Enantioselective Entry to the *Homalium* Alkaloid Hoprominol: Synthesis of an (*R*,*R*,*R*)-Hoprominol Derivative

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The diastereoselective synthesis of the *N*- and *O*-protected hoprominol derivative (*R*,*R*,*R*)-**6** is described. The building up of the bicyclic *O*-silylated and di(*N*-tosylated) asymmetric scaffold **6** succeeded by convergent preparation of the two basic chiral azalactam units **7a** and **7b** and their subsequent iterative linking by a known method (*Scheme 5*). Both 4-alkyl-hexahydro-1,5-diazocin-2(1*H*)-ones **7a** and **7b** were prepared from the chiral *β*-amino acid portions **10a** and **10b**, respectively, by application of a set of reactions (*e.g.*, *N*-alkylation of **10a**,**b** and $Sb(OEt)_3$-assisted cyclization of the resulting open-chain intermediates) already known. In comparison with the total syntheses of homaline (**1**) and homoprine (**2**), the newness of the described synthesis lies in the asymmetric approach to the difunctionalized fatty acid derivative **10b** starting from (−)-(*S*)-malic acid (**9**) (*Schemes 3* and *4*). Key step in the preparation of **10b** was the diastereoselective amination of the optically pure *α*,*β*-unsaturated *δ*-hydroxy homoallylic ester **14** *via* conjugate intramolecular aza-*Michael* cyclization of the acylic *δ*-(carbamoyloxy) intermediate **11**.

Introduction. – Isolated from the leaves of the New Caledonian plant *Homalium pronyense* Guillaum. (Flacourtiaceae) [2], the four *Homalium* alkaloids homaline (**1**), hopromine (**2**), hoprominol (**3**), and hopromalinol (**4**) constitute a small family of optically active natural products characterized by a unique bis-eight-membered lactam structure incorporating a spermine (**5**) backbone (*Fig.*). The structures of the *Homalium* alkaloids were elucidated in the seventies by *Pais* and co-workers [3], and the correctness of the proposed formulae was confirmed by several total syntheses since then.

A single-crystal X-ray analysis [4] as well as manifold asymmetric syntheses [5][6] allowed the determination of the absolute (*S*,*S*)-configuration of the major alkaloid homaline (**1**). In a preceding paper [1], we presented a new, potent synthetic entry to the *Homalium* scaffold that enabled us to prepare (±)-homaline (**1**) and (−)-hopromine (**2**) and, hence, to determine the absolute configuration of the natural hopromine (**2**) as being (*R*,*R*). Since, hitherto, all the syntheses of the remaining, unsymmetrically substituted parent molecules hoprominol (**3**) and hopromalinol (**4**) are nonstereospecific [7], the absolute configurations of the alkaloids **3** and **4** are still unknown. Hereafter, we now wish to report the application of our previously described synthetic strategy for building up the bicyclic *Homalium* core by the preparation of the *N*- and *O*-protected (*R*,*R*,*R*)-hoprominol precursor **6** (*Fig.*), with the higher aim of elucidating the yet-undefined configuration of the natural product (−)-homprominol (**3**).

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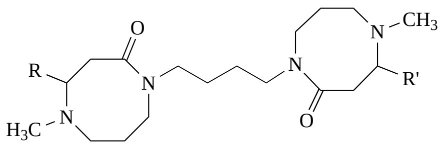
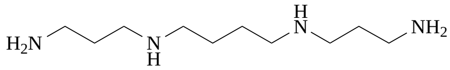
1) Part of the Ph.D. thesis of *C. E.*, University of Zürich, 2002.



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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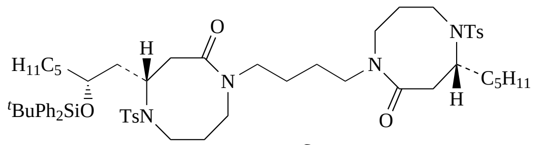

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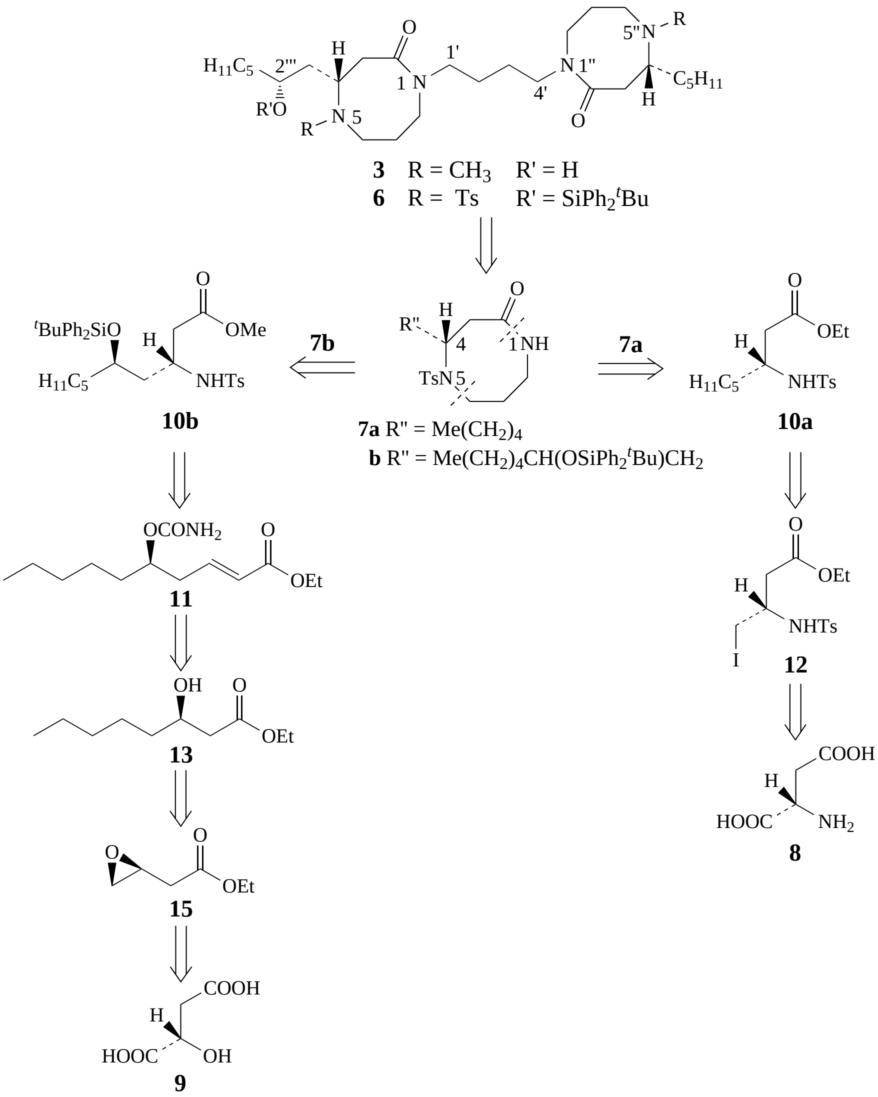
Figure. *The* Homalium *alkaloids* **1**–**4**, *their spermine backbone* **5**, *and the hoprominol derivative* **6**

One chiral structural unit of the bis-eight-membered structure, namely the *N*-tosylated, 4-pentyl-substituted hexahydro-1,5-diazocin-2(1*H*)-one **7a** (*Scheme 1*) could be efficiently prepared from (+)-L-aspartic acid (**8**) according to [1], whereas the second building block **7b**, carrying a supplementary OH group at the C_7 side chain, was synthesized starting from (−)-(*S*)-malic acid (**9**). The choice of **9** as chiral starting material for the construction of **10b** was motivated on the one hand by the supposition that all the members of the *Homalium* family share the same three-dimensional orientation of the residues at their corresponding stereogenic centers of the lactam rings (*i.e.*, (4*S*)-configuration for the phenyl-substituted lactams and (4*R*)-configuration for the alkyl-substituted ring systems). On the other hand, it resulted from the idea (*Scheme 2*) to introduce the chiral N-functional group in **10b** *via* the key step of an 1,3-*syn*-selective intramolecular conjugate aza-*Michael*-cyclization reaction of the optically pure α,β-unsaturated δ-(carbamoyloxy) ester **11**. This plan involved that, to be able to generate a (4*R*)-configured stereogenic center at the ring system **7b**, the later OH group at C(2) of the C_7-alkyl side chain had to have the absolute (*R*)-configuration. The set of reaction methods elaborated for the preparation of different 4-substituted hexahydro-1,5-diazocin-2(1*H*)-ones, and optimized earlier in the course of our homaline (**1**) and hopromine (**2**) syntheses, proved to remain valid for the preparation of the eight-membered lactam system **7b** from the doubly functionalized linear precursor **10b**.

