Total Syntheses of the Spermine Alkaloids (−)-(*R*,*R*)-Hopromine and (±)-Homaline

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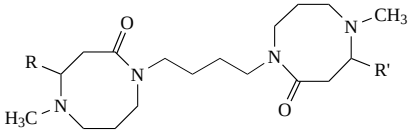
The diastereoselective synthesis of the spermine alkaloid (*R*,*R*)-hopromine (**2**) is described. The as yet unknown absolute configuration of naturally occurring (−)-hopromine (**2**) is (*R*,*R*) and was established by comparison of the reported specific rotation of the natural product with that of the synthetic one. Preparation of the characteristic bis-8-membered lactam scaffold was carried out by convergent build-up of basic chiral azalactam units **21a** and **21b** and subsequent iterative linking (*Schemes 5* and *6*). Key steps in the analogous syntheses of 4-alkyl-hexahydro-1,5-diazocin-2(1*H*)-ones **21a** and **21b** were the introduction of the unbranched alkyl side chains into their common precursor **14** *via* cuprate reaction and the $Sb(OEt)_3$-assisted cyclization of the open-chain intermediates **20a** and **20b**, respectively (*Schemes 3* and *4*). The chiral iodoester **14** was prepared from commercially available (+)-L-aspartic acid (**12**). Based on the synthetic strategy developed for (*R*,*R*)-hopromine (**2**), a rapid access to the parent alkaloid homaline (**1**) in its (±)-form is given.

Introduction. – The *Homalium* alkaloids homaline (**1**), hopromine (**2**), hoprominol (**3**), and hopromalinol (**4**) constitute a group of alkaloids isolated from the leaves of an African *Homalium* species and *Homalium pronyense* GUILLAUM. (Flacourtiaceae) found in the forests of New Caledonia [1] (*Fig. 1*). They were investigated in the early seventies by *Pais et al.* and found to have unique bis-8-membered lactam structures with a polyamine backbone [2][3]. They are based biogenetically on a combination of two α,β-unsaturated carboxylic acid residues (fatty or cinnamic acid) with spermine (**5**).



1	R = Ph	R' = Ph	homaline
2	R = $Me(CH_2)_4$	R' = $Me(CH_2)_6$	hopromine
3	R = $Me(CH_2)_4$	R' = $Me(CH_2)_4CH(OH)CH_2$	hoprominol
4	R = Ph	R' = $Me(CH_2)_4CH(OH)CH_2$	hopromalinol

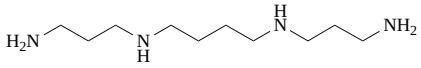


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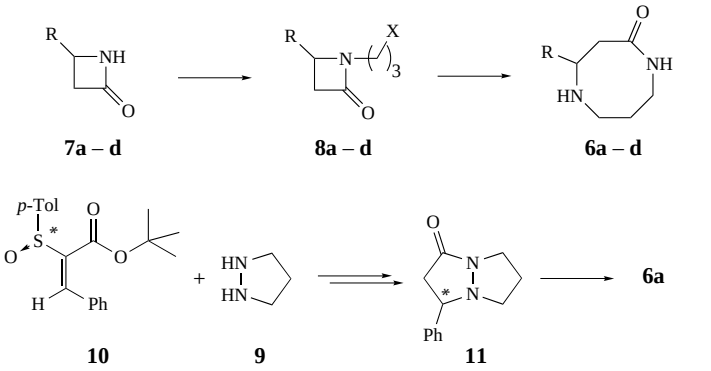
Fig. 1. *The* Homalium *alkaloids* **1**–**4** *and their spermine backbone* **5**

[1]) Part of the Ph.D. Thesis of *C. E.*, University of Zürich, 2002.

The best-defined member of the *Homalium* family is the major alkaloid homaline (**1**), the structure and absolute (*S*,*S*)-configuration of which have been confirmed by X-ray single-crystal analysis [4] and manifold diastereoselective total synthesis [5][6]. The configuration of the remaining three alkaloids **2**–**4** is yet to be determined since the few reported preparations of these unsymmetrically substituted alkaloids are nonstereospecific [7]. Up to now, the methods employed for building up the characteristic 8-membered lactam units **6a**–**d** (*Scheme 1*) were either 'Zip' ring expansion in liquid ammonia of 4-substituted azetidin-2-ones **7a**–**d** after conversion into the corresponding *N*-(3-halopropyl)-*β*-lactams **8a**–**d**, or the conjugate addition-cyclization reaction of pyrazolidine **9** to optically active vinyl sulfoxide **10** followed by successive reduction of the chiral auxiliary and reductive cleavage of the N–N bond of the bicyclic acylhydrazine **11**.

Scheme 1. *Methods for the Prepartion of 8-Membered Lactam Building Blocks* **6a**–**d**



7a – d **8a – d** **6a – d**

10 **9** **11**

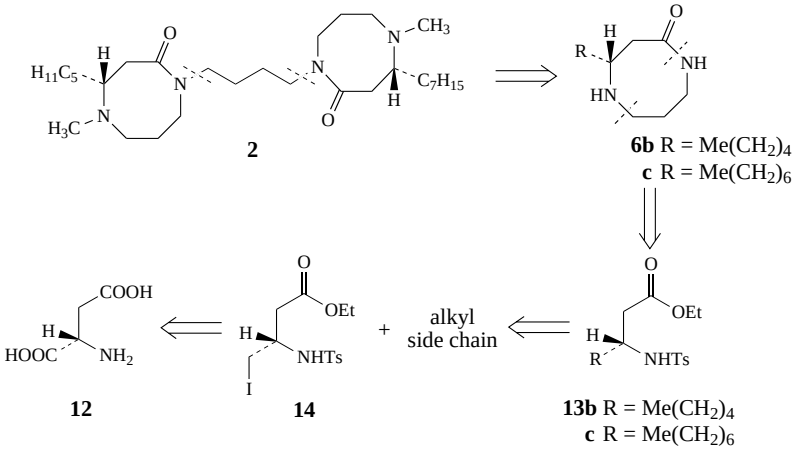
a R = Ph **b** R = $Me(CH_2)_4$ **c** R = $Me(CH_2)_6$ **d** R = $Me(CH_2)_4CH(OSiMe_2{}^tBu)CH_2$

We wish to report the convergent and diastereoselective total synthesis of (*R*,*R*)-hopromine (**2**) starting from (+)-L-aspartic acid (**12**). The choice of **12** as chiral starting material was based on the belief that all members of the *Homalium* family share the same three-dimensional orientation of the residues at the corresponding chiral centers. The stereocontrolled preparation of (*R*,*R*)-configured **2** allowed us to determine the absolute configuration of the natural product by comparison of the specific-rotation values. In addition to this, the elaboration of the total synthesis of (*R*,*R*)-hopromine (**2**) led to the establishment of a set of reaction methods whose general applicability of the preparation of different 4-substituted hexahydro-1,5-diazocin-2-(1*H*)-ones of the type **6a**–**d** was confirmed by the successful synthesis of (±)-homaline (**1**).

Results and Discussion. – Retrosynthetically, (*R*,*R*)-hopromine (**2**) can be decomposed into two 4-alkyl-substituted 8-membered lactam units **6b** and **6c** linked by a C_4 bridge (*Scheme 2*). Each of the lactam blocks **6b** and **6c** contains a *β*-alkyl-*β*-amino acid portion as the asymmetric structural unit as well as a C_3-N moiety. The two

β-amino fatty acid units **13b** and **13c**, again, were divided into their respective linear alkyl rests and one common synthon, chiral iodoester **14**, easily obtainable from L-aspartic acid (**12**) by regioselective modification of its α-carboxylic acid group [8].

Scheme 2. *Retrosynthetic Analysis of Hopromine* (**2**)

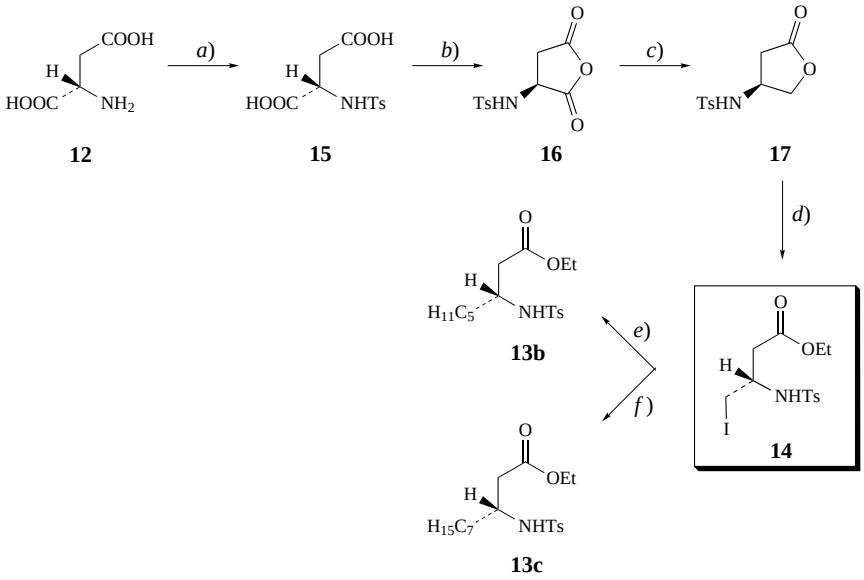


First, the amino group was protected by converting **12** to *N*-tosyl-L-aspartic acid **15** under biphasic alkaline conditions (*Scheme 3*). Lengthy exposure of **15** to thionyl chloride in AcOEt gave the succinic anhydride **16**, which, by selective reduction with $NaBH_4$ [9], led to the lactone **17**. Next, reaction of **17** with trimethylsilyl iodide in $EtOH/CH_2Cl_2$ under mild conditions [10] furnished the key chiral intermediate iodoester **14**.

Introduction of the aliphatic C_4 and C_6 side chains by nucleophilic substitution at **14** was carried out by adding **14** carefully to a twofold excess of the appropriate lithium organocuprate in Et_2O/THF 1:2 at $-65°$ [11]. Bu_2CuLi was successfully prepared by dropwise addition of commercially available BuLi to a suspension of LiCl and $CuBr \cdot Me_2S$ in Et_2O/THF at $-65°$, while Hx_2CuLi (Hx = hexyl) was best prepared by first generating HxLi *in situ* from ^{t}BuLi and iodohexane and then only adding $CuBr \cdot Me_2S$. The temperature of the cuprate reaction after mixture of all the components had to be kept strictly below $-35°$, since above this limit, the basic character of the lithium organocuprate induced undesired cyclization of iodoester **14** to aziridine and α,β-elimination reaction. Aqueous workup finally yielded the chiral ethyl 3-(tosylamino)alkanoates **13b**,**c**.

