl-N^1,N^2-di-Boc-N^4-(2-methylpropanoyl)-1-butene-1,2,4-triamines (**3a + 4a**): To a stirred solution of *N*-(2-methylpropanoyl)histamine (**2a**; 7.85 g, 43.3 mmol) in MeCN (700 mL) + aq. 10% KOAc (395 mL) is added di-*tert*-butyl dicarbonate (34.92 g, 160 mmol) and stirring at room temperature is continued for 10 days. The oily product thus obtained gives 2 spots on TLC (silica gel, EtOAc); it is column-chromatographed on silica gel using EtOAc/MeOH (98:2) as eluent to give the mixture **3a + 4a** as a solid which shows only one spot on TLC (silica gel, hexane/EtOAc 1:1); yield: 7.4 g (43%).

$C_{19}H_{33}N_3O_6$	calc.	C 57.12	H 8.32	N 10.51
(399.5)	found	57.03	8.22	10.02

Deformylated Compound **5a**: The mixture **3a + 4a** (7.4 g, 18.5 mmol) is dissolved in MeOH (200 mL) and this solution is allowed to stand at r.t. for 48 h [IR and ^{1}H-NMR spectrometry then indicate the disappearance of the formyl group (ν = 1730 cm^{-1}; δ = 9.5)]. The solution is evaporated; yield: 6.9 g (100%, based on **3a + 4a**; 43% based on **2a**); mp 132–133 °C.

$C_{18}H_{33}N_3O_5$	calc.	C 58.20	N 8.86	N 11.31	O 21.54
(371.5)	found	57.86	8.72	10.02	

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.12 (d, 6H, J = 9 Hz, $2CH_3$); 1.45 [s, 9H, $C(CH_3)_3$]; 1.47 [s, 9H, $C(CH_3)_3$]; 2.25 (t, 2H, J = 8 Hz, CH_2CH_2); 2.93 [q, 1H, $CH(CH_3)_2$]; 3.12–3.16 (m, 2H, CH_2NH); 6.02 (br s, 1H, NH); 6.21 (d, 1H, J = 12 Hz, CH=C).

N^1,N^2-Di-Boc-N^4-(2-methylpropanoyl)-1,2,4-butanetriamine (6a) (from 5a):

A solution of compound **5a** (1.02 g, 2.7 mmol) in MeOH (25 mL) is hydrogenated in the presence of 10% Pd-C (0.4 g) in a Parr apparatus at 5.6 bar and 50 °C for 15 h. The catalyst is then filtered off, the solvent evaporated, and the residue crystallized from EtOAc/hexane; yield: 0.25 g (24%); mp 129–130 °C.

$C_{18}H_{35}N_3O_5$	calc.	C 57.88	H 9.44	N 11.25
(373.4)	found	57.62	9.26	10.96

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.15 (d, 6H, J = 8 Hz, $2CH_3$); 1.43 [s, 18H, $2C(CH_3)_3$]; 2.12–2.53 (m, 2H, CH_2CH_2); 2.74–3.17 [m, 1H, $CH(CH_3)_2$]; 3.17 (t, 4H, J = 8 Hz, $2CH_2NH$); 3.39–3.88 (m, 1H, CHNH); 4.72–5.29 (m, 2H, 2NH); 6.59 (br s, 1H, NH).

N^4-(2-Methylpropanoyl)-1,2,4-triaminobutane Bis(trifluoroacetic Acid) Salt (7a):

The di-Boc compound **6a** (830 mg, 2.2 mmol) is added to trifluoroacetic acid (5 mL). This mixture is stirred at 0 °C for 2 h and then worked up by one of the following two methods:

Work-up A: The trifluoroacetic acid is removed under reduced pressure (10 mm Hg). Then, CCl_4 (2 mL) is added and the solvents are removed at 1 Torr and r.t. To the residue, Et_2O (20 mL) is added, the resultant precipitate is isolated by filtration and triturated with Et_2O (50 mL). The solid product is isolated by suction and dissolved in MeOH (50 mL). This solution is treated with active charcoal (1 g), filtered, and evaporated to leave **7a**; yield: 0.54 g (61%).