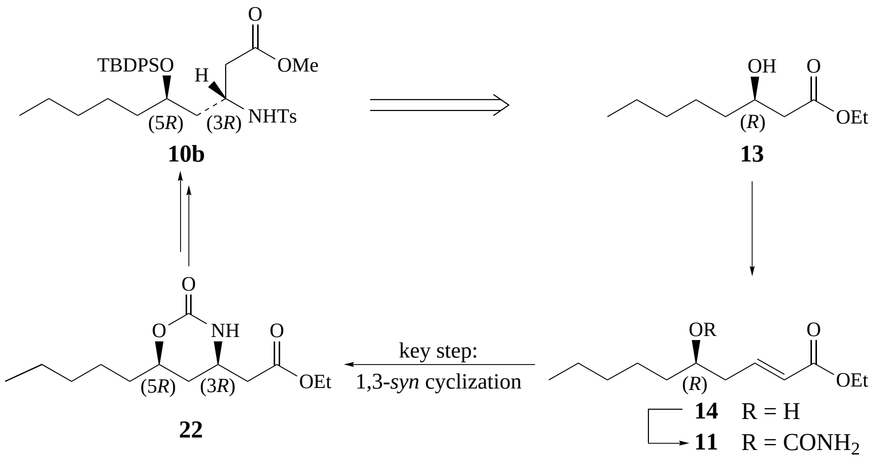
Results and Discussion. – Analogously to the retrosynthetic analysis of homaline (**1**) and hopromine (**2**), the parent hoprominol (**3**) might be fragmented into two 4-alkyl-substituted eight-membered lactam rings **7a** and **7b** bridged by a C_4 chain (*Scheme 1*). The azalactams **7a** and **7b**, then, can be decomposed into a nonchiral C_3-N

Scheme 1. *Retrosynthetic Analysis of Hoprominol* (**3**)



chain and two β-alkyl-β-amino acid portions **10a** and **10b**, respectively, as the asymmetric structural units. The β-amino fatty acid unit **10a**, on the one hand, was divided into a linear C_5-alkyl rest and the chiral iodoester **12**, easily obtainable from (+)-L-aspartic acid (**8**) by modification of the α-carboxylic acid group [8] through intramolecular condensation, regioselective $NaBH_4$ reduction [9], and EtOH/trimethylsilyl iodide-mediated lactone cleavage [10]. Based on **10a**, the corresponding enantiomerically pure *N*-tosylated 4-pentyl-substituted azalactam **7b** was prepared according to the procedures described in [1].

Scheme 2. *Plan for the Construction of the Difunctionalized Fatty Acid Derivative* **10b**



TBDPS = ${}^{t}BuPh_2Si$ = (*tert*-butyl)diphenylsilyl

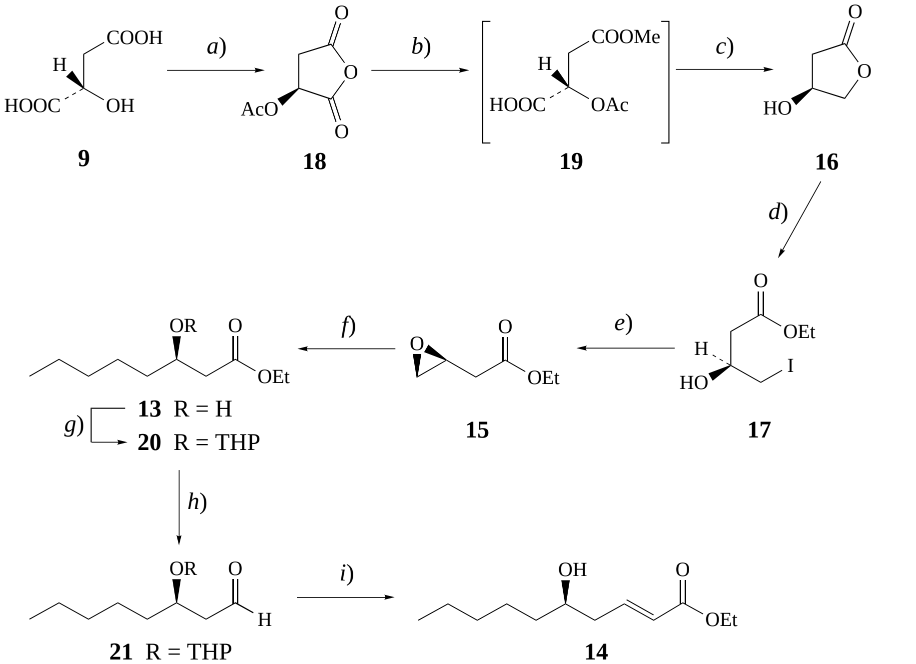
The doubly functionalized C_{10} moiety **10b**, in turn, was traced back in a first step to the chiral β-hydroxy ester **13** (*Scheme 2*), which, after a simple C_2 homologation to the corresponding α,β-unsaturated δ-hydroxy ester **14**, should serve as a basis for the diastereoselective introduction of the required amino function. The β-hydroxy ester **13** belongs to a class of valuable chiral precursors commonly prepared by the reaction of organocuprates with optically pure β,γ-epoxy esters, like **15** in our case. The synthesis of the first key intermediate **15** was planned to involve the chemoselective modification of a commercially available chiral-pool material, (−)-(*S*)-malic acid (**9**).

An efficient chemical method for the preparation of the chiral synthon **15** was elaborated by *Larchevêque* and *Henrot* [11b,c]: it is achieved (*Scheme 3*) by chemoselective ring opening of the β-hydroxybutyrolactone **16** (without any supplementary protection of the free OH function) with trimethylsilyl iodide [10b] in the presence of an excess of EtOH in CH_2Cl_2, followed by stereoselective cyclization of the resulting iodohydrin **17** with 1.2 equiv. of silver oxide at room temperature in dry MeCN. In our hands, the silver-mediated epoxidation of **17** gave the epoxybutanoate **15** in 82% chemical yield and *ca.* 93% optical purity (determined by comparison of the optical-rotation value of **15** with the data of the optically pure product given in [11c]).

The required lactone **16** was easily prepared in three steps from (−)-(*S*)-malic acid (**9**) according to [12] by quantitative acylation of the starting material in boiling acetyl chloride, methanolysis of the anhydride **18** to the intermediate half-ester **19**, and subsequent reduction with $NaBH_4$ in ${}^{t}BuOH/MeOH$ into a transitional dihydroxy acid that cyclized spontaneously to the desired lactone **16** under acidic conditions.

The prolongation of the C_4 chain present in the key element **15** to the C_8 backbone of **13** was accomplished by submitting the oxirane-acetate **15** to the action of a twofold

Scheme 3. *Synthesis of the β,γ-Unsaturated δ-Hydroxy Ester* **14** *from (−)-(*S*)-Malic Acid* (**9**)



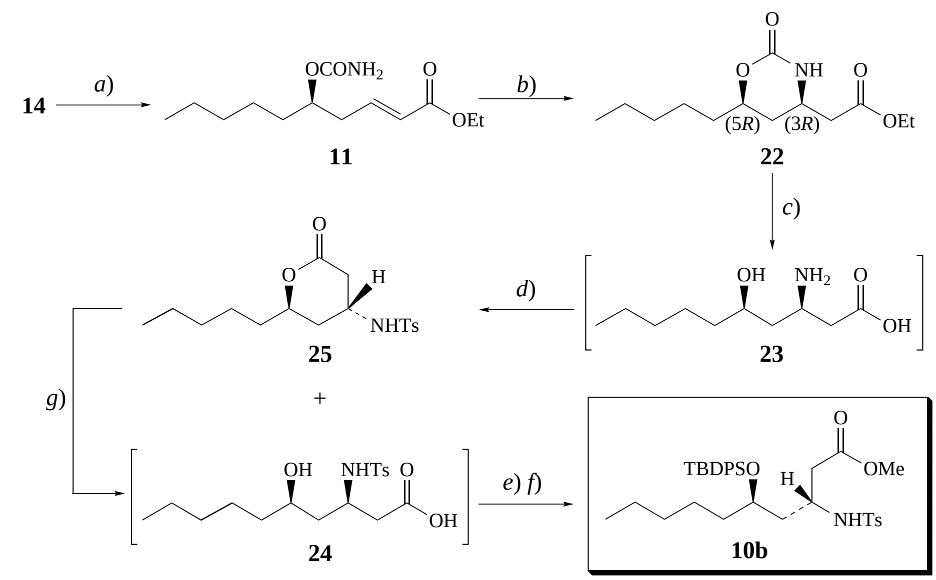
a) AcCl, reflux, 3 h; 99%. *b*) MeOH, r.t., overnight; quant. *c*) 1. $NaBH_4$, ^tBuOH/MeOH, reflux, 2 h; 2. AcCl, MeOH, 0° → r.t., 1 h; 76%. *d*) Me_3SiI, EtOH, CH_2Cl_2, 3 Å mol. sieves, r.t., overnight; 89%. *e*) Ag_2O, MeCN, r.t., 4 h; 81.5%. *f*) BuLi, CuBr · Me_2S, Et_2O/THF 1.5 : 1, −65° → −35°, 3.5 h; 61%. *g*) 3,4-dihydro-2*H*-pyran, TsOH · H_2O (1 mol-%), CH_2Cl_2, r.t., 3 h; 96%. *h*) 1. $LiAlH_4$, THF, r.t. → 55°, 2.5 h; 2. PDC, CH_2Cl_2, reflux, 4 h; 76%. *i*) 1. $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, MeCN, r.t., 1 h; 2. TsOH · H_2O (10 mol-%), MeOH, r.t., 1 h; 62%.

excess of the lithiocuprate Bu_2CuLi under anhydrous conditions in dry Et_2O/THF 1.5 : 1 between −65 and −35°. The necessary cuprate reagent was successfully generated *in situ* from commercially available BuLi and CuBr · Me_2S in Et_2O/THF at −65° in an analogous manner to that described in [1]. As expected from the previously reported results of *Larchevêque* and co-workers [11], the attack of the cuprate nucleophile occurred exclusively at the less-substituted C-atom of the oxirane ring of **15** to give the desired (*R*)-configured *β*-hydroxy ester **13** in 61% chemical yield and near enantiomeric purity (e.e. *ca.* 98%).