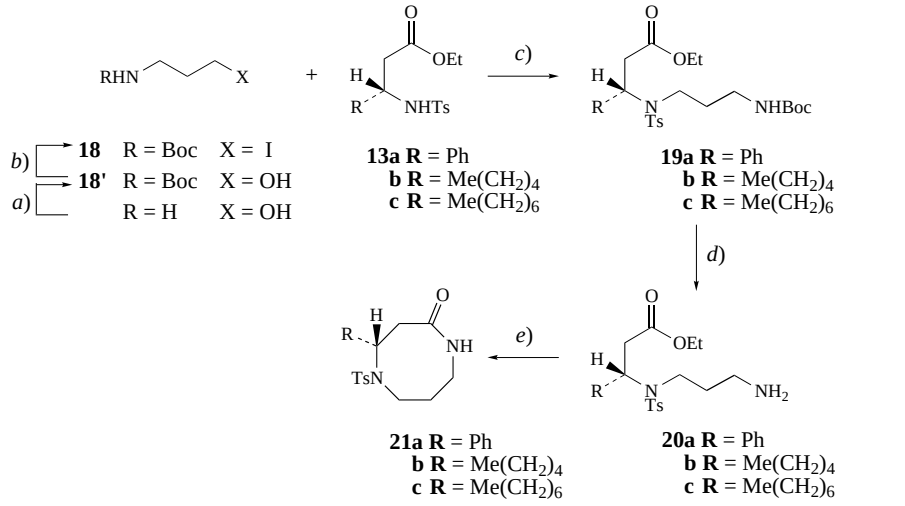
The missing C_3-N fragment was inserted into the β-alkyl-β-amino ester portions **13b** and **13c** by alkylating their *N*-tosyl terminus with *tert*-butyl (3-iodopropyl)carbamate **18** (*Scheme 4*), readily available from 3-aminopropan-1-ol after Boc-protection to **18**′ and iodination. Optimum conditions for the *N*-alkylation of the sulfonamides **13b** and **13c** were heterogeneous deprotonation by cesium carbonate and slow reaction with iodide **18** in DMF at 55° overnight. Subsequent removal of the Boc-protection group from the resulting *N*-alkylated sulfonamides **19b**,**c** by means of a several-fold excess of

Scheme 3. *Synthesis of the Common Precursor* **14** *and Subsequent Cuprate Reactions*



a) TsCl, aq. 4N NaOH, Et_2O, r.t., overnight; quant. *b*) $SOCl_2$, AcOEt, r.t., 4 h; 81%. *c*) 1. $NaBH_4$, THF, 0°, 2 h; 2. conc. HCl soln., EtOH, reflux, 2 h; 63%. *d*) Me_3SiI, EtOH, CH_2Cl_2, 0° → r.t., overnight; 88%. *e*) BuLi, LiCl, $CuBr \cdot Me_2S$, Et_2O/THF 1:2, −65° → −40°, 5 h; 66%. *f*) 1. $C_6H_{13}I$, ^{t}BuLi, Et_2O, −65° → −40°, 2 h; 2. $CuBr \cdot Me_2S$, Et_2O/THF, −65° → −40°, 5 h, 79%.

Scheme 4. *Synthesis of the 8-Membered* N-*Tosylated 4-Substituted Hexahydro-1,5-diazocin-2(1*H*)-ones* **21a**–**c**



a) Boc_2O, Et_3N, CH_2Cl_2, reflux, overnight; 99%. *b*) I_2, PPh_3, 1*H*-imidazole, CH_2Cl_2, r.t., 3.5 h; 84%. *c*) Cs_2CO_3, DMF, 55°, overnight; **19a**: 80%; **19b**: 73%; **19c**: 69%. *d*) CF_3COOH, $CHCl_3$, 40°, overnight, quant. *e*) $Sb(OEt)_3$, dry benzene, 4-Å mol. sieves, reflux, 16 h; **21a**: 83%; **21b**: 88%; **21c**: 91%.

CF_3COOH in $CHCl_3$ yielded quantitatively the amino esters **20b**,**c** as linear ring precursors.

Since all attempts to close the 8-membered lactam rings by methods commonly employed in peptide synthesis (*e.g.*, DCC/DMAP (=dicyclohexylcarbodiimide/*N*,*N*-dimethylpyridin-4-amine), (Bu_3N/2-chloro-1-methyl-pyridinium iodide)-, or (dipyridyl disulfid)-mediated condensation of amino acids [12], or the anhydride method [13]) were unsuccessful, we had recourse to the works of *Yamamoto* and *Furuta* [14]. Notwithstanding the apparent risk of forming undesired sixteen-membered dimers, we decided to try cyclizing **20b** and **20c**, with the aid of $Sb(OEt)_3$, which had already been successfully used in the macrolactamization of linear tetraamino esters [15] and is supposed to assist cyclization of polyamino esters by a template effect [16]. Refluxing **20b** and **20c**, with 1.2 equiv. of $Sb(OEt)_3$ under high-dilution conditions in dry benzene for 16 h yielded the 8-membered lactams **21b** and **21c** in 88 and 91%, respectively. The exclusive formation of monomeric 4-substituted hexahydro-1,5-diazocin-2-(1*H*)-ones **21b**,**c** was confirmed by ESI-MS analysis. In addition to the mass-spectrometric evidence, a single-crystal X-ray analysis of **21b** (*Fig. 2*) allowed us to verify both the monomeric 8-membered ring structure and the (*R*)-configuration at the stereogenic centre. In fact, due to the presence of anomalous scattering in the compound, *e.g.*, of the S-atom, it was possible to independently determine the absolute configuration by X-ray-diffraction analysis. Refinement of the absolute structure parameter [17] yielded a value of 0.05(6), which confidently confirms that the refined coordinates represent the true enantiomorph.

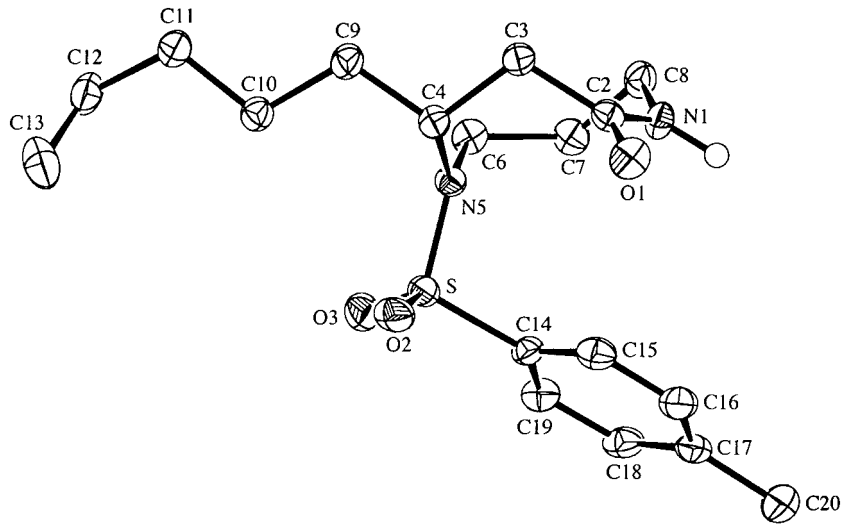
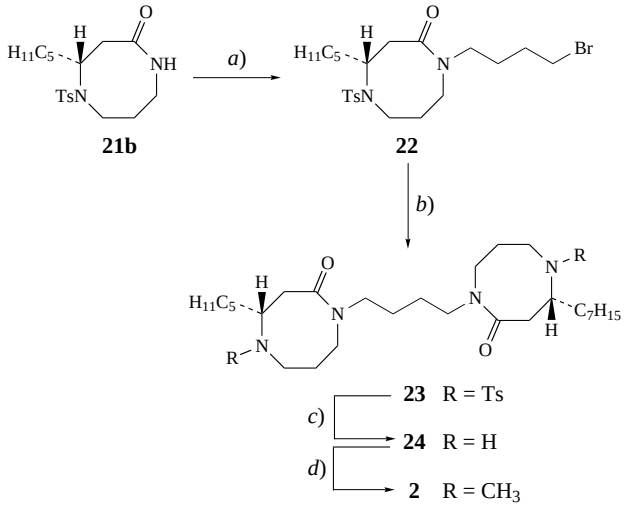


Fig. 2. *ORTEP* [26] *Representation of the* N-*tosylated 4-substituted 8-membered lactam* **21b** (50% probability ellipsoids; H-atoms are omitted for clarity)

Bridging of both lactam units **21b** and **21c** by the C_4 chain was accomplished iteratively [6][18]: first **21b** was mono-alkylated with 1,4-dibromobutane under the action of powdered KOH in dry DMSO at room temperature overnight, then the resulting bromo derivative **22** was attached to **21c** by adding a mixture of both to a

frozen suspension of KOH in dry DMSO at 0° and slowly defreezing the solid reaction mixture overnight (*Scheme 5*). This treatment gave the bis-8-membered core **23** in 71% yield. The identification of the coupling product by NMR spectroscopy was not unambiguously possible. Most probably due to the interconversion of conformational ring isomers, the ^{1}H-NMR spectrum showed no clearly interpretable signals, nor in the ^{13}C-NMR spectrum could all signals be detected. The structural characterization of **23** was thus based on the fragmentation pattern obtained by nano ESI-MS/MS analysis of the isolated product.

Scheme 5. *Iterative Coupling of the Lactam Rings and Completion of the Synthesis of Hopromine* (**2**)



a) $Br(CH_2)_4Br$, KOH, dry DMSO, r.t., overnight; 82%. *b*) **21c**, KOH, dry DMSO, 0° → r.t., overnight; 71%. *c*) Electrolysis, $(Me_4N)Cl$, aq. EtOH soln., 5°; 64%. *d*) 1. 37% aq. HCOH soln., AcOH, 0°, 15 min; 2. $NaBH_3CN$, MeOH, 0° → r.t., 4 h; quant.

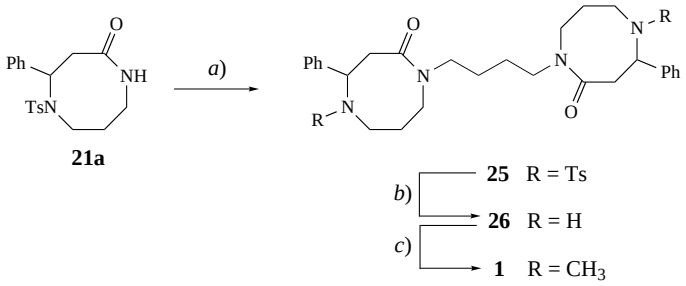
Mild electrolytic detosylation of **23** in EtOH [19] afforded 64% of crude didemethylhopromine **24**, which was quantitatively converted to the title compound (*R*,*R*)-hopromine (**2**) by reductive methylation upon treatment with excess aqueous formaldehyde solution and AcOH at 0° and subsequent exposure to $NaBH_3CN$/MeOH at room temperature for 4 h.

Synthetic (*R*,*R*)-hopromine (**2**) was characterized by IR, ^{1}H-, ^{13}C-NMR, and mass spectra and revealed to be equal in all respects to the natural product as described in [3]. Both the synthetic and the natural products showed comparable specific rotation values, so that the postulated (*R*,*R*)-configuration of natural (−)-hopromine (**2**) can be assumed. It should be noted that, despite the different stereodescriptors (*S*,*S*) *vs.* (*R*,*R*) (change of CIP priority of Ph *vs.* alkyl), homaline (**1**) and hopromine (**2**), respectively, have the same three-dimensional orientation of their residues at the stereogenic center.