Work-up B: Addition of Et_2O (25 mL) to the mixture gives a liquid and an oily phase. The liquid phase is decanted and the oil is triturated with Et_2O (3 × 25 mL). The insoluble product is isolated by suction and dissolved in EtOAc (5 mL). This solution is allowed to stand at 4 °C for 20 h. The precipitated product is isolated by suction; yield: 780 mg (89%); mp 149–150 °C.

$C_{12}H_{21}F_6N_3O_5$	calc.	C 35.91	H 5.27	N 10.47
(401.3)	found	36.20	5.21	10.21

^{1}H-NMR (D_2O/CH_3OH): δ = 1.10 (d, 6H, $2CH_3$); 1.96 (q, 2H, CH_2CH_2); 2.49–2.70 (m, 1H, CH); 3.19–3.68 (m, 5H, $CH_2NH_3 + CHNH_3 + CH_2NH$).

N^4-(2-Methylpropanoyl)-1,2,4-butanetriamine-N^1,N^1,N^2,N^2-tetraacetic Acid (9a):

Method A, directly from **7a**: A solution of bromoacetic acid (550 mg, 3.75 mmol) in H_2O (10 mL) is cooled to 0 °C and 1 N aq. KOH is added dropwise until pH 7.0 is reached. Then, compound **7a** (300 mg, 0.75 mmol) is added and the pH adjusted to 11.0, the mixture is warmed at 50 °C for 24 h, the pH being adjusted to 10–11 after 1 h by the addition of 1 N aq. KOH; this adjustment is repeated after 3 h and after 6 h. After 48 h, 6 N aq. HCl is added to pH 2 and the mixture liophilized. The residue is extracted with EtOH (3 × 10 mL) to remove excess bromoacetic acid and glycolic acid. The remaining product **9a** is a white powder; yield: 130 mg (43%); mp 165 °C.

Method B, from **7a** via **8a**:

Tetrabenzyl N^4-(2-Methylpropanoyl)-1,2,4-butanetriamine-N^1,N^1,N^2,N^2-tetraacetate (**8a**): To a solution of the free diamine **7a** (0.20 g, 1.2 mmol) in MeOH (10 mL) are added *N,N,N',N'*-tetramethyl-1,8-naphthalenediamine (1.60 g, 7.1 mmol) and NaI (0.10 g, 0.7 mmol), followed by benzyl bromoacetate (1.2 mL, 7.1 mmol), and the mixture is refluxed for 22 h under N_2. It is then allowed to cool, $CHCl_3$ (100 mL) is added, and the solids are filtered off. The solvents are removed under reduced pressure and the oily residue is washed with EtOAc/hexane (11:9) and dried under high vacuum to give 0.86 g of a brown oil. This crude product is flash-chromatographed on silica gel and eluted with $CHCl_3$/hexane (4:1) to give pure **8a**; yield: 0.2 g (22%); yellow-brown oil.

$C_{44}H_{51}N_3O_9$	calc.	C 69.00	H 6.71	N 5.49
(765.9)	found	68.71	6.46	5.66

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.08, 1.10 (2d, 6H, $2CH_3$); 1.45–1.75 (m, 2H, CH_2CH_2); 2.30 [q, 2H, $CH(CH_3)_2$]; 2.50–3.00 (m, 3H, $CH_2N + CHN$); 3.15–3.40 (m, 2H, CH_2NH); 3.50, 3.55 (2s, 8H, $4NCH_2CO_2$); 5.07, 5.09 (2s, 8H, $4CH_{2benzyl}$); 7.30, 7.31 (2s, 20H$_{arom}$).