To obtain the final C-chain length of the doubly functionalized C_{10} moiety **10b**, the enantiomerically pure *β*-hydroxy ester **13** had to undergo a classical C_2 homologation. Since the attempted direct half-reduction of ester **13** with diisobutylaluminium hydride to the corresponding aldehyde was always accompanied by considerable amounts of over-reduction products, a complete reduction of the ester function to the primary alcohol followed by re-oxidation to the aldehyde was employed. Therefore, the OH group of **13** was first quantitatively THP-protected (THP = tetrahydro-2*H*-pyran-2-yl) by treatment with cat. TsOH · H_2O (Ts = tosyl = *p*-toluenesulfonyl) and dihydro-2*H*-pyran in CH_2Cl_2 at room temperature to give **20**, then the ester function was totally reduced with $LiAlH_4$ in dry THF under reflux, and, finally, the primary alcohol was oxidized with pyridinium dichromate (PDC) in boiling CH_2Cl_2, thus yielding the aldehyde **21** in 76% yield (from **20**). A very mild olefination procedure developed by *Roush*, *Masamune*, and co-workers [13], which involves a phosphonate in combination with chelating LiCl and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in dry MeCN, allowed a very rapid *Horner-Wadsworth-Emmons* transformation of aldehyde **21** into the corresponding THP-protected α,β-unsaturated δ-hydroxy ester, which was immediately deprotected with cat. $TsOH \cdot H_2O$ in MeOH to give the desired homoallylic δ-hydroxy ester **14** in 62% chemical yield.

For the planned diastereoselective amination of the (*E*)-olefinic C_{10} framework by intramolecular conjugate addition of a carbamate group (*Scheme 4*), the key intermediate **14** was transformed into the δ-(carbamoyloxy) ester **11** according to the standard procedure of *Graf* [14]: by treatment of the δ-hydroxy ester **14** with chlorosulfonyl isocyanate in CH_2Cl_2 for 1 h at $-78°$ and subsequent hydrolysis of the chlorosulfonyl group, the carbamoylation of the homoallylic group was achieved in 94% yield. In the next step, cooled 0.1M ^{t}BuOK in dry THF was added dropwise at 0° to 0.1M δ-(carbamoyloxy) ester **11** in THF, and the mixture was kept at 0° for 2.5 h. In accordance with the related studies made by *Hirama* and co-workers [15], the thermodynamically controlled, base-catalyzed aza-*Michael* cyclization of **11** to the 6-membered oxazinone system **22** succeeded with 80% chemical yield and remarkably

Scheme 4. *Preparation of* **10b** *by Conjugate aza-*Michael *Cyclization of the δ-(Carbamoyloxy) Ester* **11**, *Cleavage of the Oxazinone Ring, and Protection of the Functional Groups*



a) 1. $ClSO_2NCO$, CH_2Cl_2, $-78° \rightarrow -60°$, 1 h; 2.H_2O, r.t. $\rightarrow$ 60°, 4 h; 94%. *b*) ^{t}BuOK, THF, 0°, 2.5 h; 80%. *c*) 4N aq. NaOH, EtOH, 60°, overnight. *d*) 1. 0°, CO_2; 2. $NaHCO_3$, TsCl, acetone, r.t., 6 h. *e*) 1. ^{t}BuPh$_2$SiCl (TBDPS-Cl), 1*H*-imidazole, cat. DMAP, dry DMF, 55°, overnight; 2.H_2O, 60°, 2 h. *f*) CH_2N_2, Et_2O, r.t., 0.5 h; **10b**: 54%; **25**: *ca.* 25%. *g*) $NaHCO_3$, H_2O/acetone 1:1, r.t., overnight.

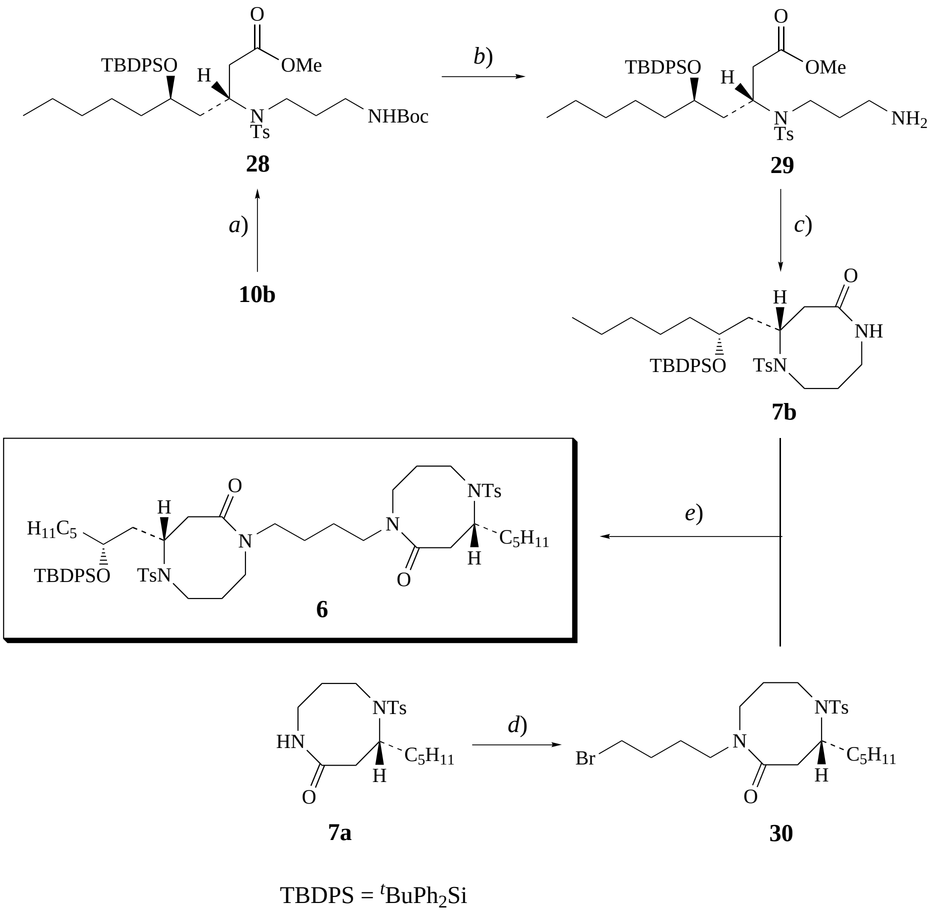
high 1,3-*syn* selectivity. The ^{1}H-NMR studies (300 MHz) of the purified product **22** showed a diastereoisomer ratio $>19:1$ in favor of the desired (3*R*,5*R*)-configured cyclic carbamate.

To preserve the ethyl ester function of **22**, the cleavage of the carbamate ring was first attempted under anhydrous biphasic conditions with carbonate (K_2CO_3, Na_2CO_3, Cs_2CO_3) and hydroxide (KOH, NaOH) bases in various dry organic solvents (THF, DMF, MeCN, and CH_2Cl_2), but this did not meet with success. Unlike the descriptions of *Ishizuka* and *Kunieda* [16], even the mild cleavage procedure *via N*-Boc activation of the carbamate ring did not produce the desired results. The only conditions capable of splitting the 1,3-oxazin-2-one into a free 1,3-amino alcohol required strong aqueous bases but were not compatible with the conservation of the ethyl ester function, so that the concomitant hydrolysis to the highly polar amino acid **23** could not be avoided. Thus, oxazinone **22** was first heated overnight at 60° with an excess of 4N aqueous NaOH in EtOH, then the mixture was saturated with dry-ice, followed by the addition of $NaHCO_3$ and a 4.5-fold excess of TsCl in acetone. After acidic workup, the crude reaction mixture (composed of the *N*-tosylated (3*R*,5*R*)-3-amino-5-hydroxydecanoic acid **24** and the chiral lactone **25**) was subjected to bis-silylation with 5.0 equiv. of both $^{t}BuPh_2SiCl$ (TBDPS-Cl) and 1*H*-imidazole and catalytic amounts of *N*,*N*-dimethylpyridin-4-amine (DMAP) in dry DMF at 55° overnight. Mild hydrolysis of the undesired silyl ester and subsequent treatment with diazomethane in Et_2O gave the final *N*-tosylated, *O*-silylated ester **10b** in 54% overall yield starting from **22**. Up to 25% of the starting material **22** were lost in the formation of the rather stable 6-membered lactone **25**, which was isolated together with the desired linear moiety **10b** at the end of the reaction sequence. With $NaHCO_3$ in aqueous acetone, it was possible to cleave the lactone ring without racemization and to recover a small quantity of the chiral (tosylamino)hydroxy acid **24** re-usable in a new reaction cycle.

With the chiral synthon **10b** in hands, we could apply the ring-construction strategy optimized in our synthesis of (*R*,*R*)-hopromine (**2**) [1] to build up the corresponding diastereoisomerically pure *N*-tosylated 4-substituted hexahydro-1,5-diazocin-2(1*H*)-one **7b**. The insertion of the missing C_3-N fragment (*Scheme 5*) was achieved by alkylating the TsNH group of **10b** with *tert*-butyl (3-iodopropyl)carbamate (**26**; readily available from 3-aminopropan-1-ol after Boc-protection to **27** followed by iodination with I_2, 1*H*-imidazole, and PPh_3 in CH_2Cl_2), after heterogeneous deprotonation by cesium carbonate in dry DMF at 55°. Subsequent removal of the Boc protection group from the resulting *N*-alkylated tosylamino ester **28** by means of a several-fold excess of CF_3COOH in toluene gave the linear ring precursor **29** in 93% yield. Fortunately, the presence of the bulky *O*-silyl protection group at the C_7 side chain of **29** did not have any negative influence on the directing metal effects of $Sb(OEt)_3$ in the following Sb-mediated cyclization: refluxing **29** with 1.2 equiv. of $Sb(OEt)_3$ under high-dilution conditions overnight in dry benzene yielded the eight-membered lactam **7b** in an excellent 95% yield. The exclusive formation of the monomeric azalactam system **7b** was confirmed by an ESI-MS analysis.