The ease with which the 8-membered 4-alkyl-substituted lactam units **21b** and **21c** could be prepared in only a few steps from the fatty acid moieties **13b** and **13c**, respectively, tempted us to apply the same ring-construction strategy to the preparation

of 4-phenyl-hexahydro-1,5-diazocin-2-(1*H*)-one (**21a**) from ethyl (±)-3-phenyl-3-(tosylamino)propanoate (**13a**) and hence to the total synthesis of (±)-homaline (**1**) [20]. Compound **13a** was readily obtained by conversion of commercially available (±)-(3-amino-3-phenylpropanoic acid by *N*-tosylation with TsCl and subsequent esterification with EtOH/$SOCl_2$. Treatment of **13a** analogous to that of **13b**,**c**, *i.e.*, *N*-alkylation followed by Boc-deprotection and $Sb(OEt)_3$-assisted ring closure (*Scheme 4*), led to the cyclic lactam **21a** in good yields. The symmetric, bis-8-membered scaffold **25** was built up by double alkylation of 1,4-dibromobutane with **21a** and powdered KOH in dry DMSO [6][18] (*Scheme 6*) under conditions comparable to those employed for the iterative linking of **21b** with **21c**. Electrolytic detosylation of **25** similarly to that of **23** and reductive methylation of didemethylhomaline **26** as described for **24** completed the total synthesis of (±)-homaline (**1**).

Scheme 6. *Synthesis of (±)-Homaline* (**1**)



a) $Br(CH_2)_4Br$, KOH, dry DMSO, 0° → r.t., overnight; 53%. *b*) Electrolysis, $(Me_4N)Cl$, MeOH/DMF, 5°; 76%. *c*) 1. 37% aq. HCOH soln., AcOH, 0°, 15 min; 2. $NaBH_3CN$, MeOH, 0° → r.t., 3.5 h; 88%.

Conclusions. – The naturally occurring spermine alkaloid (−)-(*R*,*R*)-hopromine (**2**) was successfully prepared by convergent synthesis from two chiral 4-alkyl-substituted hexahydro-1,5-diazocin-2-(1*H*)-ones. The diastereoisomer purity of the target compound **2** was guaranteed by the use of the commercially available chiral-pool material (+)-L-aspartic acid (**12**) as the starting material. Ring closure of the linear amino esters **20a**–**c** to the 8-membered lactam building blocks **21a**–**c** under the assistance of $Sb(OEt)_3$ worked remarkably well and with total conservation of the configuration of the chiral-ring precursors. The synthetic strategies described should also be applicable to the preparation of the remaining members of the *Homalium* family.

We thank the analytical departments of our institute for all measurements and gratefully acknowledge the financial support of the *Swiss National Science Foundation*. Special thanks go to *Richard Detterbeck* for many fruitful discussions and his helping hand with the optimization of the cuprate reactions, and to *Armin Guggisberg* for performing the electrolytic detosylation reactions. Dr. *A. Linden* is thanked for recording of the X-ray crystallographic data and for his assistance with the evaluation and presentation of the latter.

Experimental Part

General. All commercially available reagents were used without further purification. Solvents were either *puriss. p.a.* grade (*Fluka*) or were distilled prior to use. Benzene, THF, and Et_2O were dried over NaH or Na-benzophenone and freshly distilled before use. Dry DMSO was purchased from *Fluka* and stored over 4-Å molecular sieves. $CuBr \cdot Me_2S$ was prepared by recrystallization of CuBr from Me_2S. $Sb(OEt)_3$ was purchased from *Aldrich* and had to be handled with care under Ar. Reactions were carried out under N_2, unless otherwise stated (TLC monitoring). TLC: *Merck* precoated silica-gel plates *60 F_{254}*. Column chromatography (CC): silica gel *60* (230–400 mesh ASTM) from *Merck*. M.p.: *Mettler FP5*. Optical rotations $[\alpha]_D^{21}$: in $CHCl_3$ (*Fluka*, for IR spectroscopy), unless otherwise stated; *Perkin-Elmer 241* polarimeter. IR Spectra: in $CHCl_3$ (*Fluka*, for IR spectroscopy); *Perkin-Elmer 781*; in cm^{-1}. NMR Spectra: in $CDCl_3$, unless otherwise stated; *Bruker ARX-300* (300 (^{1}H) or 75 MHz (^{13}C)) or *Bruker DRX-600* (600 (^{1}H) or 150 MHz (^{13}C)); chemical shifts δ in ppm rel. to Me_4Si (= 0 ppm) as internal standard, coupling constants *J* in Hz. MS: *Finnigan SSQ-700* for chemical ionization (CI) with NH_3, *Finnigan MAT-90* for electron impact (EI, 70 eV), and *Finnigan TSQ-700* for electrospray ionization (ESI); *m*/*z* (rel. intensity in %).

(+)-(2S)-2-(Tosylamino)butanedioic Acid (= N^2-Tosyl-L-*aspartic Acid*; **15**). To a soln. of (+)-L-aspartic acid (**12**; 34 g, 0.26 mol) in aq. 4N NaOH (130 ml) at 0°, a soln. of TsCl (73 g, 0.38 mol, 1.5 equiv.) in Et_2O (300 ml) was added, followed by a supplementary volume of aq. 4N NaOH (210 ml). The resulting biphasic mixture was vigorously stirred at r.t. overnight. The Et_2O layer was then discarded and the basic aq. layer washed with Et_2O (2 × 100 ml). Then the aq. phase was acidified at −10° with conc. HCl soln. to pH 1 and extracted with AcOEt (3 × 200 ml). The combined org. extracts were washed with brine, dried ($MgSO_4$), and evaporated: **15** (72 g, 98%). Colorless, amorphous solid. M.p. 112–114°. $[\alpha]_D^{21} = +12.1$ ($c = 4.0$, MeOH). IR: 3500–2500*s*, 1730*s*, 1600*w*, 1500*w*, 1410*m*, 1330*m*, 1308*w*, 1290*w*, 1230*w*, 1190*w*, 1160*s*, 1120*w*, 1090*s*, 1040*w*, 1010*w*, 960*w*, 860*w*, 840*w*, 815*m*, 780*s*, 705*s*, 665*s*, 625*w*. ^{1}H-NMR: 8.07 (br. *s*, 2 H); 7.72 (*d*, *J* = 8.3, 2 H); 7.26 (*d*, *J* = 8.6, 2 H); 6.57 (*d*, *J* = 8.3, 1 H); 4.13 (*m*, 1 H); 3.06 (*dd*, *J* = 17.5, 3.8, 1 H); 2.86 (*dd*, *J* = 17.5, 4.6, 1 H); 2.39 (*s*, 3 H). ^{13}C-NMR: 174.5, 173.9, 144.0, 136.1 (4 *s*); 129.7, 127.1, 51.5 (3 *d*); 37.4 (*t*); 21.4 (*q*). CI-MS: 305 (29, $[M + NH_4]^+$) 287 (100, $[M + NH_4 - H_2O]^+$).

(−)-(3S)-3,4-Dihydro-3-(tosylamino)furan-2,5-dione (**16**). To a soln. of **15** (72 g, 0.25 mol) in AcOEt (200 ml), $SOCl_2$ (73 ml, 1.0 mmol, 4.0 equiv.) was aded over 45 min. The slightly yellow mixture was stirred at r.t. for 4 h and then carefully evaporated. The sticky oily residue was washed with toluene and dried *in vacuo:* **16** (54.5 g, 81%). Pale yellow solid, which was considered sufficiently pure for use in the next step. M.p. 118–120°. $[\alpha]_D^{21} = -14.1$ ($c = 1.35$, DMSO). IR: 3640*w*, 3420*m*, 3300*s*, 3070*w*, 2950*m*, 1870*s*, 1790*s*, 1730*m*, 1597*s*, 1495*w*, 1450*s*, 1400*m*, 1340*m*, 1300*m*, 1255*w*, 1200*s*, 1160*s*, 1090*m*, 1065*m*, 1030*m*, 965*m*, 907*m*, 655*w*, 817*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.10 (*d*, *J* = 9.2, 1 H); 7.60 (*d*, *J* = 8.3, 2 H); 7.30 (*d*, *J* = 8.6, 2 H); 4.71 (*m*, 1 H); 2.91 (*dd*, *J* = 18.1, 9.7, 1 H); 2.56 (*dd*, *J* = 18.1, 6.9, 1 H); 2.29 (*s*, 3 H). ^{13}C-NMR ((D$_6$)DMSO): 170.8, 168.7, 143.2, 137.8 (4 *s*); 129.7, 126.3, 52.0 (3 *d*); 35.4 (*t*); 20.9 (*q*). CI-MS: 287 (100, $[M + NH_4]^+$), 286 (59, $[M + NH_3 - H_2O + NH_4]^+$).

(−)-(4S)-4,5-Dihydro-4-(tosylamino)furan-2(3H)-one (**17**). To a stirred suspension of $NaBH_4$ (8.4 g, 0.22 mol, 1.1 equiv.) in dry THF (150 ml) at 0°, soln. of **16** (54.5 g, 0.20 mol) in THF (300 ml) was added dropwise. The intensively yellow colored mixture was allowed to warm to r.t. and then stirred for 1 h before being cooled to 0°. Then EtOH (50 ml) and conc. HCl soln. (10 ml) were slowly added. The resulting mixture was stirred for 2 h under reflux and then allowed to cool to r.t. and partially evaporated. The residual oil was quenched with sat. aq. NaCl soln. (100 ml) and extracted with AcOEt (3 × 150 ml). The combined extracts were washed with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. The crude product was recrystallized from AcOEt/hexane to yield pure **17** (32.6 g, 63%). Colorless solid. M.p. 109–112°. $[\alpha]_D^{21} = -6.3$ ($c = 2.0$, $CHCl_3$). IR: 3490*w*, 3270*s*, 3260*s*, 3006*m*, 2940*m*, 2905*w*, 2780*w*, 1925*w*, 1770*s*, 1600*s*, 1460*s*, 1405*w*, 1375*w*, 1340*s*, 1305*w*, 1290*w*, 1245*w*, 1190*s*, 1160*s*, 1090*s*, 1060*w*, 1000*s*, 920*m*, 880*w*, 840*w*, 815*m*, 750*w*, 700*m*, 665*s*. ^{1}H-NMR: 7.75 (*d*, *J* = 8.3, 2 H); 7.33 (*d*, *J* = 8.1, 2 H); 5.51 (*d*, *J* = 6.9, 1 H); 4.38 (*m*, 1 H); 4.15 (*m*, 2 H); 2.67 (*dd*, *J* = 17.9, 7.5, 1 H); 2.44 (*s*, 3 H); 2.39 (*dd*, *J* = 17.9, 5.1, 1 H). ^{13}C-NMR: 174.3, 144.3, 136.6 (3 *s*); 130.0, 126.9 (2 *d*); 72.9 (*t*); 49.7 (*d*); 34.8 (*t*); 21.4 (*q*). CI-MS: 273 ($[M + NH_4]^+$).

