Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9239–9247

TETRAHEDRON

Total synthesis of the marine alkaloid halitulin

Markus R. Heinrich,[a] Wolfgang Steglich,[a,*] Martin G. Banwell[b] and Yoel Kashman[c]

[a]*Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, D-81377 München, Germany*
[b]*Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia*
[c]*School of Chemistry, Tel Aviv University, Tel Aviv 69978, Israel*

Received 8 January 2003; revised 28 February 2003; accepted 28 February 2003

Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday

Abstract—The structure of the strongly cytotoxic marine alkaloid halitulin (**1**) has been confirmed by total synthesis and its absolute configuration determined as (15*S*). The synthesis follows a strategy previously reported by one of us and uses an efficient preparation of the quinoline-7,8-diol unit by modified Baeyer–Villiger and Skraup reactions. The *O*-benzyl protecting groups were removed in the last step of the synthesis by transfer hydrogenolysis without concomitant reduction of the quinoline ring. The method can be applied for the synthesis of halitulin analogues.

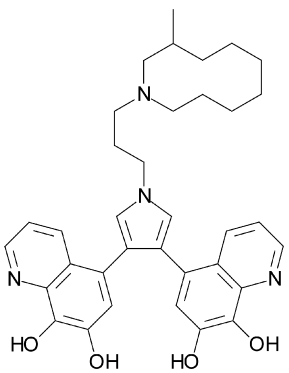
1. Introduction

Halitulin (**1**) was isolated by Kashman et al.[1] from the South African marine sponge *Haliclona tulearensis*. It is accompanied by the 1,5-diazacyclotetradecane derivative haliclorensin (**2**),[2] which is closely related to isohaliclorensin (**3**),[3] the hypothetical precursor to halitulin. Whereas haliclorensin was shown to consist of a 3:1 mixture of the (*S*)- and (*R*)-enantiomers[2b] the absolute configuration of halitulin has not been determined to date.

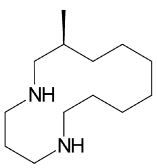
Compound **1** exhibits strong cytotoxic activity against several human tumor cell lines with IC_{50} values in the 0.012–0.025 μg range.[1] This and the unique structure of **1**, including two quinoline-7,8-diol residues and an azecane moiety, have stimulated several synthetic efforts. Syntheses of isohaliclorensin (**3**)[3–5] and the diquinolinylpyrrole unit of halitulin[6] have been reported, and one of us[7] has recently accomplished the synthesis of racemic halitulin tetra-*O*-methyl ether. In this publication we describe the first total synthesis of halitulin (**1**) which proves the proposed structure[1] and defines the absolute configuration of this unique marine alkaloid. Our synthesis combines the convergent strategy (Scheme 1) developed in Canberra[7] with efficient syntheses of subunits **4** and **7** devised in München.[3,8]

2. Results and discussion

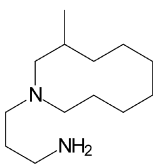
The synthesis of building block **4** commences with



1



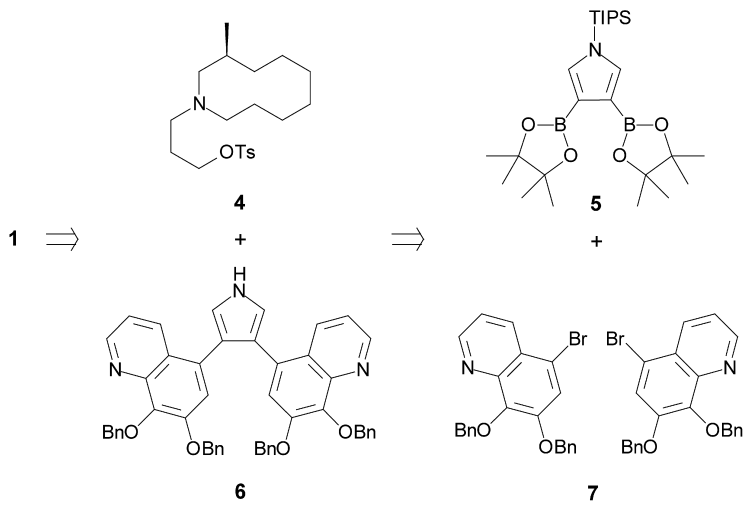
2



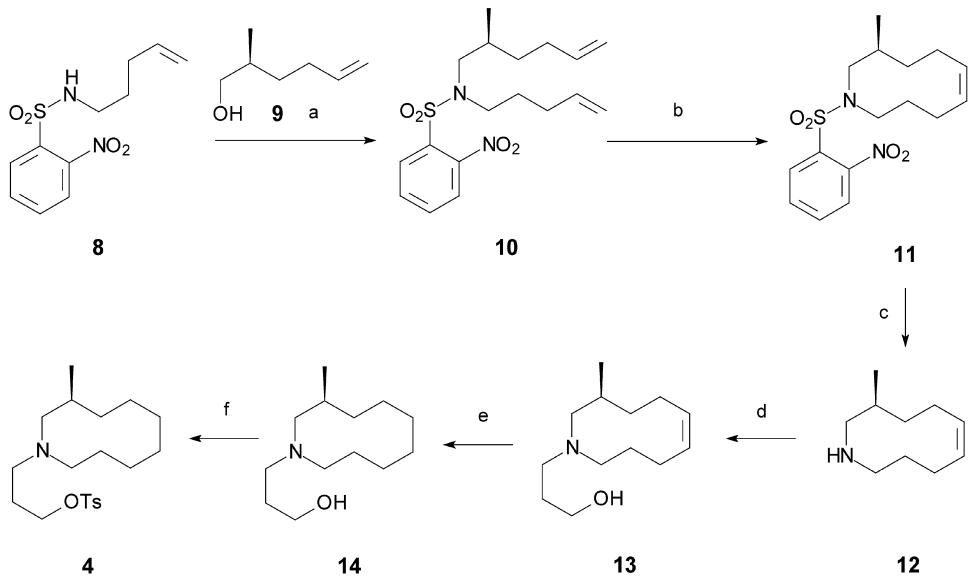
3

Keywords: natural product synthesis; marine metabolites; halitulin; quinoline-7,8-diols; Baeyer–Villiger oxidation; Suzuki reaction.
* Corresponding author. Tel.: +49-89-2180-77757; fax: +49-89-2180-77756; e-mail: wos@cup.uni-muenchen.de

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.02.005

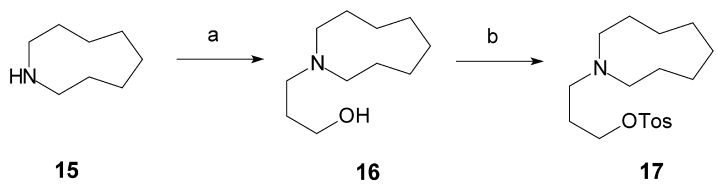


Scheme 1. Retrosynthetic analysis of halitulin (**1**).