Together with **7a**, we had now at our disposal of the necessary chiral building blocks to assemble the bis-8-membered azalactam structure of hoprominol (**3**). The bridging of the two structural elements **7a** and **7b** by a C_4 chain was attempted iteratively [6] [17] (*Scheme 5*). In a first step, **7a** was mono-alkylated with 1,4-dibromobutane to the

Scheme 5. *Synthesis of the* N-*Tosylated 4-Substituted Hexahydro-1,5-diazocin-2(1*H*)-one* **7b** *and Attempted Iterative Coupling with* **7a** *to the Hoprominol Precursor* **6**



a) $I(CH_2)_3NHBoc$ (**26**; from $HO(CH_2)_3NHBoc$ (**27**)), Cs_2CO_3, DMF, r.t., overnight; 73%. *b*) CF_3COOH, toluene, 50°, overnight; 93%. *c*) $Sb(OEt)_3$, dry benzene, 3-Å mol. sieves, reflux, overnight; 95%. *d*) $Br(CH_2)_4Br$, powdered KOH, dry DMSO, 0° → r.t., overnight; 71%. *e*) 1. Powdered KOH, dry DMSO, 0° → r.t., 4 h; 2. cat. KOH, r.t., overnight; 8%.

bromo derivative **30** under the action of powdered KOH in dry DMSO at room temperature overnight. Several trials to subsequently attach **30** to **7b** analogously to our slightly modified KOH/DMSO-coupling method [1], *i.e.*, by adding a mixture of both compounds to a frozen suspension of 2.0 equiv. of KOH in dry DMSO at 0° and slowly defreezing the solid reaction mixture overnight, were only moderately successful: apart from mostly unreacted educts, the desired bis-eight-membered structure **6** was isolated in low yield. The identification of the coupling product **6** was achieved by IR- and ^1H-NMR spectroscopy (600 MHz) and through the fragmentation pattern obtained by an ESI-MS analysis.

We are, however, confident that, by changing the order of the iterative coupling sequence, *i.e.*, by first mono-alkylating the azalactam **7b** with a large excess of the cheap 1,4-dibromobutane and then attaching the second building block **7a** to the resulting bromo derivative, it is possible to achieve the assembly of the bicyclic scaffold in good yield, and to get sufficiently great amounts of the chiral *N*-tosylated, *O*-silylated hoprominol precursor **6** to successfully terminate the total synthesis of (*R*,*R*,*R*)-hoprominol (**3**) by a simple exchange of the protection groups.

Conclusions. – The diastereoisomerically pure (*R*,*R*,*R*)-compound **6**, an *N*-tosyl- and *O*-silyl-protected derivative of the naturally occurring spermine alkaloid (−)-hoprominol (**3**), was prepared by convergent synthesis from the two chiral 4-alkyl-substituted hexahydro-1,5-diazocin-2(1*H*)-ones **7a** and **7b**, respectively (see also [1]). The optical purity of the target compound **6** was assured by the use of the commercially available chiral-pool materials (+)-L-aspartic acid (**8**) and (−)-(*S*)-malic acid (**9**) as (*S*)-configured starting materials for the syntheses of the basic chiral β-amino fatty acid moieties **10a** and **10b**. The diastereoselective preparation of the difunctionalized C_{10} synthon **10b** from **9** *via* the key step of an intramolecular 1,3-*syn*-selective cyclocarbamation is described in detail. The build up of the corresponding eight-membered azalactam **7b**, based on the $Sb(OEt)_3$-assisted cyclization of the linear amino ester **29**, was successfully achieved by means of the ring-construction strategy optimized for the syntheses of (*R*,*R*)-hopromine (**2**), thus establishing the general applicability of the earlier developed set of reactions. With the synthesis of **7b**, we completed the list of the four basic chiral lactam systems into which the members of the *Homalium* family (*Fig.*) can be decomposed *retro*-synthetically. By coupling **7b** with the pentyl-substituted azalactam **7a** to the fully protected, bis-eight-membered product **6**, we were able to disclose an asymmetric entry to (*R*,*R*,*R*)-hoprominol (**3**), since the remaining steps of the total synthesis, *i.e.*, the electrolytic detosylation of the secondary amines, the deprotection of the OH function, and finally the reductive methylation of the free amino groups should be feasible without substantial problems.

We thank the analytical departments of our institute for all measurements and gratefully acknowledge the financial support of the *Swiss National Science Foundation*.

Experimental Part

General. See [1].

*(−)-(4*R*)-Hexahydro-4-pentyl-5-tosyl-1,5-diazocin-2(1*H*)-one* (**7a**). For the preparation of **7a** from (+)-L-aspartic acid (**8**), see [1].

*(−)-(3*S*)-3-(Acetyloxy)-3,4-dihydrofuran-2,5-dione* (**18**). (−)-(S)-Malic acid (**9**, 17.8 g, 0.13 mol) was treated according to [12]. After evaporation, the viscous residue was crystallized from CH_2Cl_2, washed with Et_2O (2×), and dried *in vacuo:* **18** (20.7 g, 99%). Small colorless plates. M.p. 54–56°. $[\alpha]_D^{21} = -25.9$ ($c = 5.0$, $CHCl_3$) ([12]): $[\alpha]_D^{21} = -26$ ($c = 5.11$, $CHCl_3$)). ^{1}H-NMR: 5.52 (*dd*, $J = 9.8, 5.8$, 1 H); 3.41 (*dd*, $J = 18.7, 9.6$, 1 H); 3.05 (*dd*, $J = 18.9, 5.8$, 1 H); 2.19 (*s*, 3 H). ^{13}C-NMR: 169.7, 167.9, 166.7 (3 *s*); 67.8 (*d*); 35.0 (*t*); 20.2 (*q*).

*(−)-(4*S*)-4,5-Dihydro-4-hydroxyfuran-2(3*H*)-one* (**16**). The soln. of **18** (20.7 g, 0.13 mol) in MeOH (40 ml) was stirred at r.t. overnight. Evaporation yielded the half-ester **19** as a pale yellow oil (24.9 g, 0.13 mol, quant.), which was immediately taken up in ^{t}BuOH/MeOH 5:1 (120 ml). This soln. was added dropwise over 1 h to a refluxing suspension of $NaBH_4$ (20.1 g, *ca.* 96% purity, 0.52 mol, 4.0 equiv.) in ^{t}BuOH (250 ml). Boiling was continued for additional 2 h, then the mixture was cooled to 0° and quenched by the slow addition of HCl/MeOH previously prepared by adding AcCl (48 ml) to MeOH (300 ml) at 0°. The acidic mixture was allowed to

warm to r.t. over 1 h and was then evaporated. The solid residue was taken up in AcOEt, the insoluble salts eliminated by filtration, and the org. filtrate neutralized by washing several times with sat. aq. Na_2CO_3 soln. Evaporation and purification of the oily residue by CC (AcOEt) gave **16**. Colorless oil (10.2 g, 76%). $[\alpha]_D^{21} = -81.6$ ($c = 1.95$, EtOH) ([12]: $[\alpha]_D^{21} = -81.0$ ($c = 1.97$, EtOH)). IR: 3640–3100*m*, 3600*w*, 3020*m*, 2960*w*, 2930*w*, 2900*w*, 1775*s*, 1465*w*, 1405*m*, 1370*m*, 1325*m*, 1300–1220*w*, 1240*m*, 1180*s*, 1170*s*, 1085*s*, 1050*s*, 1025*m*, 1000*s*, 970*m*, 890*w*, 865*w*, 840*w*, 685*w*, 615*w*. ^{1}H-NMR: 4.71–4.67 (*m*, 1 H); 4.42 (*dd*, *J* = 10.3, 4.5, 1 H); 4.29 (*dm*, *J* = 10.3, 1 H); 2.81 (br. *s*, 1 H); 2.75 (*dd*, *J* = 17.9, 6.0, 1 H); 2.52 (*dm*, *J* = 17.9, 1 H). ^{13}C-NMR: 176.2 (*s*); 75.9 (*t*); 67.4 (*d*); 37.7 (*t*). CI-MS: 120 ($[M + NH_4]^+$).

*Ethyl (–)-(3*S*)-3-Hydroxy-4-iodobutanoate* (**17**). To a soln. of **16** (5.26 g, 51.6 mmol) in abs. EtOH (9 ml, 0.15 mol, 3.0 equiv.) and activated molecular sieves (3 Å; 5 g) in dry CH_2Cl_2 (215 ml) at r.t., Me_3SiI (10.5 ml, 77.3 mmol, 1.5 equiv.) was slowly added within 45 min. After stirring for one night at r.t., the solvent was evaporated and the oily brown residue dissolved in Et_2O. The soln. was twice washed with 5% aq. $Na_2S_2O_3$ soln., dried ($MgSO_4$), and evaporated, the residual oil subjected to CC (AcOEt/hexane 1:3): **17** (11.9 g, 89%). Pale yellow oil. $[\alpha]_D^{21} = -9.9$ ($c = 3.1$, EtOH) ([11b]: $[\alpha]_D^{21} = -10.7$ ($c = 3.0$, EtOH)). IR: 3630–3200*w*, 3020*w*, 3000*m*, 2980*m*, 2940*w*, 2900*w*, 1725*s*, 1475*w*, 1465*w*, 1445*w*, 1405*m*, 1375*m*, 1350-1230*m*, 1180*s*, 1170*s*, 1125*m*, 1095*m*, 1075*m*, 1035*m*, 1020*m*, 980*w*, 950*w*, 885*w*, 860*w*, 840*w*, 640*w*, 620*w*. ^{1}H-NMR: 4.19 (*q*, *J* = 7.1, 2 H); 4.04–3.96 (*m*, 1 H); 3.38–3.26 (*m*, 2 H); 3.15 (br. *s*, 1 H); 2.67 (*dd*, *J* = 16.5, 4.4, 1 H); 2.59 (*dd*, *J* = 16.5, 7.8, 1 H); 1.28 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 171.6 (*s*); 67.4 (*d*); 60.9, 40.6 (2 *t*); 14.0 (*q*); 11.8 (*t*). CI-MS: 276 (100, $[M + NH_4]^+$), 259 (10, $[M + H]^+$), 241 (17, $[M - H_2O + H]^+$), 148 (16, $[M - HI + NH_4]^+$).