N^4-(2-Methylpropanoyl)-1,2,4-butanetriamine-N^1,N^1,N^2,N^2-tetraacetic Acid (**9a**): A solution of the tetraester **8a** (0.095 g, 0.12 mmol) in 95% MeOH (6.5 mL) containing AcOH (0.16 mL) is hydrogenated over Pd black (100 mg) at 5.2 bar and ≈ 15 °C for 45 h. The resultant mixture is slightly milky. After addition of H_2O (5 mL) and mild heating, a clear solution is obtained. The Pd is filtered off and the solvents are removed under reduced pressure. The residue is washed with MeOH to give **9a** as a white powder; yield: 0.0325 g (67%); mp 165 °C.

$C_{16}H_{27}N_3O_9$	calc.	C 47.40	H 6.71	N 10.36
(405.4)	found	46.95	6.52	10.15

^{1}H-NMR (D_2O/CH_3OH): δ = 1.17 (d, 6H, J = 9 Hz, $2CH_3$); 1.80–2.20 (q, 2H, $CHCH_2$); 2.52 [m, 1H, $CH(CH_3)_2$]; 3.10–3.60 (m, 5H, $CH_2N + CHN + CH_2NHCO$); 3.77–3.80 (2s, 4H, CH_2CO_2); 4.07 (s, 4H, CH_2CO_2).

N^1,N^2-Di-Boc-N^4-(2-methylpropanoyl)-1,2,4-butanetriamine (6a); One-Pot Synthesis from 2a:

In a 3000 mL, three-neck round-bottom flask with stirrer are placed *N*-(2-methylpropanoyl)histamine (**2a**; 18 g, 99.5 mmol), di-*tert*-butyl dicarbonate (87 g, 0.4 mol), MeCN (750 mL), and 10% aq. KOAc (300 mL). The two-phase mixture is thoroughly stirred at r.t. for 24 h. Then, the solvents are evaporated almost to dryness and MeOH (250 mL) is added to the oily residue. This solution is refluxed until TLC shows almost complete disappearance of the formyl products

3a/4a, and appearance of a major spot of **6a** (8 h)[a]. The MeOH is evaporated under reduced pressure to a residual volume of 170 mL and the mixture is hydrogenated over 10% Pd-C (2 g) at 5.6 bar and 40–50°C for 40 h. Fresh catalyst (2 g) is added and the hydrogenation continued for 23 h. The catalyst is filtered off and MeOH is evaporated to dryness under reduced pressure. Then, brine (200 mL) is added slowly to the residue and this mixture is extracted with EtOAc (3 × 200 mL). The extract is dried (Na_2SO_4) and concentrated to a volume of 375 mL. Upon refrigeration, colorless crystals of the starting material **2a** precipitate and are isolated by suction; yield: 4.3 g (24%). The filtrate is concentrated to a voluminous white solid, a mixture of **2a** and **6a**; yield: 17.2 g (43%). This mixture is dissolved in $CHCl_3$[b] (500 mL) and the solution extracted with 10% aq. HCl (2 × 350 mL) and with brine (100 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give 14.5 g of a solid. A solution of this solid in MeOH (160 mL) is hydrogenated over 10% Pd-C (2 g) at 5.60 bar and 25°C for 41 h. The solvent is removed and the residue (11.4 g) dissolved in $CHCl_3$ (100 mL) this solution washed with 10% aq. HCl,[c] dried (Na_2SO_4), and evaporated under reduced pressure to leave pure **6a**; yield: 6.4 g (15%); mp 129°C.

[a] *Note:* Compounds **5a** and **6a** have identical R_f values. On silica gel (EtOAc), compound **5a** is visible under UV light whereas compound **6a** is invisible but becomes visible on spraying with ninhydrin.

[b] *Note:* The reason for changing solvents from EtOAc to $CHCl_3$ is that **2** can be completely extracted from $CHCl_3$ into aq. HCl.

[c] *Note:* Rapidly and cold to avoid cleavage of the Boc groups. Another procedure for purifying **6a** is flash chromatography on silica gel using EtOAc/hexane (1:1) as eluent.