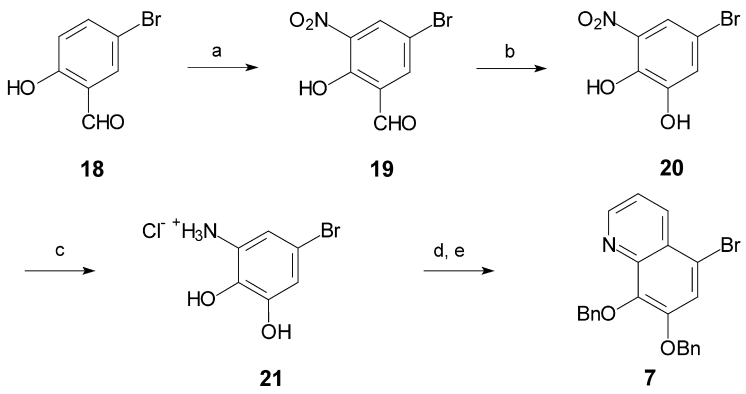


Scheme 2. Construction of the 10-membered ring. *Reagents and conditions*: (a) (2*S*)-2-methylhex-5-en-1-ol (**9**, 1.2 equiv.), PPh_3 (1.3 equiv.), DEAD (1.3 equiv.), dry THF, rt, 24 h, 84%. (b) Grubbs' catalyst (0.1 equiv.), CH_2Cl_2, reflux, 18 h, 56%. (c) PhSH, (1.2 equiv.), K_2CO_3 (3 equiv.), dry DMF, rt, 1.5 h. (d) 3-bromopropan-1-ol (1.1 equiv.), K_2CO_3 (1.0 equiv.), CH_3CN, 70°C, 2 h. (e) H_2 (25 atm), Pd/C (10%), 0.25 M HCl in dry MeOH, rt, 12 h, 90% (from **11**). (f) TsCl (1.2 equiv), NEt_3 (2.5 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 0°C→rt, 2 h, 78% DMAP=4-(dimethylamino)pyridine.

sulfonamide **8**,[9,10] which was converted into the protected secondary amine **10** by reaction with (2*S*)-2-methylhex-5-en-1-ol (**9**) under Mitsunobu conditions[11] (Scheme 2). Alcohol **9** was obtained in optically pure form in five steps from commercially available methyl (2*R*)-3-hydroxy-2-methylpropanoate and in 73% overall yield.[12] The ring-closing metathesis of diene **10** to the azacyclodecene **11** was carried out under standard conditions using the Grubbs' catalyst in dry dichloromethane.[13] We observed that the formation of dimers and oligomers is the predominant reaction, which can, however, be minimized by using concentrations lower than 0.5 mmol/L. The removal of the protecting group from **11** with PhSH and K_2CO_3 according to Fukuyama[10] furnished (*S*)-3-methyl-6-azacyclodecene (**12**) that was converted to alcohol **13** by treatment with 3-bromo-1-propanol without formation of by-products. Hydrogenation of **13** in dry MeOH under acidic conditions yielded the saturated alcohol **14** that was converted into the desired tosylate **4**. The latter could be easily purified by chromatography, in contrast to the corresponding triflate.[7]



Scheme 3. Synthesis of analogue **17**. *Reagents and conditions*: (a) 3-bromopropan-1-ol (1.0 equiv.), K_2CO_3 (1.0 equiv.), dioxane, 95°C, 18 h, 45%. (b) TsCl (1.2 equiv), NEt_3 (2.5 equiv), DMAP (0.2 equiv.), CH_2Cl_2, 0°C→rt, 2 h, 80%.

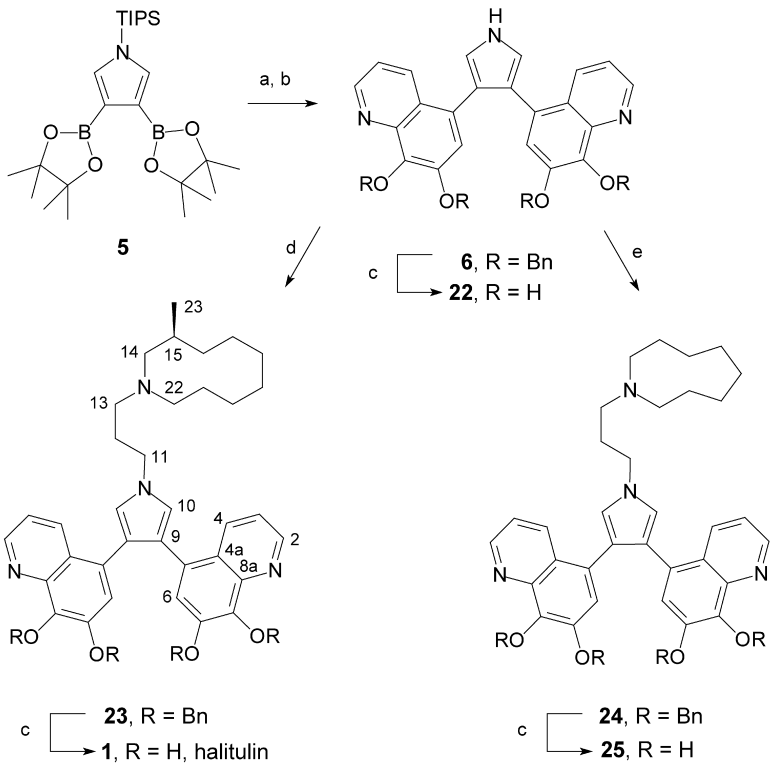


Scheme 4. Synthesis of the quinoline building block. *Reagents and conditions*: (a) 100% HNO_3 (1.2 equiv.), AcOH, 10°C→rt, 1 h, 81%. (b) peracetic acid (35% in AcOH, 2.0 equiv), 2.6 M NH_3 in MeOH (5.5 equiv), CH_2Cl_2, rt, 3 h, >95%. (c) H_2 (1 atm), Pd/C (10%), 1.5 M HCl in MeOH, rt, 3–6 h, ca. 80%. (d) acrolein (7.5 equiv.) air, 1.3 M HCl in dry MeOH, 0°C→rt, 4–6 d. (e) BnBr (4.0 equiv.), K_2CO_3 (5 equiv.), dry DMF, 0°C→rt, 24 h, 40% (2 steps). Bn=benzyl.

In the same manner as described for tosylate **4**, the lower homologue **17** was prepared from azonane (**15**) (Scheme 3). Interestingly, the alkylation of the saturated amine **15** with 3-bromopropan-1-ol required more drastic conditions than that of the cyclic alkene **12** (95°C, 18 h vs. 70°C, 2 h). The pronounced nucleophilicity of **12** was also observed in the reaction with acrylonitrile, which was completed within 12 h at rt,[3] whereas saturated cyclic amines require more drastic reaction conditions.[4]

Achieving a synthesis of halitulin required surmounting two obstacles: the lack of an efficient synthesis of the quinoline-7,8-diol unit[14] and the problem of selecting a suitable *O*-protecting group.