Ethyl (−)-(3S)-4-Iodo-3-(tosylamino)butanoate (**14**). To a soln. of **17** (13 g, 51 mmol) and abs. EtOH (15 ml, 0.26 mol, 5.0 equiv.) in dry CH_2Cl_2 (150 ml) at 0° under N_2, Me_3SiI (17.3 ml, 0.13 mol, 2.5 equiv.) was added dropwise over 40 min. The soln. was kept at 0° for 3 h and then stirred at r.t. overnight. H_2O (100 ml) was added and stirring continued for 10 min. The org. layer was washed with 5% aq. $Na_2S_2O_3$ soln. and H_2O, dried ($MgSO_4$), and evaporated. The resulting crude oil was subjected to flash CC (CH_2Cl_2/MeOH 30:1): **14** (18.3 g, 88%). Pale yellow solid. M.p. 60–62°. $[\alpha]_D^{21} = -6.0$ ($c = 1.0$, $CHCl_3$). IR: 3363*w*, 3020*s*, 2980*w*, 2920*w*, 1726*s*, 1600*w*, 1495*w*, 1414*m*, 1378*m*, 1340*s*, 1306*w*, 1207*s*, 1185*m*, 1160*s*, 1090*m*, 1025*m*, 955*m*, 872*m*, 815*m*, 760*s*, 676*s*,

617*w*, 580*w*, 550*m*. ^{1}H-NMR: 7.76 (*d*, *J* = 8.3, 2 H); 7.32 (*d*, *J* = 8.0, 2 H); 5.29 (*d*, *J* = 8.9, 1 H); 4.10 (*m*, 2 H); 3.56 (*m*, 1 H); 3.33 (*dd*, *J* = 10.3, 4.1, 1 H); 3.24 (*dd*, *J* = 10.3, 6.7, 1 H); 2.70 (*dd*, *J* = 16.6, 5.3, 1 H); 2.54 (*dd*, *J* = 16.6, 6.2, 1 H); 2.43 (*s*, 3 H); 1.24 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR: 170.3, 143.7, 137.4 (3 *s*); 129.7, 127.0 (2 *d*); 61.0 (*t*); 50.4 (*d*); 38.8 (*t*); 21.4, 13.9 (2 *q*); 10.4 (*t*). CI-MS: 429 (100, $[M + NH_4]^+$), 412 (11, $[M + H]^+$), 301 (42, $[M - HI + NH_4]^+$), 284 (25, $[M - HI + H]^+$).

Ethyl 3-Phenyl-3-(tosylamino)propanoate (**13a**). To a soln. of (±)-3-amino-3-phenylpropanoic acid (3.0 g, 18.2 mmol) in aq. 2N NaOH (36 ml) at 0°, a soln. of TsCl (5.7 g, 29.9 mmol, 1.6 equiv.) in Et_2O (50 ml) was added. The resulting biphasic mixture was vigorously stirred at r.t. overnight, after which the Et_2O layer was discarded and the pH of the alkaline aq. phase adjusted to pH 1 by the addition of conc. HCl soln. at 0°. The aq. layer was then extracted with AcOEt (3 × 50 ml) and the combined org. extract washed with brine, dried ($MgSO_4$), and evaporated to give 3-phenyl-3-(tosylamino)propanoic acid as a colorless, amorphous solid (3.55 g, 61%). The crude *N*-tosylated acid (3.55 g, 11.1 mmol) was dissolved in EtOH (50 ml) and cooled to 0° before $SOCl_2$ (1.61 ml, 22.2 mmol, 2.0 equiv.) was carefully added by syringe. After the addition, the mixture was allowed to warm to r.t. over 2.5 h. The solvent and excess $SOCl_2$ were evaporated, and the residual oil was taken up in AcOEt (50 ml) and washed twice with H_2O. The aq. layer was extracted with AcOEt (2 × 50 ml) and the combined extract washed with brine, dried ($MgSO_4$), and evaporated: **13a** (3.72 g, 96%). Colorless, amorphous powder, which was pure enough (by ^{1}H- and ^{13}C-NMR) to be used in the next step without further purification. M.p. 75.5–77.5°. IR: 3500–3150*w*, 3460*w*, 3020*w*, 2980*w*, 2930*w*, 1725*s*, 1600*w*, 1495*w*, 1465*w*, 1450*w*, 1430–1385*m*, 1375*m*, 1345*s*, 1330*s*, 1305*m*, 1290*w*, 1270*w*, 1235*w*, 1190*m*, 1180*m*, 1160*s*, 1120*m*, 1090*s*, 1070*w*, 1025*w*, 965*w*, 950*w*, 885*w*, 860*w*, 810*m*, 700*m*, 660*m*, 615*w*. ^{1}H-NMR: 7.59 (*d*, *J* = 8.3, 2 H); 7.18–7.09 (*m*, 7 H); 5.73 (*d*, *J* = 7.7, 1 H); 4.73 (*dt*, *J* = 13.9, 6.2, 1 H); 3.99 (*q*, *J* = 7.1, 2 H); 2.82 (*dd*, *J* = 15.8, 6.2, 1 H); 2.72 (*dd*, *J* = 15.8, 6.3, 1 H); 2.37 (*s*, 3 H); 1.12 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR: 170.5, 143.1, 139.3, 137.4, (4 *s*); 129.3, 128.4, 127.6, 127.0, 126.4 (5 *d*); 60.6 (*t*); 54.3 (*d*); 41.2 (*t*); 21.3, 13.9 (2 *q*).

*Ethyl (+)-(3*R*)-3-(Tosylamino)octanoate* (**13b**). At −65°, 1.6M BuLi in hexane (3.27 ml, 5.2 mmol, 2.0 equiv.) was added dropwise to a mixture of LiCl (222 mg, 5.2 mmol, 2 equiv.) and $CuBr \cdot Me_2S$ (538 mg, 2.6 mmol, 1.0 equiv.) in dry Et_2O/THF (30 ml, 1:2). The resulting deep-orange suspension was warmed up to −40° until all the copper(I) salts were dissolved and then cooled to −65° before a soln. of **14** (1.1 g, 2.6 mmol, 1.0 equiv.) in dry THF (5 ml) was added. The mixture was stirred at −65° → −40° for 5 h and then quenched with sat. aq. NH_4Cl soln. (40 ml). Stirring was continued for 0.5 h until a clear blue aq. phase was obtained, which was subsequently extracted with Et_2O. The combined org. layer was washed with brine, dried ($MgSO_4$), and evaporated and the resulting crude oil subjected to CC (AcOEt/hexane 1:3): **13b** (587 mg, 66%). Colorless oil. $[\alpha]_D^{21} = +19.5$ (*c* = 0.8, $CHCl_3$). IR: 3380*w*, 3020*w*, 2960*m*, 2930*m*, 2860*w*, 1725*s*, 1600*w*, 1425*w*, 1415*m*, 1375*m*, 1340*s*, 1185*w*, 1160*s*, 1095*m*, 1025*w*, 970*w*, 812*m*, 705*w*, 660*s*. ^{1}H-NMR: 7.75 (*d*, *J* = 8.3, 2 H); 7.29 (*d*, *J* = 8.0, 2 H); 5.15 (*d*, *J* = 9.0, 1 H); 4.07 (*m*, 2 H); 3.50 (*m*, 1 H); 2.42 (*s*, 3 H); 2.39 (*m*, 2 H); 1.45 (*m*, 2 H); 1.22 (*t*, *J* = 7.15, 3 H); 1.26–1.10 (*m*, 6 H); 0.81 (*t*, *J* = 6.4, 3 H). ^{13}C-NMR: 171.3, 143.1, 138.1 (3 *s*); 129.5, 127.0 (2 *d*); 60.5 (*t*); 50.6 (*d*); 38.7, 34.6, 31.1, 25.3, 22.3 (5 *t*); 21.4, 14.0, 13.7 (3 *q*).

*Ethyl (+)-(3*R*)-3-(Tosylamino)decanoate* (**13c**). To a soln. of 1-iodohexane (0.77 ml, 5.2 mmol, 2.0 equiv.) in dry Et_2O (10 ml) at −65°, 1.5M *t*BuLi in hexane (7.0 ml, 10.5 mmol, 4.0 equiv.) was added dropwise over 10 min. The mixture was stirred at −65° → −40° for 2 h and diluted with dry THF (20 ml) before being cooled down to −65° again. Then $CuBr \cdot Me_2S$ (538 mg, 2.6 mmol, 1.0 equiv.) was added and the resulting suspension allowed to warm to −40° until all the crystalline $CuBr \cdot Me_2S$ was dissolved. The homogeneous mixture was again cooled to −65° prior to the addition of a soln. of **14** (1.08 g, 2.6 mmol, 1.0 equiv.) in THF (5 ml) and then stirred below −40° for 5 h until no more educt **14** could be traced by TLC. The mixture was then quenched with sat. aq. NH_4Cl soln. (40 ml), and stirring was continued for 0.5 h until a clear blue aq. phase was obtained. The aq. layer was extracted with Et_2O, the combined extract washed with brine, dried ($MgSO_4$), and evaporated, and the remaining crude residue purified by CC (AcOEt/hexane 1:3): **13c** (764 mg, 79%). Pale yellow oil. $[\alpha]_D^{21} = +26.7$ (*c* = 0.6, $CHCl_3$). IR: 3380(br.), 3020*w*, 2980*w*, 2960*s*, 2930*s*, 2860*w*, 1725*s*, 1600*w*, 1465*w*, 1415*w*, 1380*w*, 1340*s*, 1305*w*, 1185*w*, 1160*s*, 1095*m*, 1020*w*, 960(br.), 865*w*, 810*m*, 705*w*, 660*m*. ^{1}H-NMR: 7.75 (*d*, *J* = 8.3, 2 H); 7.29 (*d*, *J* = 8.0, 2 H); 5.15 (br. *d*, *J* = 9.0, 1 H); 4.10 (*m*, 2 H); 3.50 (*m*, 1 H); 2.41 (*s*, 3 H); 2.38 (*m*, 1 H); 2.34 (*d*, *J* = 4.7, 1 H); 1.45 (*m*, 2 H); 1.22 (*t*, *J* = 7.15, 3 H); 1.28–1.10 (*m*, 10 H); 0.84 (*t*, *J* = 6.3, 3 H). ^{13}C-NMR: 171.3, 143.2, 138.0 (3 *s*); 129.5, 127.0 (2 *d*); 60.5 (*t*); 50.6 (*d*); 40.2, 38.6, 34.6, 31.5, 28.9, 25.6, 22.5 (7 *t*); 21.4, 14.0, 13.9 (3 *q*). CI-MS: 387 (100, $[M + NH_4]^+$), 370 (35, $[M + H]^+$).