*Ethyl (–)-(2*S*)-Oxirane-2-acetate* (**15**). A soln. of **17** (4.48 g, 17.4 mmol) in dry MeCN (10 ml) was added dropwise to a suspension of Ag_2O (4.83 g, 20.8 mmol, 1.2 equiv.) in MeCN (40 ml). After stirring for 4 h at r.t., the solvent was evaporated, the residue taken up in AcOEt, the mixture filtered over *Celite*®, and the filtrate washed with 5% aq. $Na_2S_2O_3$ soln (2 ×). The collected aq. layers were extracted with AcOEt (3 ×) and the combined org. layers washed with brine, dried ($MgSO_4$), and evaporated. The residue was subjected to CC (AcOEt/hexane 1:3): **15** (1.84 g, 81.5%). Colorless oil. $[\alpha]_D^{21} = -23.5$ ($c = 3.8$, MeOH, e.e. *ca.* 93%) ([11b]: $[\alpha]_D^{21} = -25.3$ ($c = 3.7$, MeOH)). IR: 3620–3200*w*, 3530*w*, 3025*w*, 3015*m*, 3000*s*, 2980*s*, 2930*m*, 2910*w*, 2880*w*, 1730*s*, 1480*w*, 1465*w*, 1445*w*, 1420*w*, 1410*m*, 1370*m*, 1325*m*, 1300*m*, 1265*s*, 1240*w*, 1180*s*, 1165*m*, 1130*m*, 1095*m*, 1075*w*, 1050*w*, 1025*s*, 1020*m*, 980*m*, 955*w*, 940*w*, 905*w*, 870*w*, 840*m*, 615*w*. ^{1}H-NMR: 4.18 (*q*, *J* = 7.1, 2 H); 3.32–3.26 (*m*, 1 H); 2.82 (*dd*, *J* = 4.9, 4.0, 1 H); 2.57–2.54 (*m*, 3 H); 1.28 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 170.1 (*s*); 60.5 (*t*); 47.7 (*d*); 46.3, 37.8 (2 *t*); 13.9 (*q*). EI-MS: 85 (100, $[M - C_2H_5O]^+$), 72 (66, $[M - C_3H_6O]^+$), 57 (15, $[M - C_3H_5O_2]^+$).

*Ethyl (–)-(3*R*)-3-Hydroxyoctanoate* (**13**). At $-65°$, 1.6M BuLi in hexane (19.5 ml, 31.1 mmol, 2.2 equiv.) was added slowly to a suspension of CuBr · Me_2S (3.20 g, 15.6 mmol, 1.1 equiv.) in dry Et_2O/THF 5:3 (80 ml). The dark brown suspension was stirred at $-65° \rightarrow -40°$ for *ca.* 25 min until all the Cu^I salts were dissolved. Then the homogeneous mixture was recooled to $-65°$ before a soln. of **15** (1.84 g, 14.2 mmol, 1.0 equiv.) in dry Et_2O/THF 1:1 (40 ml) was added dropwise over 30 min. The mixture was stirred for 3.5 h at a temp. below $-35°$ and subsequently poured on sat. aq. NH_4Cl/25% aq. NH_3 soln. 1:1 (120 ml). The biphasic mixture was vigorously stirred for 30 min at r.t. until a clear colorless org. phase was obtained. The deep blue aq. phase was extracted with Et_2O (3 ×) and the combined org. layer washed with brine, dried ($MgSO_4$), and evaporated. Purification of the oily residue (2.12 g) by distillation under vacuum gave **13** (1.62 g, 61%). Colorless oil. B.p. 89–94°/9 mbar. $[\alpha]_D^{21} = -2.45$ ($c = 2.0$, MeOH, e.e. *ca.* 98%) ([11b]: $[\alpha]_D^{21} = -2.5$ ($c = 1.9$, MeOH, e.e. > 99%)). IR: 3640–3200*w*, 3020*w*, 3000*m*, 2980*m*, 2960*s*, 2930*s*, 2870*m*, 2860*m*, 1720*s*, 1660*w*, 1480*w*, 1465*w*, 1455*w*, 1445*w*, 1405*w*, 1375*m*, 1325*w*, 1305*m*, 1280*m*, 1240*w*, 1180*s*, 1170*m*, 1130–1060*w*, 1095*m*, 1040*w*, 1025*m*, 955*w*, 940*w*, 615*w*. ^{1}H-NMR: 4.17 (*q*, *J* = 7.1, 2 H); 4.21–3.97 (*m*, 1 H); 2.90 (br. *s*, 1 H); 2.50 (*dd*, *J* = 16.4, 3.3, 1 H); 2.45 (*dd*, *J* = 16.4, 8.8, 1 H); 1.57–1.24 (*m*, 8 H); 1.27 (*t*, *J* = 7.1, 3 H); 0.89 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR: 172.9 (*s*); 67.9 (*d*); 60.5, 41.2, 36.4, 31.6, 25.0, 22.4 (6 *t*); 14.0, 13.9 (2 *q*). CI-MS: 206 (100, $[M + NH_4]^+$), 189 (11, $[M + H]^+$), 171 (7, $[M - H_2O + H]^+$).

*Diastereoisomer Mixture Ethyl (3*R*)-3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]octanoate* (**20**). To a mixture of TsOH · H_2O (13.4 mg, 0.07 mmol, 1 mol-%) and **13** (1.32 g, 7.03 mmol) in CH_2Cl_2 (13 ml) was added dropwise over 15 min a soln. of 3,4-dihydro-2*H*-pyran (0.83 ml, 9.14 mmol, 1.3 equiv.) in CH_2Cl_2 (15 ml). After stirring the pale blue mixture for 3 h at r.t., the solvent was evaporated and the oily residue purified by CC (AcOEt/hexane 1:4): **20** (1.83 g, 96%). Colorless oil. IR: 3620–3100*w*, 3000*m*, 2950*m*, 2940*s*, 2860*m*, 1725*s*, 1660*w*, 1480*w*, 1465*m*, 1455*m*, 1440*m*, 1400*w*, 1375*m*, 1350*w*, 1340*w*, 1320*w*, 1300*m*, 1285*m*, 1275*m*, 1260*m*, 1240*w*, 1195*w*, 1185*m*, 1175*m*, 1160*m*, 1140–1095*m*, 1075*m*, 1035*m*, 1025*s*, 990*m*, 945*w*, 905*w*, 870*w*, 810*w*, 705*w*, 660*w*, 615*w*. ^{1}H-NMR: 4.71–4.66 (*m*, 2 H); 4.14 (*q*, *J* = 7.1, 2 H); 4.13 (*q*, *J* = 7.1, 2 H); 4.04 (*quint.*-like *m*, 2 H); 3.93–3.82 (*m*, 2 H); 3.55–3.42 (*m*, 2 H); 2.67 (*dd*, *J* = 15.0, 6.9, 1 H); 2.54–2.40 (*m*, 3 H); 1.87–1.20 (*m*, 28 H); 1.26

(*t*, $J = 7.1$, 3 H); 1.25 (*t*, $J = 7.1$, 3 H); 0.89 (*t*, $J = 6.7$, 6 H); ratio of diastereoisomers *ca.* 1:3. ^{13}C-NMR: 171.7, 170.9 (2 *s*); 98.3 (br., 2 *d*); 74.3, 74.1 (2 *d*); 62.6, 62.4 (2 *t*); 60.2 (br.), 41.0, 39.7, 35.5, 34.0, 31.7, 30.9, 25.3, 24.9, 24.6, 22.4, 19.7, 19.6 (13 *t*); 14.0 (2 *q*); 13.9 (2 *q*).

*Diastereoisomer Mixture (3*R*)-3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]octanal* (**21**). A soln. of **20** (1.72 g, 6.32 mmol) in dry THF (40 ml) was added dropwise over 20 min to a suspension of $LiAlH_4$ (371 mg, *ca.* 97% purity, 9.48 mmol, 1.5 equiv.) in dry THF (50 ml) at r.t. The mixture was then warmed to 55° and stirred for 2.5 h before it was cooled to 0° and carefully poured onto an ice-cold sat. aq. K,Na-tartrate soln. (70 ml). The resulting biphasic mixture was vigorously stirred until a neat phase separation was obtained. The aq. layer was extracted with Et_2O (3 ×) and the combined org. layer washed with sat. aq. NH_4Cl soln., dried ($MgSO_4$), and evaporated. The colorless residue was taken up in CH_2Cl_2 (40 ml) and added rapidly at r.t. to a suspension of PDC (4.75 g, 12.6 mmol, 2.0 equiv.) in CH_2Cl_2 (60 ml). After stirring for 4 h under reflux, the mixture was evaporated and the residue filtered over *Celite*® to discard the insoluble metal salts. Evaporation of the org. filtrate and purification of the oily residue by CC (AcOEt/hexane 1:4) gave **21** (1.10 g, 76%). Colorless oil. IR: 3620–2400*w*, 3000*m*, 2940*s*, 2860*m*, 1720*s*, 1465*w*, 1455*m*, 1440*m*, 1410*w*, 1380*m*, 1355*m*, 1345*w*, 1325*w*, 1300*m*, 1285*m*, 1275*m*, 1260*m*, 1240*w*, 1195*w*, 1185*m*, 1175*m*, 1160*m*, 1140–1110*m*, 1075*s*, 1055*w*, 1035*m*, 1025*s*, 990*m*, 945*w*, 905*w*, 870*w*, 810*w*, 705*w*, 660*w*, 615*w*. ^{1}H-NMR: 9.82–9.79 (*m*, 2 H); 4.71–4.68 (*m*, 1 H); 4.67–4.64 (*m*, 1 H); 4.14 (*quint.*-like *m*, 2 H); 3.95–3.79 (*m*, 2 H); 3.54–3.42 (*m*, 2 H); 2.73–2.44 (*m*, 3 H); 2.05 (*m*, 1 H); 1.87–1.22 (*m*, 28 H); 0.89 (*t*, $J = 6.8$, 6 H). ^{13}C-NMR: 202.0, 201.5 (2 *s*); 98.7, 97.7 (2 *d*); 72.9, 72.2 (2 *d*); 62.9, 62.7 (2 *t*); 49.2, 48.0, 35.6, 34.5, 31.6, 30.9, 25.3, 25.0, 24.7, 22.4, 19.9, 19.6 (12 *t*); 13.8 (2 *q*).