We have recently discovered that quinoline-7,8-diols can be prepared under mild conditions by treatment of 3-amino-catechols with acrolein in 1 M methanolic HCl at rt.[8] Applying this method to the present problem allowed the synthesis of doubly benzyl-protected 5-bromoquinoline-7,8-diol (**7**) in five steps from commercially available 5-bromosalicylaldehyde (**18**) (Scheme 4). Nitration of **18** in acetic acid yielded nitroaldehyde **19**, which was then treated with peracetic acid. As in similar cases,[15] the Baeyer–Villiger rearrangement of this electron-poor system failed, so we were pleased to discover that the desired nitrocatechol **20** was formed quantitatively after adding anhydrous ammonia in methanol to the reaction mixture.[8] The reduction of 5-bromo-3-nitrocatechol (**20**) to amine **21** is



Scheme 5. *Reagents and conditions*: (a) **7** (2.0 equiv.), Na_2CO_3 (10 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), toluene/MeOH/H_2O (deoxygenated by argon), 70°C, 24 h. (b) $nBu_4N^+F^-$ (1.2 equiv.), THF, rt, 10 min, 24% (2 steps). (c) 1,4-cyclohexadiene (50 equiv.), cat. Pd/C (10%), EtOH–TFA (10:1), reflux, 45 min, >95%. (d) **6**, KHMDS (0.5 M in toluene, 1.3 equiv.), DMF–THF (4:1), cat. DMPU, rt, 10 min, then **4** (1.0 equiv.), rt, 3 h, ca. 90% (isolated as the TFA salt). (e) Same conditions as for (d) but with tosylate **17** instead of **4**. TIPS=triisopropylsilyl, Bn=benzyl, DMPU=*N*,*N*′-dimethylpropyleneurea, KHMDS=potassium hexamethyldisilazide, TFA=trifluoroacetic acid.

critically dependent on the presence of mineral acid which suppresses the loss of the bromo-substituent. Interestingly, higher hydrogen pressure leads cleanly to 3-aminocatechol, which has, hitherto, only been accessible by more complicated[16a] or uneconomic[16b] routes.

The conversion of amine **21** into 5-bromoquinoline-7,8-diol proceeds under surprisingly mild conditions with acrolein in 1.3 M methanolic HCl at rt. In this Skraup-type reaction, air serves as oxidant for the dihydroquinoline intermediate. The dehydrogenation is meditated by the catechol unit which forms a redox system with the corresponding *ortho*-quinone. Compared to the classical Skraup synthesis the reaction is no longer dependent on the presence of an added oxidizing agent. When the reaction is applied to the corresponding catechol dimethyl ether, the yield is far lower, and a mixture of the quinoline and the tetrahydroquinoline is obtained.[17] Since previous experience[7] disfavored the use of *O*-protecting groups like methyl, which require strong Lewis acids or acids for removal, we selected benzyl for *O*-protection despite the prospect that reduction of the pyridine ring might accompany the final hydrogenolysis. The desired dibenzyl ether **7** was prepared from the crude 5-bromoquinoline-7,8-diol using benzyl bromide and K_2CO_3 in anhydrous DMF.

The synthesis of the core unit **6** was achieved by Pd-catalyzed Suzuki–Miyaura coupling of quinoline **7** with the pyrrole-3,4-diboronate **5**[7] (Scheme 5). After treatment of the primary coupling product with *n*-tetrabutylammonium fluoride, the bisquinolinylpyrrole **6** was obtained, which can be converted into the free tetrahydroxy compound **22** by hydrogen transfer hydrogenolysis (see below). The synthesis of halitulin was completed by alkylation of the potassium salt derived from pyrrole **6** with tosylate **4**.[18] The reaction can be easily followed by TLC and gives tetra-*O*-benzylhalitulin (**23**) in excellent yield. Not unexpectedly, removal of the benzyl groups by catalytic hydrogenation over Pd–C yielded octahydrohalitulin. However, reduction of the pyridine rings could be avoided by transfer hydrogenolysis with Pd–C/1,4-cyclohexadiene in ethanol[19] in the presence of trifluoroacetic acid. Under these conditions, the trifluoroacetate of (*S*)-halitulin (**1**) was obtained in quantitative yield. All spectral data derived from the compound (^{1}H, ^{13}C NMR, UV, MS) matched those obtained from the natural product (see also Table 1. As expected, a direct HPLC comparison of synthetic and natural halitulin proved their identity. Interestingly, salts of halitulin and the alcohol corresponding to tosylate **4** show a double set of signals in the NMR spectra, due to the formation of two diastereomers resulting from protonation of the chiral azecane moiety either *syn* or *anti* to the methyl group.

The synthetic product exhibited an optical rotation of $[\alpha]_D^{22}=-3.5$. Different samples of the natural product varied

Table 1. Comparison of the ^{13}C and ^{1}H NMR data for synthetic and natural halitulin (**1**)

Synthetic **1**×3TFA[a]				Natural **1**×3TFA[a]	
C	δ_C	δ_H (mult, *J* in Hz)	HMBC (H→C)	δ_C	δ_H
2	144.0	8.79 (dd, *J*=5.5, 1.3)	3, 4, 8a	144.0	8.78
3	118.8	7.58 (dd, *J*=8.6, 5.5)	2, 4a	118.8	7.57
4	146.8	9.00 (d, *J*=8.6)	2, 5, 8a	146.8	9.00
4a	124.8			124.8	
5	128.5			128.5	
6	124.3	7.28 (s)	4a, 5, 7, 8, 9	124.3	7.27
7	150.1			150.1	
8	133.6			133.6	
8a	132.3			132.3	
9	120.9			120.9	
10	124.6	7.32 (s)	5, 9	124.6	7.32
11	48.3	4.31 (m)	12	48.3	4.32
12	27.8 [27.9]	2.48 (m) [2.48 (m)]	11	27.8	
13	55.9 [56.5]	3.35 (m) [3.35 (m)]	11, 12	55.9 [56.5]	
14	59.7 [59.4]	3.03 (dd, *J*=14.4, 5.3) 3.46 (dd, *J*=14.4, 5.7) [3.21 (m), 3.28 (m)]	13, 22, 23	59.7 [59.4]	
15	30.3 [28.9]	2.28 (m) 2.32 (m)		30.3 [28.9]	
16	34.3 [32.1]	1.57 (m), 1.63 (m)	14, 23	34.3 [32.1]	
17[b]	25.8[b]	1.70 (m)		25.8	
18[b]	25.6[b]	1.55 (m), 1.70 (m)		25.6	
19[b]	25.2[b]	1.71 (m), 1.80 (m)		25.2	
20[b]	23.7[b]	1.62 (m), 1.68 (m)		23.7	
21[b]	21.9[b] [27.0[b]] [26.0[b]]			21.9 [27.0] [20.0]	
22	53.2 [52.3]	3.34 (m), 3.54 (m) [3.33 (m), 3.60 (m)]		53.2 [52.3]	
23	21.3 [20.7]	1.13 (d, *J*=6.7) [1.10 (d, *J*=6.3)]	14, 16	21.3 [20.7]	

[a] 4:1-Mixture of diastereomers. Values in brackets relate to the minor diastereomer.
[b] Assignments may be interchanged.

from $[\alpha]_D^{22}=-1$ to -3.0. Since the intense colour of halitulin trifluoroacetate made an exact comparison of the optical rotations unreliable, we compared the only lightly yellow tetraacetates.[1,20] The synthetic sample exhibited $[\alpha]_D^{22}=-21$, whereas the average of several measurements of the tetraacetate from natural halitulin was $[\alpha]_D^{22}=-22$ (in both cases $c=0.15$). Since our synthesis commenced from the octahydroazecin derivative (*S*)-**12**,[3] halitulin has the (15*S*)-configuration. This supports the idea that both, halitulin and haliclorensin (**2**), are derived from a common precursor.[2b]

Our convergent synthesis is flexible and allows easy access to simplified halitulin analogues in which the 'northern half' is exchanged by other residues. Thus, the achiral azonane derivative **25** was obtained from tosylate **17** and the potassium salt of **6**, followed by transfer hydrogenolysis of the resulting tetrabenzyl derivative **24** (Scheme 5). The biological evaluation of these compounds is now underway.