tert-*Butyl (3-Hydroxypropyl)carbamate* (**18**′). A soln. of 3-aminopropan-1-ol (3.0 g, 40 mmol) in dry CH_2Cl_2 (50 ml) was treated with Et_3N (5.6 ml, 40 mmol, 1.0 equiv.) at r.t. for 0.5 h before a soln. of Boc_2O (9.6 g, 44 mmol, 1.1 equiv.) in CH_2Cl_2 (50 ml) was added slowly. During the dropwise addition of the Boc_2O soln., warming and thickening of the mixture was observed. The resulting colorless mixture was stirred under reflux

overnight and quenched with sat. aq. NH_4Cl soln. The aq. layer was re-extracted twice with CH_2Cl_2, and the combined org. extracts were washed with brine, dried ($MgSO_4$), and evaporated: crude **18′** (6.9 g, 99%). Colorless oil which was pure enough (by ^{1}H-NMR) to be used in the next step without further purification. ^{1}H-NMR: 5.25 (br. *s*, 1 H); 3.84 (*dt*, *J* = 11.6, 5.8, 2 H); 3.71 (br. *s*, OH); 3.45 (*dt*, *J* = 12.45, 6.2, 2 H); 1.87 (*m*, 2 H); 1.63 (*s*, 9 H). ^{13}C-NMR: 156.9, 85.1 (2 *s*); 59.2, 36.9, 32.6 (3 *t*); 28.2 (3 *q*).

tert-*Butyl (3-Iodopropyl)carbamate* (**18**). I_2 (2.6 g, 10.3 mmol, 1.2 equiv.) was added portionwise to a soln. of 1*H*-imidazole (0.7 g, 10.3 mmol, 1.2 equiv.) and PPh_3 (2.69 g, 10.3 mmol, 1.2 equiv.) in CH_2Cl_2 (50 ml) at 0°. The resulting, deep-yellow suspension was warmed to r.t. before a soln. of **18′** (1.5 g, 8.6 mmol) in CH_2Cl_2 (10 ml) was added. The mixture was stirred at r.t. for 3.5 h, filtered over *Celite*, and washed twice with 5% aq. $Na_2S_2O_3$ soln. The combined washing phases were extracted with CH_2Cl_2 and the combined org. layers dried ($MgSO_4$) and evaporated. The residual yellow oil was subjected to CC (AcOEt/hexane 1:1): **18** (1.86 g, 84%). Amorphous, pale yellow solid. M.p. 37–40°. IR: 3457*m*, 3020*s*, 2980*m*, 2936*w*, 1710*s*, 1506*s*, 1455*w*, 1390*m*, 1370*s*, 1250*s*, 1230*s*, 1170*s*, 1070*w*, 1040*w*, 970*w*, 865*w*, 790*s*, 745–720*s*, 670*s*, 617*w*. ^{1}H-NMR: 4.65 (br. *s*, 1 H); 3.20 (*m*, 4 H); 1.99 (*m*, 2 H); 1.44 (*s*, 9 H). ^{13}C-NMR: 155.8, 79.3 (2 *s*); 41.0, 33.4 (2 *t*); 28.3 (3 *q*); 2.98 (*t*). CI-MS: 571 (15, $[2M+H]^+$), 471 (34, $[2M-Boc+H]^+$), 461 (6, $[2M-I+NH_4]^+$), 387 (6, $[2M-I-C_4H_8]^+$), 303 (100, $[M+NH_4]^+$), 286 (30, $[M+H]^+$), 247 (41, $[M-C_4H_8+NH_4]^+$), 186 (28, $[M-Boc+H]^+$), 176 (6, $[M-I+NH_4]^+$), 119 (57).

N-*Alkylation of Sulfonamides* **13**: *General Procedure A* (*G.P.A*). A soln. of sulfonamide **13** (1 equiv.) in dry DMF (10 ml/mmol) was treated with Cs_2CO_3 (1.1 equiv., dried *in vacuo* prior to use) at r.t. for 0.5 h before a soln. of **18** (1.2 equiv.) in DMF (2 ml/mmol) was added dropwise. The pale yellow suspension was heated to 55°, vigorously stirred overnight, and evaporated. The crude product was taken up in AcOEt and washed with 5% aq. $Na_2S_2O_3$ soln. and H_2O. The combined aq. phases were twice extracted with AcOEt and the collected org. layers again washed with brine, dried ($MgSO_4$), and evaporated. The residual oil was subjected to CC for purification of the alkylation product **19.**

Boc Deprotection of **19**: *General Procedure B* (*G.P.B*). A soln. of *N*-Boc-protected **19** in $CHCl_3$ (10 ml/mmol) was treated with CF_3COOH (15 equiv.) at 40° overnight. The mixture was then alkalinized at r.t. with aq. 4N NaOH, and stirring was continued for 0.5 h to ensure that the CF_3COOH salt was quantitatively reconverted to the free amino ester. The aq. layer was twice extracted with CH_2Cl_2, the extract washed with sat. aq. NH_4Cl soln., dried ($MgSO_4$), and evaporated, and the residual oil purified by CC, characterized, and stored at −20° in dry benzene (10 ml/mmol), if not immediately used in the next step, since degradation by intermolecular transamidation reactions occurred rather quickly at r.t.

Sb(OEt)$_3$-Assisted Ring-Closing Reaction of **20**: *General Procedure C* (*G.P.C*). A dry flask fitted with an N_2 inlet and a pressure-equalized addition funnel (half-filled with 4-Å molecular sieves (beads) and functioning as *Soxhlet* extractor) surmounted by a reflux condenser was charged with the unbranched amino ester **20** and dry benzene (100 ml/mmol). Under N_2, the soln. was brought to reflux. After 2 h, refluxing was briefly interrupted, and a soln. of $Sb(OEt)_3$ (1.2 equiv.) in dry benzene (1 ml/mmol) was rapidly added. The mixture was stirred under reflux for 16 h, then cooled to r.t., and quenched with sat. aq. NH_4Cl soln. Stirring was continued for 15 min before the biphasic mixture was filtered over *Celite* to discard the inorganic salts. The clear aq. layer was then extracted 3× with AcOEt and the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated. The crude ring-closed product **21** was purified either by recrystallization or by CC.

Electrolytic Detosylation of the Ditosylated Bicyclic Compounds **23** *and* **25**: *General Procedure D* (*G.P.D*). A general method for the mild removal of Ts protection groups by electrolysis is described in [19]: the tosylated **23** or **25** was taken up in 0.1M $(Me_4N)Cl$ (1.1 g, 10 mmol) in 94% aq. EtOH soln. (100 ml) as catholyte and electrolyzed at 5° under Ar in a divided cell, at −2.25 V (*vs.* SCE); cathode: mercury pool; anode: graphite rod. After depletion of the electrolysis current to background level, the reaction was complete and the ethanolic catholyte was evaporated. The residual salts were diluted in a minimum quantity of H_2O, and the resulting aq. soln. was saturated with solid K_2CO_3 before being extracted with CH_2Cl_2 (3 × 30 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give the crude deprotected product **24** or **26**, resp.

Reductive Methylation of Didemethylhopromine **24** *and Didemethylhomaline* **26**: *General Procedure E* (*G.P.E*). To a soln. of the didemethyl compound **24** or **26** (1 equiv.) in AcOH (*ca.* 48 ml/mmol) at 0°, 37% aq. formaldehyde soln. (*ca.* 15 ml/mmol) was carefully added. Stirring was continued at 0° for 15 min before a soln. of $NaBH_3CN$ (19 equiv.) in MeOH (8 ml/mmol of didemethyl compound) was slowly added. After the addition, the cooling bath was removed and the mixture could slowly warm to r.t. over 3–4 h. Then the mixture was cooled to 0° again, quenched with 2N aq. HCl and evaporated. The residue was taken up in sat. aq. Na_2CO_3 soln., the aq. layer extracted with CH_2Cl_2, and the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated: **2** and **1**, resp.

*Ethyl 3-{{3-[[(*tert*-Butoxy)carbonyl]amino}-propyl}tosylamino}-3-phenylpropanoate* (**19a**). According to *G.P.A.*, with (±)-**13a** (1 g, 2.88 mmol) and **18** (1.23 g, 4.32 mmol, 1.5 equiv.). CC (AcOEt/hexane 1:3) yielded **19a** (1.16 g, 80%). Pale yellow oil. ^{1}H-NMR: 7.72 (*d*, *J* = 8.3, 2 H); 7.31–7.25 (*m*, 5 H); 7.15 (*m*, 2 H); 5.45 (*dd*, *J* = 10.6, 4.9, 1 H); 5.29 (br. *s*, 1 H); 4.02 (*q*, *J* = 7.1, 2 H); 3.11–2.95 (br. *m*, 5 H); 2.67 (*dd*, *J* = 15.5, 4.9, 1 H); 2.44 (*s*, 3 H); 1.45–1.40 (br. *m*, 2 H); 1.42 (*s*, 9 H); 1.12 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 169.9, 155.8, 143.3, 137.4, 137.2 (5 *s*); 129.6, 128.5, 128.2, 127.6, 127.1 (5 *d*); 78.9 (*s*); 60.6 (*t*); 57.0 (*d*); 42.2, 37.2 (br.), 36.8, 30.6 (4*t*); 28.3 (3 *q*); 21.4, 13.8 (2 *q*).

*Ethyl (–)-(3*R*)-3-[(3-{[(*tert*-Butoxy)carbonyl]amino}propyl)tosylamino]octanoate* (**19b**). According to *G.P.A*, with **13b** (570 mg, 1.67 mmol). CC (CH_2Cl_2/MeOH 40:1) (607 mg, 73%) yielded **19b**. Pale yellow oil $[\alpha]_D^{21} = -7.2$ (*c* = 1.0, $CHCl_3$). IR: 3450*w*, 3000*w*, 2980*m*, 2960*m*, 2930*m*, 2870*w*, 2860*w*, 1725*s*, 1710*s*, 1600*w*, 1505*m*, 1455(br.), 1390*w*, 1370*m*, 1340*m*, 1305*w*, 1270(br.), 1250*w*, 1160*s*, 1090*m*, 1025*w*, 975(br.), 910*w*, 860*w*, 815*m*, 705*w*, 695*w*, 685*w*, 655*m*, 615*w*. ^{1}H-NMR: 7.72 (*d*, *J* = 8.3. 2 H); 7.27 (*d*, *J* = 8.0, 2 H); 4.85 (br. *s*, 1 H); 4.10 (*m*, 3 H); 3.14 (*m*, 4 H); 2.41 (*s*, 3 H); 2.39 (*m*, 2 H); 1.80 (br. *m*, 2 H); 1.45 (*s*, 9 H); 1.43 (*m*, 2 H); 1.23 (*t*, *J* = 7.1, 3 H); 1.21–1.10 (*m*, 6 H); 0.81 (br. *t*, *J* = 6.7, 3 H). ^{13}C-NMR: 171.0, 156.1, 143.3, 137.7 (4 *s*); 129.6, 127.3 (2 *d*); 79.2 (*s*); 60.6 (*t*); 55.5 (*d*); 41.7, 39.4, 38.5 (br.), 33.4, 31.4, 31.2 (6 *t*); 28.3 (3 *q*); 25.9, 22.3 (2 *t*); 21.3, 14.0, 13.7 (3 *q*).