Bis(trifluoroacetic Acid) Salt of N^4-(5-Dimethylaminonaphthalen-1-ylsulfonyl)-1,2,4-butanetriamine (N^4-Dansyl-1,2,4-butanetriamine) (7c):

N,N^{im}-Didansylhistamine (**2c**): Histamine dihydrochloride (**1** · 2HCl; 1.7 g, 9 mmol) and Et_3N (10 mL, 74 mmol) are dissolved in CH_2Cl_2 (dried with molecular sieves; 200 mL) and dansyl chloride (5 g, 18 mmol) is added with stirring at 0°C. The mixture is stirred at 0°C for 1 h and at r.t. for 20 h, then evaporated under reduced pressure. The residue is dissolved in EtOAc (200 mL), Et_3N · HCl is filtered off, and the solvent is evaporated under reduced pressure. The residue is dissolved in CH_2Cl_2 (100 mL). This solution is washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure to leave product **2c** as a white powder; 5.4 g (100%).

$C_{29}H_{31}N_5O_4S_2$	calc.	C 60.31	H 5.37	N 12.13	S 11.09
(577.7)	found	60.43	5.57	11.86	10.46

IR ($CHCl_3$): ν = 1323; 1157 cm^{-1} (SO_2).

^{1}H-NMR ($CDCl_3$/TMS) δ = 2.48, 2.56 (d, 2H, CH_2CH); 2.87 [s, 12H, $N(CH_3)_2$]; 3.10, 3.18 (d, 2H, CH_2NH); 5.52 (t, 1H, $NHSO_2$); 6.84 (9, 1 H_{im}); 7.69–7.73, 8.14–8.64 (2m, 12 H_{dansyl}); 7.90 (d, 1 H_{im}).

N-Dansylhistamine (**2c**): *N,N^{im}*-Didansylhistamine (5.4 g, 9 mmol) is stirred in EtOH (450 mL) + and 3% Na_2CO_3 solution (200 mL) for 2 days at r.t. The mixture is then evaporated under reduced pressure and the residue is extracted with EtOAc (3 × 50 mL). The organic layer is washed with 5% aq. HCl (50 mL) and 5% $NaHCO_3$ solution (50 mL), dried ($MgSO_4$); and evaporated under reduced pressure. The residue is flash-chromatographed on silica gel using CH_2Cl_2/MeOH (97:3) as eluent to give **2c** as a hygroscopic yellow solid; yield: 2.87 g (90%).

$C_{17}H_{20}N_4O_2S$	calc.	C 59.28	H 5.85	N 16.27	S 9.31
(344.4)	found	58.96	5.99	15.70	8.93

^{1}H-NMR ($CDCl_3$): δ = 2.68 (t, 2H, CH_2CH); 2.87 [s, 6H, $N(CH_3)_2$; 3.19 (t, 2H, CH_2NH); 6.65 (br s, 1H, CH_{im}); 7.09–7.68, 8.17–8.56 (2m, 7H, 8 H_{dansyl} + CH_{im}).

N^1,N^2-Di-Boc-N^4-dansyl-1,2,4-butanetriamine (**6c**): To a solution of *N*-dansylhistamine (**2c**; 3 g, 9 mmol) in MeCN (175 mL) are added 10% aq. KOAc solution (150 mL, 150 mmol) and di-*tert*-butyl dicarbonate (7.5 g, 35 mmol) and the mixture is stirred at r.t. for 20 h. (two phases are formed). Then, a further portion of di-*tert*-butyl dicarbonate (5 g, 23 mmol) is added and stirring is continued for 70 h. TLC on silica gel (EtOAc) then shows disappearance of **2c** (R_f = 0) and appearance of two major products (**3c** + **4c**; R_f[0.85 and 0.69], respectively) and a minor product (R_f = 0.21). The phases are separated, the aqueous phase is extracted with EtOAc (3 × 50 mL), the extract is combined with the organic phase, and this solution is evaporated to dryness under reduced pressure. The residue is refluxed in MeOH (100 mL) for 6 h until complecte disappearance of the formyl group as evidenced by IR and ^{1}H-NMR analysis (cf. **5a**). MeOH is evaporated and the residue is dissolved in absolute MeOH (50 mL) and hydrogenated over 10% Pd-C (1.5 g) at 5.40 bar and 40–50°C for 34 h. The catalyst is then removed and the solution evaporated to dryness under reduced pressure. The residue is flash-chromatographed with hexane/EtOAc (3:1; 1000 mL), hexane/EtOAc (2:1; 500 mL), hexane/EtOAc (1:1; 500 mL), EtOAc (200 mL), and EtOAc/MeOH (19:1; 100 mL) to give product **6c** [yield: 0.844 g (28%), oil] and the starting material **2e** [yield: 1.1 g (18.3%)].