3. Experimental

3.1. General

Silica gel 60 (230–400 mesh, Merck) was used for flash chromatography. R_f values were determined on silica gel 60 F-254 TLC plates (Merck). ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX 300, Varian VXR 400S and/or Bruker AMX 600 instruments. Chemical shifts are reported in ppm δ units relative to chloroform (7.26 ppm for ^{1}H NMR and 77.0 ppm for decoupled ^{13}C NMR). IR spectra were measured on a Perkin–Elmer FT 1000 instrument. Mass spectra were recorded with a Finnigan MAT 90 sector field mass spectrometer operating at 70 eV. HPLC was carried out on a Nucleosil 100 C-18 column (5 μm, 250×4.0 mm). Optical rotations were determined on a Perkin–Elmer 241 polarimeter. C, H, N and S analyses were performed by the microanalytical laboratory of the Chemistry Department, LMU, München.

3.2. Syntheses of the tosylates 4 and 17

3.2.1. *N*-Pent-4-enyl-2-nitrobenzenesulfonamide (8). 2-Nitrobenzenesulfonyl chloride (2.55 g, 11.5 mmol), K_2CO_3 (3.17 g, 23.0 mmol) and pent-4-enylamine (0.98 g, 11.5 mmol) were heated at reflux in dry THF (40 mL) for 24 h. The resulting reaction mixture was acidified with 2N HCl and extracted with $CHCl_3$ (3×). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography ($CHCl_3$) to provide **8** (2.48 g, 80%) as a yellow oil: R_f=0.5 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (tt, *J*=7.2, 7.1 Hz, 2H), 2.09 (td, *J*=7.2, 6.8 Hz, 2H), 3.12 (m, 2H), 4.95–5.02 (m, 2H), 5.28 (m, 1H), 5.72 (ddt, *J*=17.0, 10.3, 6.8 Hz, 1H), 7.74 (m, 2H), 7.86 (m, 1H), 8.14 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.7, 30.5, 43.2, 115.8, 125.4, 131.1, 132.8, 133.5, 133.8, 136.9, 148.1; MS (EI) *m*/*z* (rel. int.): 270 (0.3, M^+), 269 (2, M^+-H), 255 (2), 215 (6), 187 (8), 186 (100, $C_6H_4NO_4S$), 170 (3), 123 (3), 92 (7), 84 (17) ($C_5H_{10}N$), 70 (17); HRMS (EI) calcd for $C_{11}H_{15}N_2O_4S$ [M^++H] 271.0752, found 271.0776. Anal. calcd C, 48.88; H, 5.22; N, 10.36; S, 11.86; found C, 49.41; H, 5.46; N, 10.50; S, 11.78.

3.2.2. *N*-[(2*S*)-2-Methylhex-5-enyl]-*N*-pent-4-enyl-2-nitrobenzenesulfonamide (10). A solution of **8** (1.69 g, 6.25 mmol) and (2*S*)-2-methylhex-5-en-1-ol (**9**)[12] (1.07 g, 9.38 mmol) in dry THF (30 mL) was treated with PPh_3 (1.64 g, 6.25 mmol) and diethyl azodicarboxylate (DEAD) (1.09 g, 6.25 mmol) under an argon atmosphere. After being stirred for 8 h at rt, additional PPh_3 (0.55 g, 2.08 mmol) and DEAD (0.36 g, 2.08 mmol) were added to the solution, and the stirring was continued for additional 16 h. The reaction mixture was then concentrated under reduced pressure and the residue purified by silica gel flash chromatography (EtOAc–hexanes, 1:1, v/v) to yield, after removal of traces of 2-methylhex-5-en-1-ol under reduced pressure, **10** (1.92 g, 84%) as a light yellow oil: R_f=0.45 (EtOAc–hexanes, 1:1, v/v); $[\alpha]_D=-15$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J*=6.6 Hz, 3H), 1.04–1.17 (m, 1H), 1.18–1.28 (m, 1H), 1.36–1.48 (m, 1H), 1.50–1.62 (m, 1H), 1.66–1.78 (m, 1H), 1.90–2.16 (m, 4H), 3.05–3.29 (m, 4H), 4.87–4.99 (m, 4H), 5.60–5.78 (m, 2H), 7.55–7.68 (m, 3H), 7.94–7.98 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.8 (CH_3), 26.7 (CH_2), 30.3 (CH), 30.5 (CH_2), 30.8 (CH_2), 32.9 (CH_2), 46.7 (CH_2), 53.4 (CH_2), 114.6 (CH_2), 115.2 (CH_2), 124.0 (CH), 130.6 (CH), 131.5 (CH), 133.3 (CH), 133.4 (C_q), 137.0 (CH), 138.2 (CH), 147.8 (C_q); MS (EI) *m*/*z* (rel. int.): 366 (4, M^+), 311 (4), 284 (7), 283 (52, $M^+-C_6H_{11}$), 268 (11, $M^+-C_7H_{14}$), 229 (16), 215 (19), 186 (100, $C_6H_4NO_4S$); HRMS (EI) calcd for $C_{18}H_{26}N_2O_4S$ [M^+] 366.1613, found 366.1586. Anal. calcd C, 58.99; H, 7.15; N, 7.64; S, 8.75; found C, 59.21; H, 7.45; N, 7.72; S, 8.66.

3.2.3. (3*S*)-3-Methyl-1-(2-nitrobenzenesulfonyl)-1,2,3,4,5,8,9,10-octahydroazecine (11). To a refluxing solution of Grubbs' catalyst[13a] (74 mg, 0.09 mmol) in dry CH_2Cl_2 (1500 mL) maintained under argon was added a solution of **10** (330 mg, 0.9 mmol) in dry CH_2Cl_2 (10 mL) and refluxing was continued for 18 h. The reaction was monitored by TLC [R_f(**10**)=0.45, R_f(**11**)=0.3, R_f(Polymer)=<0.1; EtOAc–hexanes 1:3, v/v] and, depending on the conversion and formation of undesired polymers, additional catalyst was added and the reaction time prolonged. The cooled reaction mixture was filtered through a plug of Celite and the filtrate concentrated under reduced pressure. After silica gel flash chromatography (EtOAc–hexanes, 1:3, v/v) pure **11** (171 mg, 56%) was obtained as a colorless solid: mp 101–103°C; $[\alpha]_D=-88$ (*c* 0.9, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.82 (d, *J*=6.7 Hz, 3H), 1.43–1.49 (m, 1H), 1.54–1.58 (m, 2H), 1.88–1.95 (m, 2H), 1.97–2.03 (m, 1H), 2.14–2.20 (m, 1H), 2.53 (dd, *J*=13.0, 3.6 Hz, 1H), 2.73–2.80 (m, 1H), 2.95–2.99 (m, 1H), 3.02 (dd *J*=13.0, 4.7 Hz, 1H), 3.11 (ddd, *J*=14.4, 5.0, 1.7 Hz, 1H), 3.42 (dd, *J*=13.1, 9.7 Hz, 1H), 5.44–5.46 (m, 2H), 7.54 (dd, *J*=7.2, 1.9 Hz, 1H), 7.67–7.72 (m, 2H), 7.89 (dd, *J*=7.2, 1.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 23.2, 24.7, 26.7, 27.2, 35.0, 45.5, 57.9, 123.8, 128.5, 129.9, 131.0, 131.1, 131.9, 133.5, 149.0; MS (EI) *m*/*z* (rel. int.): 338 (1, M^+), 309 (1), 281 (9), 229 (3), 186 (32, $C_6H_4NO_4S$), 152 (100, $C_{10}H_{18}N$); HRMS (EI) calcd for $C_{16}H_{22}N_2O_4S$ [M^+] 338.1300, found 338.1300. Anal. calcd C, 56.78; H, 6.55; N, 8.28; S, 9.48; found C, 56.73; H, 6.51; N, 8.01; S, 9.02.