*Ethyl (–)-(2*E*,5*R*)-5-Hydroxydec-2-enoate* (**14**). Ethyl(diethoxyphosphinyl)acetate (1.16 ml, 5.78 mmol, 1.2 equiv.) and DBU (0.72 ml, 4.82 mmol, 1.0 equiv.) were subsequently dissolved in a suspension of LiCl (245 mg, 5.78 mmol, 1.2 equiv.; dried *in vacuo* prior to use) in dry MeCN (60 ml). The pale yellow mixture was stirred at r.t. for 10 min before a soln. of **21** (1.10 g, 4.82 mmol) in dry MeCN (40 ml) was added dropwise. After stirring for *ca.* 1 h at r.t., the end of the reaction was signaled by the formation of a white precipitate. The solvent was evaporated, the residue taken up in Et_2O, and the soln. washed first with H_2O followed by sat. aq. NH_4Cl soln. The collected aq. washing phases were extracted with AcOEt (3 ×) and the combined org. layers dried ($MgSO_4$) and evaporated. The pale yellow oily residue (THP-protected ester) was dissolved in MeOH (20 ml) and treated with TsOH · H_2O (91.7 mg, 0.48 mmol, 10 mol-%) for 1 h at r.t. After this, the deprotection was completed, the solvent evaporated, and the residue purified by CC (AcOEt/hexane 1:4): **14** (637 mg, 62%). Colorless oil. $[\alpha]_D^{21} = -4.9$ ($c = 0.95$, MeOH), $[\alpha]_D^{21} = -4.3$ ($c = 0.95$, $CHCl_3$). IR: 3640–3100*w*, 3610*w*, 3000*w*, 2960*s*, 2930*s*, 2875*m*, 2860*m*, 1710*s*, 1655*m*, 1480*w*, 1465*w*, 1445*w*, 1395*w*, 1370*m*, 1320*m*, 1280*m*, 1260*w*, 1175*w*, 1160*m*, 1140-1080*m*, 1040*m*, 985*w*, 615*w*. ^{1}H-NMR: 6.98 (*td*, $J = 15.6$, 7.5, 1 H); 5.90 (*dt*, $J = 15.6$, 1.5, 1 H); 4.18 (*q*, $J = 7.1$, 2 H); 3.78–3.71 (*m*, 1 H); 2.50–2.26 (*m*, 2 H); 1.71 (br. *s*, 1 H); 1.53–1.37 (*m*, 2 H); 1.36–1.25 (*m*, 6 H); 1.29 (*t*, $J = 7.1$, 3 H); 0.89 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR: 166.2 (*s*); 145.1, 123.8 (2 *d*); 70.5 (*d*); 60.2, 40.1, 37.0, 31.6, 25.1, 22.5 (6 *t*); 14.1, 13.9 (2 *q*). CI-MS: 232 ([$M + NH_4$]$^+$).

*Ethyl (+)-(2*E*,5*R*)-5-(Carbamoyloxy)dec-2-enoate* (**11**). To a soln. of **14** (630 mg, 2.94 mmol) in dry CH_2Cl_2 (25 ml) at –78° was added dropwise by syringe a soln. of chlorosulfonyl isocyanate (0.42 ml, *ca.* 97% purity, 4.71 mmol, 1.6 equiv.) in CH_2Cl_2 (5 ml). After stirring for 1 h at –78° → –60°, the mixture was quenched in the cold with H_2O (20 ml) and warmed to r.t. within 10 min. The biphasic mixture was heated to 60° and vigorously stirred for 4 h to remove CH_2Cl_2 and to hydrolyze the chlorosulfonyl group. The aq. soln. was saturated at r.t. with NaCl and extracted with AcOEt. The combined org. layers were washed with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. Purification of the oily residue by CC (AcOEt/hexane 1:2) gave **11** (711 mg, 94%). Colorless amorphous solid. M.p. 35.0–36.5°. $[\alpha]_D^{21} = +24.8$ ($c = 0.95$, $CHCl_3$). IR: 3550*m*, 3500*w*, 3430*m*, 3350*w*, 3260*w*, 3180*w*, 3020*w*, 3000*m*, 2980*m*, 2960*s*, 2930*s*, 2870*m*, 2860*m*, 1710*vs*, 1655*m*, 1585*m*, 1480*w*, 1465*w*, 1445*w*, 1435*w*, 1385*s*, 1370*s*, 1325*s*, 1275*s*, 1240*w*, 1175*s*, 1140–1090*m*, 1045*s*, 980*w*, 865*w*, 835*w*, 615*w*. ^{1}H-NMR: 6.91 (*td*, $J = 15.6$, 7.4, 1 H); 5.87 (*dt*, $J = 15.6$, 1.4, 1 H); 4.83 (*quint.*-like *m*, 1 H); 4.72 (br. *s*, 2 H); 4.19 (*q*, $J = 7.1$, 2 H); 2.47 (*oct.*-like *m*, 2 H); 1.59–1.50 (*m*, 2 H); 1.36–1.23 (*m*, 6 H); 1.29 (*t*, $J = 7.1$, 3 H); 0.88 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR: 166.1, 156.4 (2 *s*); 143.7, 123.9 (2 *d*); 73.2 (*d*); 60.2, 36.7, 33.6, 31.4, 24.8, 22.4 (6 *t*); 14.1, 13.8 (2 *q*). CI-MS: 275 (100, [$M + NH_4$]$^+$), 258 (7, [$M + H$]$^+$).

*Ethyl (–)-(4*R*,6*R*)-3,4,5,6-Tetrahydro-2-oxo-6-pentyl-2*H*-1,3-oxazine-4-acetate* (**22**). To a soln. of **11** (200 mg, 0.78 mmol) in dry THF (7.8 ml) at 0° was added slowly precooled 0.1M ^{t}BuOK in dry THF (1.56 ml, 0.16 mmol, 0.2 equiv.). The pale yellow mixture was stirred for 2.5 h at 0° and quenched in the cold with sat. aq. NH_4Cl soln. The aq. layer was extracted with AcOEt (3 ×), the combined org. phase dried ($MgSO_4$), and evaporated, and the residue purified by CC (AcOEt/hexane 1:1): **22** (160 mg, 80%). Colorless crystalline solid. M.p. 88.0–91.5°. $[\alpha]_D^{21} = -10.9$ ($c = 1.0$, $CHCl_3$). IR: 3620–3100*w*, 3420*m*, 3020*w*, 3000*w*, 2960*m*, 2930*m*, 2870*w*, 2860*w*, 1730*s*, 1700*s*, 1465*w*, 1450*m*, 1430*w*, 1410*w*, 1380*w*, 1350*w*, 1325*w*, 1300*w*, 1275*w*, 1260*w*, 1240*w*, 1180*m*, 1160–1130*w*, 1100*m*, 1075*w*, 1025*w*, 995*w*, 900*w*, 865*w*, 615*w*. ^{1}H-NMR: 5.88 (br. *s*, 1 H); 4.28–4.20 (*m*, 1 H); 4.17 (*q*, *J* = 7.1, 2 H); 3.91–3.82 (*m*, 1 H); 2.56 (*dd*, *J* = 16.6, 4.6, 1 H); 2.45 (*dd*, *J* = 16.5, 8.7, 1 H); 2.02 (*ddm*, *J* = 13.6, 4.7, 1 H); 1.76–1.63 (*m*, 1 H); 1.61–1.28 (*m*, 8 H); 1.27 (*t*, *J* = 7.1, 3 H); 0.89 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR: 170.5, 154.1 (2 *s*); 76.5 (*d*); 61.0 (*t*); 47.2 br. (*s*); 40.5, 34.8, 33.1, 31.4, 24.2, 22.3 (6 *t*); 14.1, 13.9 (2 *q*). CI-MS: 275 (11, $[M+NH_4]^+$), 258 (100, $[M+H]^+$).