$C_{26}H_{40}N_4O_6S$	calc.	C 58.19	H 7.51	N 10.44	S 5.97
(536.7)	found	58.45	7.30	10.15	6.03

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.32, 1.41 [d, 18H, $2C(CH_3)_3$]; 2.87 [sm, 6H, $N(CH_3)_2$]; 2.96 (m, 2H, CH_2NH); 4.49 (br s, 1H, NH); 4.09 (br s, 1H, NH); 6.18 (br s, 1H, $NH\text{-}SO_2$); 7.09–7.58, 8.16–8.56 (2 m, 6 H_{naphth}).

N^1,N^2-Di-Boc-N^4-tosyl-1,2,4-butanetriamine (6b); One-Pot Synthesis from 2b:

To a solution of *N*-tosylhistamine (**2b**; 13.25 g, 50 mmol) in MeCN (750 mL) are added 10% aq. KOAc solution (600 mL) and di-*tert*-butyl dicarbonate (43.5 g, 200 mmol) and the mixture is stirred at r.t. for 70 h. The organic layer is separated (the aqueous layer is saved) and evaporated under reduced pressure, MeOH (300 mL) is added to the residue, and this solution is stirred at 70°C for 2 h. The solvents are removed under reduced pressure to give an orange oil (21.3 g) (^{1}H-NMR analysis shows the absence of the signal of the formyl hydrogen at δ = 9.5). The oil is dissolved in MeOH (200 mL) and this solution is hydrogenated over 10% Pd-C (2 g) in a Parr apparatus at 5.6 bar and 50°C. After 52 h, an additional amount of 10% Pd-C (2 g) is added. After 94 h, the catalyst is filtered off, the solvent is removed under reduced pressure, and $CHCl_3$ (125 mL) is added to the residue. This solution is washed with 1% aq. HCl (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue (9 g) is flash-chromatographed on silica gel using hexane/EtOAc (60:40) as eluent to give product **6b** as colorless crystals; yield: 4.4 g (19%); mp 120–121°C.

$C_{21}H_{35}N_3O_6S$	calc.	C 55.14	H 7.66	N 9.19	
(457.6)	found	55.26	7.80	9.01	

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.36 [s, 9H, $C(CH_3)_3$]; 1.43 [s, 9H, $C(CH_3)_3$]; 1.55–1.90 (m, 2H, CH_2); 2.40 (s, 3H, CH_3); 2.85–3.25 (m, 4H, $2CH_2NH$); 3.40–3.85 (m, 1H, CH); 3.60–4.20 (m, 2H, 2NH); 5.93 (br s, 1H, NH); 7.26 (d, 2H, J = 10 Hz, Ts); 7.74 (d, 2H, J = 10 Hz, Ts).

N-Tosylhistamine (**2b**) is regenerated by evaporation of the aqueous layer and flash chromatography of the residue on silica gel using EtOAc/MeOH (4:1) as eluent; recovery: 5.4 g (41%).