3.2.4. (3*S*)-3-Methyl-1,2,3,4,5,8,9,10-octahydroazecine (12). To a solution of **11** (52 mg, 0.15 mmol) in dry DMF (5 mL) was added thiophenol (18 μL, 20 mg, 0.185 mmol) and K_2CO_3 (62 mg, 0.45 mmol). The mixture was stirred at rt for 2 h, then diluted with brine (15 mL) and extracted with Et_2O (3×10 mL). From the combined organic phases the amine was extracted with 1N hydrochloric acid (3×5 mL). On addition of 2N sodium hydroxide, the free amine separated as a white precipitate which was taken up in Et_2O. After drying (Na_2SO_4), the solvent was carefully removed under reduced pressure to yield **12** as a colorless oil containing traces of DMF: R_f=0.1 (EtOAc–hexanes, 1:1, v/v), R_f=0.2 ($CHCl_3$–MeOH, 5:1, v/v); $[\alpha]_D$=−24 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J*=7.0 Hz, 3H), 1.34–1.49 (m, 2H), 1.50–1.67 (m, 3H), 1.85–1.97 (m, 3H), 2.50–2.66 (m, 5H), 3.12 (m, 1H), 5.34 (dddd, *J*=11.0, 11.0, 5.8, 1.8 Hz, 1H), 5.47 (ddd, *J*=11.0, 11.0, 4.2 Hz, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 21.3, 23.1, 26.0, 26.3, 26.7, 37.3, 43.0, 57.4, 127.5, 132.5; MS (EI) *m/z* (rel. int.): 153 (20, M^+), 152 (29, M^+−H), 138 (8), 124 (17), 111 (11), 110 (60), 98 (13), 97 (30), 96 (100), 84 (34), 82 (29), 70 (21), 56 (19), 44 (60); HRMS (EI) calcd for $C_{10}H_{19}N$ [M^+] 153.1518, found 153.1494.

3.2.5. 3-[(3*S*)-3-Methyl-3,4,5,8,9,10-hexahydro-2*H*-azecin-1-yl]propan-1-ol (13). A mixture of crude amine **12** (50 mg, 0.33 mmol), 3-bromopropan-1-ol (30 μL, 45 mg, 0.33 mmol) and K_2CO_3 (45 mg, 0.33 mmol) in dry CH_3CN (5 mL) maintained under argon was stirred for 2 h at 70°C. The cooled reaction mixture was filtered and concentrated under reduced pressure to remove traces of 3-bromo-1-propanol. Compound **13** (65 mg, 94%; ~80% from **12**) was thus obtained as a light yellow oil: R_f=0.5 ($CHCl_3$–MeOH, 4:1, v/v); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 0.85 (d, *J*=6.7 Hz, 3H), 1.32 (m, 1H, 9b-H), 1.40 (m, 1H, 4b-H), 1.59 (m, 1H, 4′a-H), 1.72 (m, 1H, 2′b-H), 1.77–1.78 (m, 4H, 2′a-H, 5b-H, 8b-H, 9a-H), 1.95 (m, 2H, 3-H, 10b-H), 2.08–2.16 (m, 2H, 1′b-H, 2b-H), 2.50 (m, 1H, 8a-H), 2.58 (m, 1H, 2a-H), 2.75 (m, 1H, 1′a-H), 2.83 (m, 1H, 10a-H), 3.10 (m, 1H, 5a-H), 3.70 (t, *J*=6.4 Hz, 2H, 3′-H), 5.33 (m, 1H, 6/7-H), 5.45 (ddd, *J*=11.4, 11.3, 3.8 Hz, 1H, 6/7-H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 21.4 (C-11), 23.5 (C-8), 24.4 (C-9), 25.6 (C-5), 27.0 (C-3), 29.7 (C-2′), 37.5 (C-4), 49.5 (C-10), 52.0 (C-1′), 62.1 (C-3′), 63.5 (C-2), 127.9 (C-6/7), 132.7 (C-6/7); MS (EI) *m/z* (rel. int.): 211 (0.5, M^+), 210 (1, M^+−H), 168 (9), 167 (6), 166 (41), 154 (25), 153 (28), 152 (19), 142 (12), 138 (7), 125 (10), 124 (100), 111 (6), 110 (7), 96 (8); HRMS (EI) calcd for $C_{13}H_{24}NO$ [M^+−H] 210.1858, found 210.1846.

3.2.6. 3-[(3*S*)-3-Methyl-azecan-1-yl]propan-1-ol hydrochloride (14). To a solution of **13** (65 mg, 0.31 mmol) in dry MeOH (5 mL) were added HCl (1.25 M in MeOH, 1 mL) and palladium on charcoal (30 mg, 10% Pd). The hydrogenation was carried out at 10–20 atm H_2-pressure for 16 h. After removal of the catalyst by filtration through Celite, the solution was concentrated and the residue dried under reduced pressure to afford hydrochloride **14** (75 mg, 90%) as a colorless oil: R_f=0.35 ($CHCl_3$–MeOH, 4:1, v/v); $[\alpha]_D^{23}$=−12 (*c* 2.0, MeOH); ^{13}C NMR (75.5 MHz, CD_3OD) δ 19.8 (CH_3), 20.4 (CH_3), 22.5 (CH_2), 22.6 (CH_2), 24.3 (CH_2), 24.4 (CH_2), 25.1 (CH_2), 25.3 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.7 (CH_2), 27.1 (CH_2), 28.6 (CH_2), 30.3 (CH), 31.9 (CH_2), 32.2 (CH_2), 53.6 (CH_2), 54.7 (CH_2), 58.6 (CH_2), 59.5 (CH_2), 59.6 (CH_2), 60.1 (CH_2), 61.6 (CH_2), 62.2 (CH_2) [double set of signals due to formation of diastereomers after protonation]; MS (EI) *m/z* (rel. int.): 213 (14, M^+), 212 (4, M^+−H), 169 (12), 168 (100), 154 (10), 140 (4), 128 (4), 126 (24), 114 (7), 102 (15), 88 (44); HRMS (EI) calcd for $C_{13}H_{27}NO$ [M^+] 213.2093, found 213.2101.