*Methyl (+)-(3*R*,5*R*)-5-{[(*tert*-Butyl)diphenylsilyl]oxy}-3-(tosylamino)decanoate* (**10b**). A soln. of **22** (185 mg, 0.72 mmol) and 4N aq. NaOH (2.5 ml) in EtOH (7.5 ml) was stirred overnight at 60°. The mixture was then cooled to 0°, and small pieces of solid CO_2 were added until the precipitation of Na_2CO_3 ceased. After the suspension had warmed to r.t., $NaHCO_3$ (332 mg, 3.96 mmol, 5.5 equiv.) was added, stirring was continued for 15 min, and finally a soln. of TsCl (617 mg, 3.24 mmol, 4.5 equiv.) in acetone (5 ml) was added dropwise. After stirring for 6 h at r.t., the mixture was acidified at 0° to pH 2 by careful addition of conc. aq. HCl soln. The aq. layer was extracted with CH_2Cl_2 (2 × 15 ml) and AcOEt (2 × 15 ml) and the combined org. phase dried ($MgSO_4$) and evaporated. The oily residue (composed of (5-hydroxy-3-(tosylamino)decanoic acid **24** and the chiral lactone **25**), 1*H*-imidazole (245 mg, 3.60 mmol, 5.0 equiv.), and DMAP (17 mg, 0.14 mmol, 0.2 equiv.) were dissolved in dry DMF (7 ml), and the resulting mixture was warmed to 55° before a soln. of ^{t}BuPh$_2$SiCl (0.92 ml, 3.60 mmol, 5.0 equiv.) in DMF (1 ml) was added dropwise. After one night at 55°, H_2O (10 ml) was added, and the biphasic mixture was stirred for 2 h at 60° to hydrolyze the undesired silyl ester function. The mixture was then diluted with Et_2O, the aq. layer extracted with Et_2O (3 ×) and the combined org. layer washed with a sat. aq. NH_4Cl soln., dried ($MgSO_4$), and evaporated. The oily residue was again taken up in Et_2O (10 ml) and esterified at r.t. by dropwise addition of *ca.* 0.3M CH_2N_2 in Et_2O. Stirring was continued for 30 min at r.t., the reaction quenched with AcOH, and the org. soln. washed with a sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. Purification of the residue by CC (AcOEt/hexane 1 : 3 → 1 : 0) gave **10b** (237 mg, 54%). Colorless oil. $[\alpha]_D^{21} = +12.1$ (*c* = 1.5, $CHCl_3$). IR: 3600–3100*w*, 3350*w*, 3070*w*, 3010*w*, 2960*s*, 2930*s*, 2870*w*, 2860*m*, 1730*s*, 1600*w*, 1590*w*, 1490*w*, 1460*m*, 1440*w*, 1430*s*, 1415*w*, 1390*w*, 1375*m*, 1360*w*, 1340*m*, 1305*w*, 1290*w*, 1195*m*, 1175*m*, 1160*s*, 1110*s*, 1105*s*, 1095*s*, 1075*m*, 1050*w*, 1005*w*, 995*w*, 955*w*, 890*w*, 865*w*, 820*w*, 810*m*, 700*w*, 695*w*, 660*m*, 615*w*. ^{1}H-NMR: 7.69–7.59 (*m*, 6 H); 7.46–7.31 (*m*, 6 H); 7.21 (*d*, *J* = 8.0, 2 H); 4.62 (*d*, *J* = 9.0, 1 H); 3.54 (*s*, 3 H); 3.49–3.45 (*m*, 2 H); 2.40 (*s*, 3 H); 2.33–2.30 (*m*, 2 H); 1.59–1.52 (*m*, 2 H); 1.22–1.05 (*m*, 4 H); 1.03–0.95 (*m*, 4 H); 1.01 (*s*, 9 H); 0.79 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 171.5, 143.1, 137.6 (3 *s*); 135.8, 135.7 (2 *d*); 132.7 (*s*); 129.7, 129.4, 127.6, 127.5, 127.0 (5 *d*); 70.2 (*d*); 52.1 (*q*); 47.5 (*d*); 41.0, 38.6, 35.8, 31.5 (4 *t*); 26.9 (*q*); 24.1, 22.4 (2 *t*); 21.3 (*q*); 19.1 (*s*); 13.8 (*q*). ESI-MS: 632 ($[M+Na]^+$).

*Methyl (3*R*,5*R*)-3-{{{3-[(*tert*-Butoxy)carbonyl]amino}propyl}tosyl}amino-5-{[(*tert*-butyl)diphenylsilyl]oxy}decanoate* (**28**). A soln. of **10b** (95 mg, 0.16 mmol) in dry DMF (2.5 ml) was treated with Cs_2CO_3 (56 mg, 0.17 mmol, 1.1 equiv.; dried *in vacuo* prior to use) at r.t. for 0.5 h before the solid iodide **26** (67 mg, 0.23 mmol, 1.5 equiv.) was added in one portion. The pale yellow suspension was vigorously stirred at r.t. overnight and then evaporated. The residue was taken up in AcOEt and washed with 5% aq. $Na_2S_2O_3$ soln. and H_2O. The collected aq. washing phases were extracted with AcOEt (2 ×) and the combined org. layers re-washed with brine, dried ($MgSO_4$), and evaporated. The residual oil was purified by CC (AcOEt/hexane 1 : 3 → 1 : 1): pure **28** (87 mg, 73%). Colorless oil. IR: 3600–3100*w*, 3450*w*, 3010*w*, 3000*m*, 2980*m*, 2960*s*, 2930*s*, 2880*w*, 2860*m*, 1725*s*, 1710s, 1600*w*, 1505*m*, 1470*w*, 1460*w*, 1430*w*, 1390*w*, 1365*m*, 1340*w*, 1315*w*, 1305*w*, 1270*m*, 1250*m*, 1180*m*, 1175*m*, 1160*s*, 1110*s*, 1090*m*, 1075*m*, 1050–920*w*, 865*w*, 820*w*, 700*m*, 695*w*, 660*w*, 615*w*. ^{1}H-NMR: 7.68–7.61 (*m*, 6 H); 7.44–7.34 (*m*, 6 H); 7.21 (*d*, *J* = 8.1, 2 H); 4.63 (br. *s*, 1 H); 4.19 (*quint.*-like *m*, 1 H); 3.59 (*s*, 3 H); 3.51 (*quint.*-like *m*, 1 H); 3.01–2.90 (*m*, 4 H); 2.48 (*dd*, *J* = 15.6, 7.9, 1 H); 2.40 (*s*, 3 H); 2.30 (*dd*, *J* = 15.6, 6.7, 1 H); 1.71–1.54 (*m*, 5 H); 1.45 (*s*, 9 H); 1.27–1.0 (*m*, 7 H); 1.04 (*s*, 9 H); 0.81 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 171.2, 155.9, 143.1, 137.5 (4 *s*); 135.8 (*d*); 134.1, 133.8 (2 *s*); 129.6, 129.5, 129.4, 127.5, 127.4, 127.3 (6 *d*); 78.9 (*s*); 70.2, 52.8 (2 *d*); 51.5 (*q*); 42.4, 39.7, 38.4, 37.5, 35.7, 31.6, 30.6 (7 *t*); 28.3, 26.9 (2 *q*); 23.6, 22.4 (2 *t*); 21.3 (*q*); 19.2 (*s*); 13.8 (*q*). ESI-MS: 789 ($[M+Na]^+$).

*Methyl (−)-(3*R*,5*R*)-3-{[(3-Aminopropyl)tosyl]amino}-5-{[(*tert*-butyl)diphenylsilyl]oxy}decanoate* (**29**). A soln. of **28** (87 mg, 0.11 mmol) and CF_3COOH (0.17 ml, 2.27 mmol, 20.0 equiv.) in toluene (5 ml) was heated to 50° and stirred overnight. The mixture was then diluted with CH_2Cl_2 and alkalinized at r.t. by dropwise addition of 4N aq. NaOH. After stirring the biphasic mixture for 30 min, the aq. layer was extracted with CH_2Cl_2 (3 ×), the combined org. layer washed with brine, dried ($MgSO_4$), and evaporated, and the crude product purified by CC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 90 : 10 : 0.7): **29** (70 mg, 93%). Colorless oil. $[\alpha]_D^{21} = -7.0$ (*c* = 1.2, $CHCl_3$). ^{1}H-NMR: 7.68–7.61 (*m*, 6 H); 7.44–7.33 (*m*, 6 H); 7.19 (*d*, *J* = 8.0, 2 H); 4.17 (*quint.*-like *m*, 1 H); 3.60 (*s*, 3 H); 3.57 (*quint.*-like *m*, 1 H); 3.10–2.88 (*m*, 2 H); 2.54 (*t*, *J* = 6.7, 2 H); 2.49 (*dd*, *J* = 15.6, 7.4, 1 H); 2.39 (*s*, 3 H); 2.33 (*dd*, *J* = 15.6, 6.8, 1 H); 1.79–1.48 (*m*, 7 H); 1.26–0.98 (*m*, 7 H); 1.04 (*s*, 9 H); 0.81 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 171.5, 142.9, 137.8 (3 *s*); 135.8 (*d*); 134.1, 133.8 (2 *s*); 129.6, 129.4, 127.5, 127.4 (4 *d*); 70.2, 52.7 (2 *d*);

51.5 (*q*); 43.0, 39.7, 39.2, 38.6, 35.7, 33.9, 31.6 (7 *t*); 26.9 (*q*); 23.6, 22.4 (2 *t*); 21.5 (*q*); 19.2 (*s*); 13.8 (*q*). ESI-MS: 689 ([*M* + Na]$^+$).

*(−)-(4*R*)-4-{[(*tert*-Butyl)diphenylsilyl]oxy}heptyl}hexahydro-5-tosyl-1,5-diazocin(1*H*)-2-one* (**7b**). In a dry flask (N_2 inlet and pressure-equalized addition funnel (half-filled with 4-Å molecular sieves (beads) and functioning as *Soxhlet* extractor) surmounted by a reflux condenser)), a soln. of **29** (70 mg, 0.11 mmol) in dry benzene (25 ml) under N_2 was brought to reflux. After 2 h, refluxing was briefly interrupted, and $Sb(OEt)_3$ (21.4 µl, 0.13 mmol, 1.2 equiv.) was rapidly added. The mixture was refluxed overnight, 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 with AcOEt (3 ×), the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated, and the residue purified by CC (CH_2Cl_2/MeOH 19:1): **7b** (64 mg, 95%). Pale yellow oil. $[\alpha]^{21}_D = -50.9$ ($c = 1.5$, $CHCl_3$). IR: 3600–3100*w*, 3400*w*, 3050*w*, 2990*w*, 2960*s*, 2930*s*, 2860*m*, 1720*w*, 1680*w*, 1660*s*, 1640*m*, 1600*w*, 1465*m*, 1425*w*, 1390*w*, 1370*w*, 1335*m*, 1305*w*, 1290*w*, 1260*w*, 1200-1000*w*, 1175*m*, 1160*s*, 1110*s*, 1090*m*, 1075*m*, 990*w*, 940*w*, 910*w*, 875*w*, 830*w*, 810*w*, 700*w*, 660*w*, 615*w*. ^{1}H-NMR[2]): 7.72 (*d*, *J* = 8.4, 2 H); 7.70–7.65 (*m*, 4 H); 7.44–7.35 (*m*, 6 H); 7.24 (*d*, *J* = 8.3, 2 H); 5.74 (*q*-like *m*, 1 H); 4.59 (*sext.*-like *m*, 1 H); 3.83–3.74 (*m*, 1 H); 3.54–3.10 (*m*, 3 H); 2.88–2.58 (*m*, 2 H); 2.42 (*s*, 3 H); 2.27–2.05 (*m*, 2 H); 1.79–1.57 (*m*, 2 H); 1.50–0.82 (*m*, 9 H); 1.09 (*s*, 9 H); 0.76 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 173.5, 143.2, 137.4 (3 *s*); 135.9 (*d*); 134.5, 133.8 (2 *s*); 129.6, 129.5, 127.6, 127.4, 127.3 (5 *d*); 70.3, 52.5 (2 *d*); 39.7 (br.), 37.9, 36.9, 32.2, 31.5, 29.6 (6 *t*); 27.0 (*q*); 23.7, 22.3 (2 *t*); 21.4 (*q*); 19.3 (*s*); 13.8 (*q*). ESI-MS: 657 ([*M* + Na]$^+$).