1,2-Diamino-4-tosylaminobutane (7b):

To a solution of N^1,N^2-Di-Boc-N^4-tosyl-1,2,4-butanetriamine (**6b**; 1.39 g, 3 mmol) in absolute MeOH (11 mL) is added 18% aq. HCl (15 mL) and the mixture is stirred for 3 h at r.t. Then, dry Et_2O (200 mL) is added and the mixture is allowed to stand overnight. The supernatant liquid is decanted, the solid residue is washed with Et_2O (3×), and 5% aq. KOH solution (8 mL) and $CHCl_3$ (200 mL) are added. The mixture is vigorously shaken whereupon Na_2SO_4 (about 10 g) is added to the two phases. The mixture is then filtered by suction and washed with $CHCl_3$ (3 × 50 mL). The $CHCl_3$ phase is evaporated to give product **7b** as a hygroscopic oil; yield: 0.74 g (95%).

$C_{11}H_{19}N_3O_2S_2$	calc.	C 51.33	H 7.44	N 16.32	
(257.3)	found	50.97	7.32	16.02	

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.10–1.80 (m, 2H, CH_2); 2.30–2.85 (m, 7H, CH_2-CH, $2NH_2$); 2.40 (s, 3H, CH_3); 2.85–3.30 (m, 2H, CH_2NH); 7.27 (d, 2H, J = 10 Hz, Ts); 7.73 (d, 2H, J = 10 Hz, Ts).

Tetrabenzyl N^4-Tosyl-1,2,4-butanetriamine-N^1,N^1,N^2,N^2-tetraacetate (8b):

1,2-Diamino-4-tosylaminobutane (**7b**; 0.19 g, 0.74 mmol) is dissolved in MeCN (1.7 mL), *N,N,N′,N′*-tetramethyl-1,8-naphthalenediamine (0.99 g, 4.7 mmol) and NaI (0.07 g, 0.46 mmol) are added, and the mixture is heated to give a clear solution. Then, benzyl bromoacetate (0.74 mL, 4.6 mmol) is added, whereupon a white solid precipitates. The mixture is refluxed for 44 h under N_2, then cooled to r.t., and $CHCl_3$ (50 mL) is added. The solids are filtered off and the solvents are removed under reduced pressure. The oily residue is washed with hexane/EtOAc (9:1; 3 × 50 mL) to remove excess benzyl bromoacetate. The solvent is decanted and the residue dried under high vacuum to give product **8b** as a yellow-brown oil; yield: 0.13 g (20%).

$C_{47}H_{51}N_3O_{10}S$	calc.	C 66.41	H 6.05	H 4.94
(790.0)	found	66.02	5.48	5.01

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.40–1.90 (m, 2H, CH_2); 2.37 (s, 3H, CH_3); 2.45–3.25 (m, 5H, CH_2NH, CH_2N CHN); 3.48 (2s, 8H); 3.44 (m, 2H, CH_2CO_2)]; 5.07 (s, 8H, $4CH_{2benzyl}$); 7.28 (d, 2H, J = 10 Hz, Ts); 7.30 (s, 20 H_{arom}); 7.76 (d, 2H, J = 10 Hz, Ts).

N^4-Tosyl-1,2,4-butanetriamine-N^1,N^1,N^2,N^2-tetraacetic Acid (9b):
A solution of the ester **8b** (0.115 g, 0.14 mmol) in 95% MeOH (6 mL) containing AcOH (0.2 mL) is hydrogenated over Pd black (100 mg) at 5.2 bar and 25 °C overnight. The catalyst is then filtered off and washed with hot H_2O. The filtrate is evaporated to give product **9b** as a white solid; yield: 0.064 g (97%); mp 180 °C.

$C_{19}H_{27}N_3O_{10}S$	calc.	C 46.62	H 5.56	N 8.58
(489.5)	found	46.13	5.24	8.40

^{1}H-NMR (D_2O/CH_3OH): δ = 1.50–2.35 (m, 2H, CH_2); 2.64 (s, 3H, CH_3); 3.10–3.40 (m, 3H, CH_2N, CHN); 3.40–3.70 (m, 2H, CH_2NH); 3.85 (s, 4H, CH_2CO_2H); 4.18 (s, 4H, CH_2CO_2H); 7.69 (d, 2H, J = 9 Hz, Ts); 7.98 (d, 2H, J = 9 Hz, Ts).

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