3.2.7. 3-(Azonan-1-yl)propan-1-ol (16). A mixture of azonane[21] (**15**) (0.50 g, 3.94 mmol), 3-bromopropan-1-ol (0.34 mL, 0.55 g, 3.94 mmol) and K_2CO_3 (1.63 g, 11.82 mmol) in dry dioxane (8 mL) was heated at 95°C for 18 h under an argon atmosphere. The cooled reaction mixture was filtered and concentrated under reduced pressure. Purification of the residue by silica gel flash chromatography ($CHCl_3$–MeOH, 4:1, v/v) afforded **16** (0.33 g, 45%) as a colorless oil: R_f=0.35 ($CHCl_3$–MeOH, 4:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (m, 4H), 1.55 (m, 8H), 1.71 (tt, *J*=6.0, 5.8 Hz, 2H), 2.54 (m, 4H), 2.67 (t, *J*=6.0 Hz, 2H), 3.76 (t, *J*=5.8 Hz, 2H), 4.15 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.9 (2×CH_2), 25.2 (2×CH_2), 25.9 (2×CH_2), 28.7 (CH_2), 53.1 (2×CH_2), 57.9 (CH_2), 63.2 (CH_2); MS (EI) *m/z* (rel. int.): 185 (20, M^+), 144 (4), 141 (10), 140 (100), 126 (8), 114 (9), 112 (33), 100 (5), 88 (16), 84 (13), 70 (10), 58 (20), 57 (17), 55 (13), 44 (21), 41 (22); HRMS (EI) calcd for $C_{11}H_{23}NO$ [M^+] 185.1780, found 185.1786.

3.3. General procedure for the tosylation of alcohols 14 and 16

A solution of the alcohol (1.0 mmol) in dry CH_2Cl_2 (5 mL) under argon, maintained at 0°C, was treated with triethylamine (208 μL, 152 mg, 1.5 mmol; in case of hydrochloride **14** 2.5 mmol), DMAP (24 mg, 0.2 mmol) and tosyl chloride (229 mg, 1.2 mmol). The resulting mixture was stirred for 5 min, then, the ice-bath was removed and the reaction mixture warmed over 2 h to rt. The solution was diluted with CH_2Cl_2, washed several times with water and dried over Na_2SO_4. Purification of the crude product by silica gel flash chromatography (EtOAc–hexanes, 2:3, v/v) afforded the tosylates **4** or **17** as colorless oils, which decompose in solution at rt, but are stable in pure form over several weeks at 0°C.

3.3.1. 3-[(3*S*)-3-Methyl-azecan-1-yl]propyl toluene-4-sulfonate (4). Yield: 287 mg (78%); R_f=0.75 (EtOAc–hexanes, 1:3, v/v); R_f=0.20 (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, *J*=6.2 Hz, 3H), 1.22–1.39 (m, 5H), 1.41–1.53 (m, 2H), 1.54–1.73 (m, 5H), 1.75–1.82 (m, 2H), 2.04 (m, 1H), 2.10–2.17 (m, 2H), 2.22–2.26 (m, 1H), 2.42–2.50 (m, 2H), 2.44 (s, 3H), 2.57–2.62 (m, 1H), 4.11 (t, *J*=6.3 Hz, 2H), 7.34 (d, *J*=7.7 Hz, 2H), 7.89 (d, *J*=7.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.4, 21.6, 22.2, 24.3, 24.7, 25.9, 26.5, 30.0, 30.3, 31.8, 51.1, 53.2, 60.6, 69.7, 127.9 (2C), 129.8 (2C), 133.3, 144.6; MS (EI) *m/z* (rel. int.): 368 (4, M^++H), 367 (5, M^+), 324 (3), 312 (5), 282 (6), 256 (10), 243 (8), 242 (62), 169 (12), 168 (100), 155 (8), 154 (11), 126 (27), 106 (9), 98 (11), 91 (10), 70 (15), 58 (11); HRMS (EI) calcd for $C_{20}H_{33}NO_3S$ [M^+] 367.2181, found 367.2202.

3.3.2. 3-(Azonan-1-yl)prop-1-yl toluene-4-sulfonate (17). Yield: 272 mg (80%); R_f=0.75 (EtOAc–hexanes, 1:3, v/v);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32–1.48 (m, 12H), 1.77 (tt, J=6.7, 6.5 Hz, 2H), 2.37 (m, 4H), 2.42 (s, 3H), 2.44 (t, J=6.7 Hz, 2H), 4.10 (t, J=6.5 Hz, 2H), 7.32 (dd, J=8.5, 0.6 Hz, 2H), 7.77 (d, J=8.5 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5 (CH_3), 23.4 (2×CH_2), 25.4 (2×CH_2), 26.4 (2×CH_2), 27.3 (CH_2), 53.3 (2×CH_2), 53.9 (CH_2), 69.3 (CH_2), 127.8 (2×CH), 129.7 (2×CH), 133.0 (C_q), 144.6 (C_q); MS (EI) *m/z* (rel. int.): 339 (13, M^+), 298 (7), 282 (7), 268 (9), 242 (32), 184 (4), 155 (5), 141 (10), 140 (100), 138 (9), 126 (12), 124 (7), 112 (28), 91 (22), 84 (12), 70 (15), 58 (11), 55 (13); HRMS (EI) calcd for $C_{18}H_{29}NO_3S$ [M^+] 339.1868, found 339.1861.

3.4. Synthesis of quinolinediol 7

3.4.1. 5-Bromo-3-nitrosalicylaldehyde (19). A solution of 5-bromosalicylaldehyde (**18**, 10.0 g, 49.7 mmol) in acetic acid (50 mL), maintained at 10°C, was treated with 100% nitric acid (2.70 mL, 4.10 g, 64.6 mmol). The resulting mixture was warmed to rt over 1 h, then, the reaction mixture was quenched with water and extracted several times with EtOAc. The combined organic phases were washed with water and brine then dried over Na_2SO_4. Removal of the solvents and drying under reduced pressure gave **19** (11.9 g, 97%) as a yellow solid: mp 108–109°C; R_f=0.7 ($CHCl_3$–MeOH, 20:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J=2.5 Hz, 1H), 8.46 (d, J=2.5 Hz, 1H), 10.37 (s, 1H), 11.24 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 111.8, 126.8, 133.3, 135.7, 139.4, 155.3, 187.5; MS (EI) *m/z* (rel. int.): 247 (37, M^+, $C_7H_4^{81}BrNO_4$), 245 (37, M^+, $C_7H_4^{79}BrNO_4$), 230 (11), 229 (100), 228 (11), 227 (100), 217 (16), 215 (17), 200 (26), 199 (34), 198 (25), 197 (27), 172 (14), 171 (22), 170 (15), 169 (21), 143 (19), 141 (10), 120 (10), 91 (13), 64 (11), 63 (39), 62 (19); HRMS (EI) calcd for $C_7H_4^{79}BrNO_4$ [M^+] 244.9324, found 244.9294.