*(4*R*)-4-{(2*R*)-2-{[(*tert*-Butyl)diphenylsilyl]oxy}heptyl}hexahydro-1-{4-[(4*R*)-octahydro-2-oxo-4-pentyl-5-tosyl-1,5-diazocin-1-yl]butyl}-5-tosyl-1,5-diazocin-2(1*H*)-one* (**6**). A suspension of powdered KOH (6 mg, 0.11 mmol, 2.0 equiv.) in dry DMSO (1 ml) was stirred for 10 min at r.t. and then cooled to 0°. (−)-(4*R*)-1-(4-Bromobutyl)hexahydro-4-pentyl-5-tosyl-1,5-diazocin-2(1*H*)-one (**30**; 24 mg, 49.3 µmol, 1.0 equiv.) [1] and **7b** (30 mg, 47.3 µmol, 0.96 equiv.) were dissolved in dry DMSO (1 ml) and canulated slowly at 0° under N_2 into the frozen KOH suspension. The mixture was warmed to r.t. under vigorous stirring within 4 h before a supplementary (cat.) amount of powdered KOH was added. After stirring for one night at r.t., H_2O was added, the aq. phase extracted with Et_2O (3 × 5 ml) and the combined org. layer washed with brine, dried ($MgSO_4$), and evaporated. Separation by CC (CH_2Cl_2/MeOH 40:1 → 15:1) permitted partial recycling of the unreacted educts **30** and **7b** and the isolation of **6** (4 mg). IR: 3660*w*, 3600–3100*w*, 3000*m*, 2960*s*, 2930*s*, 2860*m*, 1625*s*, 1600*m*, 1465*m*, 1450*w*, 1430*m*, 1400*w*, 1380*w*, 1335*s*, 1305*m*, 1290*w*, 1260*w*, 1240*w*, 1185*w*, 1160*s*, 1110*m*, 1090*s*, 1075*m*, 1015*w*, 990–930*w*, 895*w*, 860*w*, 830*w*, 815*m*, 700*m*, 690*m*, 650*w*, 615*w*, 605*w*. ^{1}H-NMR (280 K)[3]): 7.77–7.70 (*m*, 8 H); 7.45–7.34 (*m*, 6 H); 7.31–7.24 (*m*, 4 H); 4.03 (br. *s*, 1 H); 3.83–3.70 (*m*, 3 H); 3.68–3.61 (*m*, 2 H); 3.52 (*t*-like *m*, 1 H); 3.34–3.12 (*m*, 2 H); 3.11–2.92 (*m*, 2 H); 2.82 (br. *s*, 1 H); 2.76–2.66 (*m*, 1 H); 2.60 (*d*-like *m*, 1 H); 2.47–2.37 (*m*, 2 H); 2.41 (*s*, 6 H); 2.23–2.08 (*m*, 2 H); 1.79–1.60 (*m*, 7 H); 1.59–1.40 (*m*, 4 H); 1.30–1.13 (*m*, 8 H); 1.09–0.92 (*m*, 8 H); 1.07 (*s*, 9 H); 0.87 (*t*, *J* = 7.1, 3 H); 0.75 (*t*, *J* = 6.8, 3 H). ESI-MS: 825 (54, [*M* − ^{t}BuSiPh$_2$ + Na]$^+$), 803 (100, [*M* − ^{t}BuSiPh$_2$ + H]$^+$).

tert-Butyl (3-Hydroxypropyl)carbamate (**27**). 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., heating and thickening of the mixture was observed. The resulting colorless mixture was stirred under reflux overnight and quenched with a sat. aq. NH_4Cl soln. The aq. layer was extracted with CH_2Cl_2 (2 ×) and the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated: crude **27** (6.9 g, 99%). Colorless oil, 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* = 12.5, 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*).

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[2]) In the ^{1}H-NMR spectrum of **7b** recorded at r.t., no fine structures were detectable except for the *O*-silyl- and *N*-tosyl protection groups and the terminal Me group of the alkyl side chain. This explains why, in the description of the spectrum, the protons are mostly gathered in groups over larger ppm ranges.

[3]) Similarly to the ^{1}H-NMR spectrum of **7b**, the only fine signals detectable in the 300-MHz ^{1}H-NMR spectrum of **6** at r.t. were those of the *O*-silyl- and the *N*-tosyl protection groups and of the terminal Me groups of the two side chains at both ring systems. A better refinement of the spectrum was obtained with a long-term measurement at +7° with a *Bruker DRX-600*. This, together with the ESI-MS analysis, allowed the unambiguous identification of **6**.

tert-*Butyl (3-Iodopropyl)carbamate* (**26**). 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 dark yellow suspension was warmed to r.t. before a soln. of **27** (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 with 5% aq. $Na_2S_2O_3$ soln (2 ×). The combined washing phases were extracted with CH_2Cl_2 and the org. layers dried ($MgSO_4$) and evaporated. The residual yellow oil was subjected to CC (AcOEt/hexane 1:1): **26** (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).

REFERENCES

[1] C. Ensch, M. Hesse, *Helv. Chim. Acta* **2002**, *85*, 1659.
[2] A. Guillaumin, 'Flore de la Nouvelle Calédonie', Paris, 1948.
[3] M. Pais, G. Ratle, R. Sarfati, F.-X. Jarreau, *C. R. Acad. Sci., Sér. C* **1968**, *266*, 37; M. Pais, R. Sarfati, F.-X. Jarreau, R. Goutarel, *C. R. Acad. Sci., Sér. C* **1971**, *272*, 1728; M. Pais, R. Sarfati, F.-X. Jarreau, R. Goutarel, *Tetrahedron* **1973**, *29*, 1001; M. Pais, R. Sarfati, F.-X. Jarreau, *Bull. Soc. Chim. Fr.* **1973**, 331; M. Pais, G. Ratle, R. Sarfati, F.-X. Jarreau, *C. R. Acad. Sci., Sér. C* **1968**, *267*, 82.
[4] O. Lefebvre-Soubeyran, *Acta Crystallogr., Sect. B* **1976**, *32*, 1305.
[5] H. H. Wasserman, G. D. Berger, K. R. Cho, *Tetrahedron Lett.* **1982**, *23*, 465; H. H. Wasserman, G. D. Berger, *Tetrahedron* **1983**, *39*, 2459; N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata, M. Iyoda, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3121.
[6] L. Crombie, R. C. F. Jones, A. R. Mat-Zin, S. Osborne, *J. Chem. Soc., Chem. Commun.* **1983**, 960; L. Crombie, D. Haigh, R. C. F. Jones, A. R. Mat-Zin, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2047.
[7] L. Crombie, R. C. F. Jones, D. Haigh, *Tetrahedron Lett.* **1986**, *27*, 5147; L. Crombie, D. Haigh, R. C. F. Jones, A. R. Mat-Zin, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2055.
[8] C. W. Jefford, J. McNulty, Z.-H. Lu, J. B. Wang, *Helv. Chim. Acta* **1996**, *79*, 1203; C. W. Jefford, J. B. Wang, *Tetrahedron Lett.* **1993**, *34*, 1111; A. E. Marini, M. L. Roumestant, P. Viallefont, D. Razafindramboa, M. Bonato, M. Follet, *Synthesis* **1992**, *11*, 1104.
[9] G. J. McGarvey, J. M. Williams, R. N. Hiner, Y. Matsubara, T. Oh, *J. Am. Chem. Soc.* **1986**, *108*, 4943; G. J. McGarvey, R. N. Hiner, Y. Matsubara, T. Oh, *Tetrahedron Lett.* **1983**, *24*, 2733.
[10] a) M. Kolb, J. Barth, *Synth. Commun.* **1981**, *11*, 763; b) G. A. Olah, S. C. Narang, B. G. B. Gupta, R. Malhotra, *J. Org. Chem.* **1979**, *44*, 1247.
[11] a) M. Larchevêque, Y. Petit, *Tetrahedron Lett.* **1987**, *28*, 1993; b) M. Larchevêque, S. Henrot, *Tetrahedron* **1990**, *46*, 4277; c) M. Larchevêque, S. Henrot, *Tetrahedron Lett.* **1987**, *28*, 1781.
[12] S. Henrot, M. Larchevêque, Y. Petit, *Synth. Commun.* **1986**, *16*, 183.
[13] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183.
[14] R. Graf, *Angew. Chem.* **1968**, *5*, 179.
[15] M. Hirama, S. Ito, *Heterocycles* **1989**, *28*, 1229; M. Hirama, T. Shigemoto, Y. Yamazaki, S. Ito, *J. Am. Chem. Soc.* **1985**, *107*, 1797; M. Hirama, T. Iwakuma, S. Ito, *J. Chem. Soc., Chem. Commun.* **1987**, 1523.
[16] T. Ishizuka, T. Kunieda, *Tetrahedron Lett.* **1987**, *28*, 4185.
[17] R. A. Johnstone, M. E. Rose, *Tetrahedron* **1979**, *35*, 2169.

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