*Ethyl (–)-(3*R*)-3-[(3-{[(*tert*-Butoxy)carbonyl]amino)propyl)tosylamino]decanoate* (**19c**). According to *G.P.A*, with **13c** (750 mg, 2.03 mmol). CC (CH_2Cl_2/MeOH 40:1) gave **19c** (738 mg, 69%). Colorless oil. $[\alpha]_D^{21} = -11.6$ (*c* = 1.15, $CHCl_3$). IR: 3450*w*, 3000*w*, 2980*w*, 2960*m*, 2920*s*, 2870*w*, 2855*w*, 1730*s*, 1710*s*, 1600*w*, 1510*m*, 1505*m*, 1455(br.), 1390*w*, 1368*m*, 1340*m*, 1305*w*, 1275(br.), 1245*w*, 1160*s*, 1090*m*, 1030*w*, 1020*w*, 865(br.), 810*m*, 805*w*, 705*w*, 690*w*, 685*w*, 655*m*, 615*w*. ^{1}H-NMR: 7.71 (*d*, *J* = 8.3, 2 H); 7.27 (*d*, *J* = 7.9, 2 H); 4.82 (br. *s*, 1 H); 4.08 (*m*, 3 H); 3.14 (*m*, 4 H); 2.41 (*s*, 3 H); 2.37 (*m*, 2 H); 1.80 (br. *m*, 2 H); 1.45 (*s*, 9 H); 1.45–1.42 (br. *m*, 2 H); 1.23 (*t*, *J* = 7.1, 3 H); 1.21–1.10 (*m*, 10 H); 0.86 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR: 170.8, 155.9, 143.1, 137.6 (4 *s*); 129.5, 127.2 (2 *d*); 79.1 (*s*); 60.6 (*t*); 55.6 (*d*); 41.8, 39.4, 38.6 (br.), 33.4, 31.5, 31.4, 29.0, 28.9 (8 *t*); 28.3 (3 *q*); 26.3, 22.5 (2 *t*); 21.3, 14.0, 13.9 (3 *q*).

Ethyl 3-[(3-Aminopropyl)tosylamino]-3-phenylpropanoate (**20a**). According to *G.P.B*, with **19a** (221 mg, 0.44 mmol) CC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 80:20:1) yielded pure **20a** (175 mg, 99%). Colorless oil. ^{1}H-NMR: 7.72 (*d*, *J* = 8.3, 2 H); 7.30–7.25 (*m*, 5 H); 7.16 (*m*, 2 H); 5.45 (*dd*, *J* = 10.5, 4.9, 1 H); 4.02 (*q*, *J* = 7.1, 2 H); 3.15–2.06 (*m*, 3 H); 2.72 (*dd*, *J* = 15.6, 4.9, 1 H); 2.51 (br. *t*, *J* = 6.5, 2 H); 2.44 (*s*, 3 H); 1.54–1.46 (*m*, 1 H); 1.45–1.33 (*m*, 1 H); 1.39 (br. *s*, 2 H); 1.13 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 170.2, 143.4, 137.8, 137.5 (4 *s*); 129.7, 128.6, 128.2, 127.8, 127.3 (5 *d*); 60.8 (*t*); 57.1 (*d*); 42.7, 39.1, 37.2, 33.9 (4 *t*); 21.5, 14.0 (2 *q*).

*Ethyl (–)-(3*R*)-3-[(3-Aminopropyl)tosylamino]octanoate* (**20b**). According to *G.P.B*, with **19b** (585 mg, 1.17 mmol) CC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 100:20:1) gave pure **20b** (442 mg, 95%). Pale yellow oil. $[\alpha]_D^{21} = -14.8$ (*c* = 1.7, $CHCl_3$). IR: 3400*w*, 3300–3100*w*, 3030*w*, 2960*s*, 2930*s*, 2870*m*, 2860*m*, 1730*s*, 1710*s*, 1655*m*, 1600*w*, 1495*w*, 1465*m*, 1455*m*, 1445*w*, 1390*w*, 1370*m*, 1335*s*, 1305*m*, 1290*m*, 1250–1230*w*, 1175*w*, 1160*s*, 1150*s*, 1135*w*, 1090*m*, 1025*w*, 990–930*w*, 920–880*w*, 812*m*, 710*w*, 700*w*, 695*w*, 685*w*, 670*w*, 655*m*, 615*w*. ^{1}H-NMR: 7.73 (*d*, *J* = 8.3, 2 H); 7.27 (*d*, *J* = 7.9, 2 H); 4.06 (*m*, 3 H); 3.17 (*m*, 2 H); 2.78 (*t*, *J* = 6.6, 2 H); 2.40 (*s*, 3 H); 2.38 (*m*, 2 H); 2.22 (br. *s*, 2 H); 1.82 (*m*, 2 H); 1.43 (br. *m*, 2 H); 1.24 (*t*, *J* = 7.1, 3 H); 1.21–1.08 (*m*, 6 H); 0.81 (br. *t*, *J* = 6.7, 3 H). ^{13}C-NMR: 171.0, 143.2, 137.7 (3 *s*); 129.6, 127.3 (2 *d*); 60.7 (*t*); 55.7 (*d*); 42.1, 39.4, 39.1, 33.8, 33.4, 31.2, 26.0, 22.3 (8 *t*); 21.3, 14.0, 13.8 (3 *q*).

*Ethyl (–)-(3*R*)-3-[(3-Aminopropyl)tosylamino]decanoate* (**20c**). According to *G.P.B*, with **19c** (382 mg, 0.72 mmol). CC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 100:20:1) yielded **20c** (279 mg, 90%). Pale yellow oil. $[\alpha]_D^{21} = -16.8$ (*c* = 0.9, $CHCl_3$). IR: 3400*w*, 3300–3100*w*, 3020*w*, 2960*s*, 2930*s*, 2875*m*, 2855*m*, 1730*s*, 1710*s*, 1655*m*, 1595*w*, 1495*w*, 1475*w*, 1465*m*, 1455*m*, 1445*w*, 1395*w*, 1370*m*, 1340*s*, 1305*m*, 1290*m*, 1270–1230*w*, 1185*w*, 1160*s*, 1110(br.), 1090*m*, 1030*w*, 1015*w*, 970–930(br.), 880*w*, 810*m*, 710*m*, 685*w*, 680*w*, 655*w*, 650*m*, 615*w*. ^{1}H-NMR: 7.73 (*d*, *J* = 8.3, 2 H); 7.27 (*d*, *J* = 7.9, 2 H); 4.08 (*m*, 3 H); 3.17 (*m*, 2 H); 2.78 (*t*, *J* = 6.7, 2 H); 2.40 (*s*, 3 H); 2.38 (*m*, 2 H); 2.04 (br. *s*, 2 H); 1.83 (*m*, 2 H); 1.43 (br. *m*, 2 H); 1.23 (*t*, *J* = 7.1, 3 H); 1.23–1.08 (*m*, 10 H); 0.86 (br. *t*, *J* = 7.0, 3 H). ^{13}C-NMR: 170.9, 143.0, 137.7 (3 *s*); 129.4, 127.2 (2 *d*); 60.6 (*t*); 55.6 (*d*); 42.0, 39.4, 39.1, 34.0, 33.4, 31.6, 29.0, 28.9, 26.3, 22.5 (10 *t*); 21.3, 14.0, 13.9 (3 *q*).

*Hexahydro-4-phenyl-5-tosyl-1,5-diazocin-2(1*H*)-one* (**21a**). According to *G.P.C*, with **20a** (650 mg, 1.6 mmol). Recrystallization from CH_2Cl_2 gave **21a** (476 mg, 83%). Colorless solid. M.p. 198–199°. IR: 3600–3100*w*, 3400*w*, 3000*w*, 2960*w*, 2920*w*, 1665*s*, 1600*w*, 1495*w*, 1465*m*, 1450*m*, 1440*w*, 1400*w*, 1370*w*, 1337*m*, 1305*w*, 1290*w*, 1260*w*, 1175*m*, 1155*s*, 1130–1070*m*, 1035*w*, 970*m*, 930*w*, 860*w*, 830*w*, 815*w*, 700*m*, 650*m*, 620*m*. ^{1}H-NMR: 7.71 (*d*, *J* = 8.3, 2 H); 7.25 (*m*, 7 H); 5.70 (*dd*, *J* = 10.5, 4.8, 1 H); 5.60 (br. *t*, 1 H); 3.88 (*dm*, *J* = 16.1, 1 H); 3.35–3.29 (br. *m*, 2 H); 3.11 (*m*, 2 H); 2.90 (*dd*, *J* = 13.1, 4.9, 1 H); 2.41 (*s*, 3 H); 2.05–1.89 (br. *m*, 1 H); 1.54–1.43 (*m*, 1 H). ^{13}C-NMR: 173.7, 143.4, 137.7, 137.5 (4 *s*); 129.6, 128.6, 127.7, 127.6, 126.8 (5 *d*); 59.7 (*d*); 43.6,

41.9, 37.6, 31.1 (4 *t*); 21.5 (1 *q*). CI-MS: 377 (20), 376 (100, $[M+NH_4]^+$), 359 (10, $[M+H]^+$), 229 (8, $[M-C_9H_9NO+NH_4]^+$).

*(−)-(4*R*)-Hexahydro-4-pentyl-5-tosyl-1,5-diazocin-2(1*H*)-one* (**21b**). According to *G.P. C*, with **20b** (550 mg, 1.4 mmol). The crude colorless, amorphous solid **21b** (427 mg, 88%) was crystallized from $CHCl_3$. M.p. 172.5–174.0°. $[\alpha]_D^{21} = -63.0$ ($c = 1.0$, $CHCl_3$). IR: 3600–3100*w*, 3400*w*, 3030*w*, 3000*w*, 2960*m*, 2920*m*, 2870*w*, 2860*w*, 1690*w*, 1655*s*, 1600*w*, 1495*w*, 1465*m*, 1440*w*, 1395*w*, 1375*w*, 1335*m*, 1305*w*, 1195*w*, 1185*w*, 1160*s*, 1115*m*, 1090*m*, 1040*w*, 1017*w*, 950*w*, 925*w*, 900(br.), 835*w*, 812*w*, 705*w*, 695*w*, 690*m*, 685*w*, 650*m*, 620*m*. ^{1}H-NMR: 7.71 (*d*, $J = 8.3$, 2 H); 7.29 (*d*, $J = 8.0$, 2 H); 6.02 (br. *s*, 1 H); 4.12 (br. *m*, 1 H); 3.59 (*dd*, $J = 15.6$, 4.4, 1 H); 3.46 (*m*, 1 H); 3.27 (*m*, 1 H); 2.99–2.85 (*m*, 2 H); 2.47–2.41 (*m*, 1 H); 2.42 (*s*, 3 H); 2.19 (*m*, 1 H); 1.63–1.45 (br. *m*, 2 H); 1.24–0.88 (br. *m*, 7 H); 0.78 (*t*, $J = 6.8$, 3 H). ^{13}C-NMR: 173.8, 143.3, 137.7 (3 *s*); 129.5, 127.0, 55.7 (3 *d*) 40.0 (br.), 39.4 (br.), 38.8 (br.), 32.1, 31.2, 30.4 (br.), 25.8, 22.2 (8 *t*); 21.4, 13.7 (2 *q*). CI-MS: 370 (100, $[M+NH_4]^+$), 353 (19, $[M+H]^+$), 199 (12), 197 (10, $[M-C_7H_7SO_2]^+$). EI-MS: 281 (28, $[M-C_5H_{11}]^+$), 239 (76), 197 (17, $[M-C_7H_7SO_2]^+$), 155 (21, $C_7H_7SO_2$), 91 (100, $C_7H_7^+$). ESI-MS: 727 (28, $[2M+Na]^+$), 705 (98, $[2M+H]^+$), 353 (100, $[M+H]^+$).