3.4.2. 5-Bromo-3-nitrocatechol (20). A solution of **19** (17.8 g, 72.4 mmol) in CH_2Cl_2 (500 mL) was treated with peracetic acid (39% in AcOH, 20.5 mL, 120 mmol) and stirred at 20°C for 1 h. After the addition of ammonia (2.5 M in MeOH, 144 mL, 360 mmol), the mixture was stirred for another hour. The solution was then diluted with CH_2Cl_2, washed with 2N HCl (2×250 mL) and dried (Na_2SO_4). Removal of the solvents and drying under reduced pressure afforded **20** (15.8 g, 93%) as a red solid: mp 82–84°C; R_f=0.55 ($CHCl_3$–MeOH, 10:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 1H), 7.35 (d, J=2.3 Hz, 1H), 7.79 (d, J=2.3 Hz, 1H), 10.54 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 111.6, 118.0, 124.6, 133.8, 142.1, 147.3; MS (EI) *m/z* (rel. int.): 236 (6), 235 (93, M^+, $C_6H_4^{81}BrNO_4$), 234 (7) 233 (94, M^+, $C_6H_4^{79}BrNO_4$), 205 (12), 203 (12), 189 (14), 188 (14), 187 (100), 186 (8), 185 (89), 173 (10), 171 (10), 159 (24), 157 (17), 79 (24); HRMS (EI) calcd for $C_6H_4^{79}BrNO_4$ [M^+] 232.9324, found 232.9326.

3.4.3. 3-Amino-5-bromocatechol hydrochloride (21). A mixture of catechol **20** (2.35 g, 10.0 mmol) and 10% Pd on charcoal (0.20 g) in MeOH (90 mL) and HCl (5–6 M in isopropanol, 20 mL) was stirred under H_2 (1 atm). After completion of the hydrogenation, as indicated by ^{1}H NMR and TLC analysis, the mixture was filtered through a small pad of Celite and the filtrate concentrated under reduced pressure to yield **21** (2.16 g, 90%) as a greenish brown foam: ^{1}H NMR (300 MHz, CD_3OD) δ 7.04 (d, J=2.2 Hz, 1H), 7.07 (d, J=2.2 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 111.6, 118.3, 120.1, 121.1, 141.3, 149.0; MS (EI) *m/z* (rel. int.): 206 (49, M^++H, $C_6H_7^{81}BrNO_2$), 205 (100, M^+, $C_6H_6^{81}BrNO_2$), 204 (48, M^++H, $C_6H_7^{79}BrNO_2$), 203 (84, M^+, $C_6H_6^{79}BrNO_2$), 187 (39), 185 (33), 160 (23), 159 (52), 158 (21), 157 (45), 125 (27), 107 (19), 82 (21), 80 (21), 79 (63), 51 (39), 44 (43), 36 (95); HRMS (EI) calcd for $C_6H_6^{79}BrNO_2$ [M^+] 202.9582, found 202.9602.

3.4.4. 5-Bromo-7,8-dibenzyloxyquinoline (7). A solution of **21** (2.3 g, 9.6 mmol) in MeOH (120 mL), maintained at 0°C, was treated with HCl (5–6 M in isopropanol, 30 mL) and acrolein (4.8 mL, 4.0 g, 72 mmol). Then, the ice-bath was removed and the mixture stirred for at least 5 d at rt in a flask equipped with a drying tube. After completion of the quinoline formation (^{1}H NMR monitoring!), the solution was carefully concentrated under reduced pressure and the residue dried in vacuo. The crude 5-bromoquinoline-7,8-diol hydrochloride (4.95 g) was obtained as a brown foam that was used directly for the next reaction step: ^{1}H NMR (200 MHz, CD_3OD) δ 7.86 (s, 1H), 7.92 (dd, J=8.6, 5.5 Hz, 1H), 8.99 (dd, J=5.5, 1.4 Hz, 1H), 9.14 (dd, J=8.6, 1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 119.9 (CH), 120.2 (CH), 126.0 (C_q), 129.8 (C_q), 132.2 (C_q), 135.6 (C_q), 143.6 (CH), 145.5 (C_q), 147.7 (CH).

A solution of the crude quinolinediol (4.95 g, diol content ~50–55% besides polymerisation products of acrolein, ~9.0 mmol) in dry DMF maintained under argon at 0°C, was treated with K_2CO_3 (6.22 g, 45 mmol) and benzyl bromide (4.28 mL, 6.16 g, 36 mmol). The resulting mixture was stirred for 24 h at rt, then diluted with water and extracted several times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2–acetone, 20:1, v/v) yielded **7** (1.61 g, 40% from **21**) as a light brown solid: mp 67–69°C; R_f=0.7 (CH_2Cl_2–acetone, 20:1, v/v); ^{1}H NMR (300 MHz, CD_3OD) δ 5.30 (s, 2H), 5.31 (s, 2H), 7.26–7.30 (m, 3H), 7.37–7.46 (m, 3H), 7.47–7.53 (m, 4H), 7.54 (dd, J=8.5, 4.3 Hz, 1H), 7.92 (s, 1H), 8.53 (dd, J=8.5, 1.6 Hz, 1H), 8.90 (dd, J=4.3, 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 72.5, 76.1, 115.8, 120.4, 121.8, 123.8, 127.4, 127.8, 128.1, 128.1, 128.5, 128.5, 135.7, 136.3, 137.5, 142.8, 144.0, 150.5, 150.9; MS (EI) *m/z* (rel. int.): 421 (0.5, M^+, $C_{23}H_{18}^{81}BrNO_2$), 419 (0.5, M^+, $C_{23}H_{18}^{79}BrNO_2$), 331 (4), 330 (25), 329 (5), 328 (25), 91 (100); HRMS (EI) calcd for $C_{23}H_{18}^{79}BrNO_2$ [M^+] 419.0521, found 419.0485.

3.5. Syntheses of halitulin and bisnorhalitulin

3.5.1. Bis-3,4-(3,3,4,4-tetramethyl-2,5-dioxaborolan-1-yl)-1-(triisopropylsilyl)pyrrole (5).[7] The successful synthesis of **5** depends critically on dry solvents. To a stirred solution of 3,4-diiodo-1-(triisopropylsilyl)pyrrole[7] (0.57 g, 1.20 mmol) in dry dioxane (14 mL) under argon were added at 15–20°C triethylamine (1.66 mL, 1.22 g, 12.0 mmol) and $PdCl_2$(dppf)×CH_2Cl_2 (69 mg, 0.08 mmol). After the addition of pinacolborane (0.78 mL, 335 mg, 2.62 mmol), the mixture was heated at reflux for 24 h. The reaction mixture was then cooled to rt and after the addition of water, the solution was extracted several times with $CHCl_3$. The

combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in a mixture of hexanes and EtOAc (10:1, v/v, 33 mL), filtered and dried under reduced pressure to give crude **5** (0.38 g) as a light brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (d, J=7.3 Hz, 18H), 1.28 (s, 24H), 1.40 (sept, J=7.3 Hz, 3H), 7.11 (s, 2H).