*(−)-(4*R*)-4-Heptylhexahydro-5-tosyl-1,5-diazocin-2(1*H*)-one* (**21c**). According to **20c** *G.P. C*, with (279 mg, 0.65 mmol). CC (CH_2Cl_2/MeOH 30:1) gave **21c** (226 mg, 91%). Colorless oil. $[\alpha]_D^{21} = -54.0$ ($c = 1.0$, $CHCl_3$). IR: 3600–3100*w*, 3400*w*, 3030*w*, 3000*w*, 2960*m*, 2925*m*, 2855*w*, 1655*s*, 1600*w*, 1495*w*, 1465*m*, 1440*w*, 1400*w*, 1375*w*, 1338*m*, 1305*w*, 1160*s*, 1120(br.), 1090*m*, 1040*w*, 1017*w*, 925(br.), 840*w*, 815*w*, 695*m*, 685*w*, 650*m*, 620*m*. ^{1}H-NMR: 7.72 (*d*, $J = 8.3$, 2 H); 7.28 (*d*, $J = 8.0$, 2 H); 6.01 (br. *m*, 1 H); 4.13 (br. *m*, 1 H); 3.59 (*dd*, $J = 15.5$, 4.5, 1 H); 3.47 (*m*, 1 H); 3.22 (*m*, 1 H); 2.99–2.89 (*m*, 1 H); 2.87–2.79 (br. *m*, 1 H); 2.44–2.39 (*m*, 1 H); 2.41 (*s*, 3 H); 2.19 (br. *m*, 1 H); 1.61–1.47 (*m*, 2 H); 1.27–0.92 (br. *m*, 11 H); 0.86 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR: 173.6, 143.3, 137.7 (3 *s*); 129.5, 127.0, 55.6 (3 *d*); 39.9 (br.), 39.4 (br.), 38.9 (br.), 32.1, 31.5, 30.8 (br.), 29.0, 28.9, 26.2, 22.5 (10 *t*); 21.4, 13.9 (2 *q*). CI-MS: 399 (14), 398 (54, $[M+NH_4]^+$), 382 (21), 381 (100, $[M+H]^+$), 227 (14), 225 (13, $[M-C_7H_7SO_2]^+$).

*(−)-(4*R*)-1-(4-Bromobutyl)hexahydro-4-pentyl-5-tosyl-1,5-diazocin-2(1*H*)-one* (**22**). To a suspension of powdered KOH (24 mg, 0.43 mmol, 1.5 equiv.; dried *in vacuo* prior to use) in dry DMSO (1 ml) at r.t., a mixture of **21b** (100 mg, 0.28 mmol) and 1,4-dibromobutane (74 µl, 0.62 mmol, 2.2 equiv.) in dry DMSO (1.5 ml) was added dropwise. The resulting pale yellow suspension was vigorously stirred at r.t. overnight (no educt left). The mixture was quenched at 0° with sat. aq. NH_4Cl soln., washed with H_2O, and extracted with Et_2O (3 × 10 ml). The combined Et_2O layers were washed with brine, dried ($MgSO_4$), and evaporated. The residual crude oil was subjected to CC (CH_2Cl_2/MeOH 30:1): **22** (113 mg, 82%). Pale yellow oil. $[\alpha]_D^{21} = -34.5$ ($c = 2.3$, $CHCl_3$). IR: 3600–3100*w*, 2990*w*, 2955*m*, 2930*m*, 2860*w*, 1630*s*, 1600*w*, 1460*m*, 1430(br.), 1395*w*, 1380*w*, 1340*m*, 1305*w*, 1260–1200*w*, 1180*w*, 1155*s*, 1115*m*, 1090*m*, 1045*w*, 1020*w*, 1000–930*w*, 955*m*, 910*m*, 860*w*, 840*w*, 810*w*, 700–630*w*, 650*m*, 615*w*. ^{1}H-NMR (263 K)[2]: 7.70 (*d*, $J = 8.3$, 2 H); 7.28 (*d*, $J = 8.0$, 2 H); 4.02 (*m*, 1 H); 3.82–3.67 (*m*, 2 H); 3.49 (*m*, 1 H); 3.42 (*t*, $J = 6.4$, 2 H); 3.19 (*dm*, $J = 16$, 1 H); 3.3 (*dm*, $J = 13.7$, 1 H); 2.84 (*m*, 1 H); 2.72 (*tm*, $J = 13.7$, 1 H); 2.44 (*dd*, $J = 13.7$, 5.0, 1 H); 2.42 (*s*, 3 H); 2.13 (*m*, 1 H); 1.84–1.58 (*m*, 5 H); 1.43 (*m*, 1 H); 1.22–1.08 (br. *m*, 1 H); 1.07–0.94 (*m*, 4 H); 0.94–0.77 (*m*, 2 H); 0.72 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR (263 K): 170.7, 143.3, 137.0 (3 *s*); 129.5, 126.9, 55.5 (3 *d*); 44.7, 43.9, 40.3, 38.7, 33.2, 31.2, 29.8, 29.6, 29.4, 26.2, 25.8, 22.2 (12 *t*); 21.3, 13.7 (2 *q*). ESI-MS: 511 (67, $[M+Na+2]^+$), 509 (50, $[M+Na]^+$), 489 (92, $[M+H+2]^+$), 487 (82, $[M+H]^+$), 445 (31), 443 (52), 429 (58, $[M-HBr+Na]^+$), 407 (100, $[M-HBr+H]^+$).

The mass balance of the reaction was equilibrated by the isolation of a small quantity of the symmetric, bicyclic by-product *(−)-(4*R*,4′*R*)-1,1′-(butane-1,4-diyl)bis[hexahydro-4-pentyl-5-tosyl-1,5-diazocin-2(1*H*)-one]* (14 mg, 18%). $[\alpha]_D^{21} = -53.6$ ($c = 0.75$, $CHCl_3$).

*(−)-(4*R*)-4-Heptylhexahydro-1-[(4*R*)-octahydro-2-oxo-4-pentyl-5-tosyl-1,5-diazocin-1-yl]-5-tosyl-1,5-diazocin-2(1*H*)-one* (**23**). Powdered KOH (34 mg, 0.62 mmol, 2.0 equiv., dried *in vacuo* prior to use) was suspended in dry DMSO (1 ml) and stirred at r.t. for 15 min before the mixture was cooled to 0°. A soln. of **22** (120 mg, 0.29 mmol, 1.0 equiv.) and **21c** (117 mg, 0.31 mmol, 1.1 equiv.) in dry DMSO (2 ml) was slowly canulated under N_2 into the frozen suspension at 0°. The resulting frozen mixture was progressively thawed under vigorous stirring overnight, then quenched with H_2O, and extracted with Et_2O (3 × 10 ml). The combined Et_2O phase was washed with brine, dried ($MgSO_4$), and evaporated. Purification by CC (CH_2Cl_2/MeOH 30:1) afforded **23**

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[2]) The ^{1}H- and ^{13}C-NMR spectra of **22** recorded at r.t. were uninterpretable due to conformational isomerism of the molecule. Only the absence of δ(H) of the amide proton and the clearly detectable δ(H) and δ(C) of the CH_2Br group (3.42 (*t*, $J = 6.4$, 2 H) and 33.2 (*t*), resp.) indicated the incorporation of the bromobutyl chain. The fully reported data were obtained at 600 MHz and −10° in $CDCl_3$.

(160 mg, 71%). Colorless oil. $[\alpha]_D^{21} = -50.2$ ($c = 1.5$, $CHCl_3$). IR: 3600–3100*w*, 3030*w*, 3000*w*, 2960*m*, 2930*m*, 2870*w*, 2860*w*, 1630*s*, 1600*w*, 1490*w*, 1470*m*, 1465*m*, 1440(br.), 1395(br.), 1380*w*, 1335*m*, 1305*w*, 1290*w*, 1275–1230*w*, 1195*w*, 1185*w*, 1155*s*, 1115*m*, 1090*s*, 1045*m*, 1025*w*, 1015*w*, 990–940(br.), 875*w*, 835*w*, 812*m*, 705*w*, 695*m*, 690*w*, 650*m*, 640*w*, 615*w*. ^{1}H-NMR[3]): 7.70 (*d*, $J = 8.3$, 4 H); 7.28 (*d*, $J = 8.0$, 4 H); 4.08 (br. *m*, 2 H); 3.80–2.81 (br. *m*, 14 H); 2.47 (br. *m*, 2 H); 2.41 (*s*, 6 H); 2.11 (br. *m*, 2 H); 1.84–1.36 (br. *m*, 9 H); 1.28–-0.98 (br. *m*, 17 H); 0.86 (*t*, $J = 7.0$, 3 H); 0.78 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR (263 K): 170.7, 143.4, 137.0 (3 *s*); 129.7, 127.0 (2 *d*); 53.4 (br. *d*); 44.7–43.9 (br. *t*); 40.1–38.9 (br. *t*); 31.7, 31.4, 29.5, 29.2, 29.0, 26.4, 26.0, 25.1, 22.6, 22.4 (10 *t*); 21.5, 14.0, 13.8 (4 *q*). Nano ESI-MS: 809 (100, $[M + Na]^+$), 787 (79, $[M + H]^+$). Nano ESI-MS/MS (*m*/*z* 787.5): 787 (15, $[M + H]^+$), 663 (100), 635 (86), 616 (21), 435 (26), 407 (36), 283 (12).

*(+)-(4*R*)-4-Heptylhexahydro-[(4*R*)-octahydro-2-oxo-4-pentyl-1,5-diazocin-1-yl]-1,5-diazocin-2(1*H*)-one* (= *Didemethylhopromine*; **24**). According to *G.P. D*, with **23** (160 mg, 0.20 mmol): crude **24** (62 mg, 64%). Pale yellow oil, which was pure enough (by NMR and MS) to be used in the next step without further purification. $[\alpha]_D^{21} = +13.8$ ($c = 0.4$, $CHCl_3$). IR: 3600–3100*w*, 3000*w*, 2960*m*, 2930*s*, 2870*w*, 2860*m*, 2510–2400*w*, 1620*s*, 1490–1440*w*, 1430*w*, 1420*w*, 1375*w*, 1352*w*, 1335*w*, 1300(br.), 1280–1230*w*, 1215*m*, 1170*m*, 1120(br.), 1100–1060*w*, 1050*w*, 1000*w*, 990–930*w*, 710*m*, 660*w*, 640(br.), 615*w*. ^{1}H-NMR: 3.86 *td*, $J = 13.3$, 3.4, 2 H); 3.71 (*m*, 2 H); 3.23 (*dm*, $J = 14.8$, 2 H); 3.07 (*dm*, $J = 14.8$, 2 H); 2.97–2.85 (*m*, 4 H); 2.51 (*dd*, $J = 12.5$, 9.7, 2 H); 2.41–2.26 (*m*, 4 H); 1.99–1.80 (br. *s*, 2 H); 1.76–1.20 (*m*, 28 H); 0.87 (*m*, 6 H). ^{13}C-NMR: 173.5 (2 *s*); 59.6 (2 *d*); 45.2, 44.8, 43.6, 42.9, 37.1, 31.6, 31.2, 29.4, 29.1, 26.2, 25.8, 25.1, 22.5, 22.4 (14 *t*); 13.9, 13.8 (2 *q*). ESI-MS: 479 (48, $[M + H]^+$), 240 (100, $[(M + 2\,H)/2]^+$).

*(−)-(4*R*)-4-Heptylhexahydro-5-methyl-1-[(4*R*)-octahydro-2-oxo-4-pentyl-1,5-diazocin-1-yl]-1,5-diazocin-2(1*H*)-one* (= *Hopromine*; **2**). According to the *G. P. E*, with **24** (60 mg, 0.12 mmol). CC ($CHCl_3$/MeO/25% aq. NH_3 soln. 90:10:0.7) gave **2** (63 mg, 99%). Colorless oil. $[\alpha]_D^{21} = -14.4$ ($c = 2.1$, $CHCl_3$) (for natural hopromine, see [3]: $[\alpha]_D^{21} = -10$ ($c = 3$, $CHCl_3$) IR: 2810*w*, 2780*w*, 2520–2400*w*, 1725*w*, 1620*s*, 1465*m*, 1430*w*, 1420*w*, 1375*w*, 1360*w*, 1350*w*, 1320*w*, 1285–1190*w*, 1170*w*, 1120*w*, 1110*w*, 1070*w*, 1050*w*, 1020–930(br.), 910*m*, 860*w*, 835(br.), 660*w*, 605*w*. ^{1}H-NMR: 3.47–3.30 (*m*, 6 H); 3.20 (*m*, 2 H); 2.96–2.82 (*m*, 4 H); 2.56–2.44 (*m*, 6 H); 2.41 (*s*, 6 H); 1.88–1.68 (br. *m*, 2 H); 1.65–1.20 (*m*, 26 H); 0.88 (*m*, 6 H). ^{13}C-NMR: 173.5 (2 *s*); 63.2 (2 *d*); 47.5, 47.1 (br.); 45.4 (3 *t*); 39.6 (2 br. *q*); 38.4, 31.8, 31.7, 30.8 (br.), 29.5, 29.2, 28.6, 26.9, 26.5, 25.2, 22.5 (11 *t*);13.95, 13.90 (2 *q*). CI-MS: 507 ($[M + H]^+$).

*Diastereoisomer Mixture 1,1′-(Butane-1,4-diyl)bis[hexahydro-4-phenyl-5-tosyl-1,5-diazocin-2(1*H*)-one]* (**25**). Powdered KOH (69 mg, 1.23 mmol, 2.2 equiv.; dried *in vacuo* prior to use) was suspended in dry DMSO (1 ml) and stirred at r.t. for 15 min. Then the mixture was cooled to 0° and a soln. of 1,4-dibromobutane (36 µl, 0.31 mmol, 0.55 equiv.) and **21a** (200 mg, 0.56 mmol, 1.0 equiv.) in dry DMSO (1 ml) was added dropwise by syringe to the frozen suspension. The mixture was allowed to defreeze slowly overnight upon which it was diluted with Et_2O (10 ml) and quenched with sat. aq. NH_4Cl soln. (15 ml). After extraction of the aq. phase with Et_2O (3 × 10 ml), the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residual pale yellow solid was recrystallized from CH_2Cl_2: **25** (113 mg, 53%). Colorless solid. M.p. 243–245°. IR: 3600–3100*w*, 3000*w*, 2960*w*, 2920*w*, 2860*w*, 1635*s*, 1600*w*, 1495*w*, 1485*w*, 1470*m*, 1450*w*, 1425*w*, 1375*w*, 1335*m*, 1305*w*, 1260*w*, 1155*s*, 1130–1090*m*, 1045*w*, 965*m*, 835*w*, 810*w*, 700*m*, 650*m*, 620*m*. ^{1}H-NMR[4]): 7.65 (*m*, 4 H); 7.25–7.19 (*m*, 14 H); 5.66 (*m*, 2 H); 3.90 (*m*, 2 H); 3.52–2.70 (br. *m*, 14 H); 2.39 (*s*, 3 H); 2.38 (*s*, 3 H); 2.12–1.42 (br. *m*, 10 H). ^{13}C-NMR[4]): 170.4, 143.4, 137.7, 137.5 (4 *s*); 129.4, 128.4, 127.3, 127.0, 126.6 (5 *d*); 59.8 (*d*); 46.1, 44.2 (br.), 38.8, 29.1 (br.), 24.9 (5 *t*); 21.3 (2 *q*). ESI-MS: 809 (48, $[M + K]^+$), 793 (100, $[M + Na]^+$), 771 (71, $[M + H]^+$).

*Diastereoisomer Mixture 1,1′-(Butane-1,4-diyl)bis[hexahydro-4-phenyl-1,5-diazocin-2(1*H*)-one* (= *Didemethylhomaline*; **26**). According to *G.P. D*, with **25** (107 mg, 0.14 mmol). CC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 90:10:0.7) yielded **26** (49 mg, 76%). Colorless, amorphous solid. ^{1}H-NMR: 7.40–7.23 (*m*, 10 H); 4.20–4.07 (*m*, 2 H); 4.02 (*dd*, $J = 10.9$, 1.6, 2 H); 3.95–3.78 (*m*, 2 H); 3.26 (*dd*, $J = 14.9$, 2.8, 2 H); 3.15 (*dm*, $J = 14.8$, 2 H); 3.10–2.89 (*m*, 4 H); 2.49 (*dt*, $J = 12.7$, 2.0, 2 H); 2.38 (*ddd*, $J = 12.0$, 11.6, 3.5, 2 H); 1.86–1.55 (*m*, 10 H). ^{13}C-NMR: 172.9; 144.9 (2 *s*); 128.5, 127.4, 126.3 (3 *d*); 64.6 (*d*); 45.4, 45.0, 44.9, 44.7, 44.1, 31.5, 25.3, 25.2 (8 *t*). CI-MS: 464 (31), 463 (100, $[M + H]^+$).

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[3]) In the ^{1}H-NMR spectrum of **23**, no fine structures were detectable, except for the Ts groups and the terminal Me groups of the alkyl side chains. Identification of **23** was based on a nano ESI-MS analysis measured with *Bruker Esquire LC-00028*.

[4]) In the ^{1}H-NMR spectrum of **25**, no clear signals were observed, and in the ^{13}C-NMR spectrum not all the signals could be detected. Compound **25** was identified on the basis of its ESI-MS analysis.

*Diastereoisomer Mixture 1,1′-(Butane-1,4-diyl)bis[hexahydro-5-methyl-4-phenyl-1,5-diazocin-2(1*H*)-one* (= *Homaline*; **1**). According to *G.P. E*, with **26** (49 mg, 0.11 mmol). The crude solid was recrystallized from CH_2Cl_2: **1** (46 mg, 88%). Colorless solid. M.p. 195–196°. IR: 3600–3100*w*, 3080*w*, 3060*w*, 3020*w*, 2990*s*, 2930*s*, 2860*m*, 2800*w*, 2780*w*, 1620v*s*, 1485*s*, 1470*s*, 1450*s*, 1430*w*, 1420*m*, 1375*m*, 1350*m*, 1315*m*, 1260*m*, 1240*w*, 1195–1060*w*, 1030–965*w*, 925*w*, 860*w*, 700*s*, 660*m*, 630*w*, 615*w*. ^{1}H-NMR: 7.35–7.21 (*m*, 10 H); 4.00 (*dd*, *J* = 11.6, 3.1, 2 H); 3.93–3.70 (*m*, 4 H); 3.32 (*m*, 2 H); 3.25–3.05 (*m*, 4 H); 3.04–2.93 (*m*, 2 H); 2.60–2.45 (*m*, 4 H); 2.26 (*s*, 6 H); 1.90–1.74 (*m*, 2 H); 1.73–1.52 (*m*, 6 H). ^{13}C-NMR: 173.3, 142.0 (2 *s*); 128.2, 127.4, 127.0 (3 *d*); 67.9 (*d*); 50.9, 48.0, 47.9, 45.9, 45.7 (5 *t*); 43.6 (*d*); 41.2, 29.9, 29.8, 25.5, 25.4 (5 *t*). ESI-MS: 513 (10, $[M+Na]^+$), 492 (34), 491 (100, $[M+H]^+$). CI-MS: 492 (33), 491 (100, $[M+H]^+$).

X-Ray Crystal-Structure Determination of Compound **21b**[5]). The data collection and refinement parameters are summarized in the *Table*, and a view of the molecule is shown in *Fig. 2*. All measurements were made on a *Rigaku AFC5R* diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The intensities were collected by means of $\omega/2\theta$ scans and were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections, other than *Friedel* pairs, were merged. The structure was solved by direct methods with SIR92 [21], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom. Refinement of the structure was carried out on *F* with full-matrix least-squares procedures, which minimized the function $\Sigma\omega(|F_o|-|F_c|)^2$. A correction for secondary extinction was applied. Neutral-atom scattering factors for non-H-atoms were taken from [22], and the scattering factors for H-atoms from [23]. Anomalous dispersion effects were included in F_c [24]; the values for f' and f'' were those of [22b]. The values of the mass attenuation coefficients were those of [22c]. All calculations were performed with the teXsan crystallographic software package [25].

Table. *Crystallographic Data for Compound* **21b**

Crystallized from	$CHCl_3$	D_x [g cm^{-3}]	1.283
Empirical formula	$C_{18}H_{28}N_2O_3S$	μ(Mo$K\alpha$) [mm^{-1}]	0.196
M_r	352.49	$2\theta_{(max)}$ [°]	55
Crystal color, habit	colorless, tablet	Total reflections measured	4816
Crystal dimensions [mm]	0.20 × 0.45 × 0.45	Symmetry-independent reflections	4181
Temperature [K]	173 (1)	Reflections used ($I > 2\sigma(I)$)	3755
Crystal system	orthorhombic	Parameters refined	219
Space group	$P2_12_12_1$	Final R	0.0373
Z	4	wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0372
Reflections for cell determination	25	Goodness-of-fit s	1.652
2θ range for cell determination [°]	33–40	Secondary extinction coefficient	4.5 (5) · 10^{-7}
Unit cell parameters a [Å]	13.914 (2)	Final Δ_{max}/σ	0.0006
b [Å]	15.942 (1)	$\Delta\rho$ (max, min) [e Å^{-3}]	0.27; –0.33
c [Å]	8.228 (1)		
V [Å^3]	1825.0 (3)		

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5) Crystallographic data (excluding structure factors) for the structure of **21b** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-176204. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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