3.5.2. Bis-3,4-(7,8-dibenzyloxyquinolin-5-yl)pyrrole (6). To a stirred solution of crude **5** (0.36 g, 0.76 mmol), **7** (0.63 g, 1.50 mmol) and $Pd(PPh_3)_4$ (88 mg) in a mixture of toluene (15 mL) and MeOH (20 mL) under argon was added Na_2CO_3 (0.80 g in 4 mL H_2O). Then, the flask and the reflux condenser were evacuated and flashed several times with argon to remove oxygen. The mixture was then heated for 24–30 h to 65–75°C, cooled to rt, diluted with water and extracted with $CHCl_3$ (3×30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (toluene–$CHCl_3$–MeOH, 15:10:1, v/v/v) to afford bis-3,4-(7,8-dibenzyloxyquinolin-5-yl)-1-(triisopropylsilyl)pyrrole as a brown oil, which, according to the ^{1}H NMR spectrum, still contained traces of triphenylphosphine: R_f=0.45 ($CHCl_3$–MeOH, 10:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J=7.5 Hz, 18H), 1.56 (sept, J=7.5 Hz, 3H), 4.82 (s, 4H), 5.31 (s, 4H), 6.95 (s, 2H), 7.02 (dd, J=8.5, 4.3 Hz, 2H), 7.03 (s, 2H), 7.22–7.25 (m, 16H), 7.47–7.50 (m, 4H), 8.19 (dd, J=8.5, 1.6 Hz, 2H), 8.85 (dd, J=4.3, 1.6 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.7 (3×CH), 17.9 (6×CH_3), 72.1 (2×CH_2), 76.0 (2×CH_2), 118.8 (2×CH), 119.3 (2×CH), 123.3 (2×C_q), 123.7 (2×C_q), 125.1 (2×CH), 127.3 (4×CH), 127.7 (2×CH), 127.9 (2×CH), 128.1 (4×CH), 128.4 (4×CH), 128.6 (4×CH), 129.7 (2×C_q), 132.0 (2×C_q), 132.1 (2×C_q), 136.7 (2×C_q), 137.8 (2×C_q), 149.3 (2×CH), 150.6 (2×C_q) [only 22 of the expected 23 signals were visible]; MS (EI) m/z (rel. int.): 902 (0.2, M^++H), 901 (0.3, M^+), 811 (2), 810 (4), 720 (1), 704 (1), 655 (2), 654 (3), 628 (2), 472 (2), 262 (48), 250 (18), 183 (32), 108 (19), 91 (100).

The deprotection of the TIPS derivative (0.53 g, 0.59 mmol) was carried out in THF (5 mL) with a solution of tetra-*n*-butyl ammonium fluoride in THF (1 M, 0.7 mL). After stirring for 10 min at 20°C, the solution was diluted with water and extracted with CH_2Cl_2. Drying over Na_2SO_4 and purification by silica gel flash chromatography (EtOAc–hexanes, 1:1, v/v) gave **6** (0.38 g, 86%; 25% from 3,4-diiodo-1-TIPS-pyrrole) as an orange solid: mp 54–55°C; R_f=0.4 (EtOAc–hexanes 1:1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.79 (s, 4H, 8′-benzyl-H), 5.28 (s, 4H, 7′-benzyl-H), 6.95 (d, J=2.8 Hz, 2H, 2-H), 6.98 (dd, J=8.3, 4.1 Hz, 2H, 3′-H), 7.03 (s, 2H, 6′-H), 7.17–7.23 (m, 16H, benzyl-H), 7.43–7.44 (m, 4H, benzyl-H), 8.22 (dd, J=8.3, 1.7 Hz, 2H, 4′-H), 8.80 (dd, J=4.1, 1.7 Hz, 2H, 2′-H), 10.52 (s, 1H, 1-H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 71.8, 76.0, 118.7, 119.0, 119.3, 120.4, 123.6, 127.2, 127.7, 127.9, 128.0, 128.4, 128.5, 130.2, 135.8, 136.5, 137.6, 140.4, 143.0, 149.1, 150.6; MS (EI) m/z (rel. int.): 746 (3, M^++H), 745 (5, M^+), 655 (14), 654 (25), 564 (7), 549 (13), 548 (29), 472 (17), 458 (5), 382 (4), 347 (4), 262 (8), 108 (25), 107 (21), 106 (35), 105 (35), 92 (18), 91 (100), 79 (16), 77 (28); HRMS (EI) calcd for $C_{50}H_{39}N_3O_4$ [M^+] 745.9241, found 745.9206.

3.6. General procedure for the N-alkylation of pyrrole 6

A stirred solution of pyrrole **6** (0.031 mmol) in dry DMF (2 mL+cat. DMPU) maintained under argon at 0°C, was treated with potassium hexamethyldisilazide (0.5 M in toluene, 80 μL, 0.04 mmol). After 10 min, a solution of the relevant tosylate (0.032 mmol) in dry THF (0.5 mL) was added dropwise. The resulting mixture was stirred for 24 h at rt, quenched with aqueous $NaHCO_3$ and extracted several times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by HPLC [solvent A: H_2O–CH_3CN (9:1)+0.05% TFA, solvent B: CH_3CN; gradient: start: 100% A, 40–60 min: 45% A, 70 min: 100% B, flow: 3 mL/min] provided **23** or **24** as yellow oils.

3.6.1. (*S*)-Tetra-*O*-benzylhalitulin tris-trifluoroacetate (23). Yield: 80–95%; TLC R_f=0.2 (EtOAc–hexanes, 3:1, v/v); HPLC R_t=58.5 min; UV λ_{max}(qual.): 263 nm (1.00), 341 (0.10), 412 (0.15); ^{1}H NMR (400 MHz, CD_3OD) δ 1.10*/1.13* (2×d, J=6.7/6.6 Hz, 3H), 1.52–1.78 (m, 10H), 1.87–2.10 (m, 2H), 2.29–2.36 (m, 1H), 2.44–2.54 (m, 2H), 3.14 (m, 1H), 3.20–3.59 (m, 5H), 4.30 (t, J=6.8 Hz, 2H), 5.21 (s, 4H), 5.44 (s, 4H), 7.21–7.42 (m, 22H), 7.49 (s, 2H), 7.61 (dd, J=8.4, 5.4 Hz, 2H), 8.91 (dd, J=5.4, 1.3 Hz, 2H), 8.98 (dd, J=8.4, 1.3 Hz, 2H) [2 diastereomers due to protonation]; ^{13}C NMR (100.7 MHz, CD_3OD) δ 21.4 (CH_3), 21.9 (CH_2), 23.7 (CH_2), 25.2 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 27.7 (CH_2), 30.2 (CH), 34.4 (CH_2), 48.6 (CH_2), 53.1 (CH_2), 55.8 (CH_2), 59.7 (CH_2), 73.1 (2×CH_2), 76.8 (2×CH_2), 120.4 (2×CH), 120.6 (2×C_q), 121.7 (2×CH), 125.2 (2×C_q), 125.3 (2×CH), 128.7 (4×CH), 129.7 (4×CH), 129.9 (2×CH), 130.1 (4×CH+2×CH), 130.4 (4×CH), 133.0 (2×C_q), 135.3 (2×C_q), 136.1 (2×C_q), 137.2 (2×C_q), 137.6 (2×C_q), 146.0 (2×CH), 146.9 (2×CH), 155.1 (2×C_q) [only signals of the major diastereomer are given]; MS (FAB) m/z 941 [M^++H]; HRMS (FAB) calcd for $C_{63}H_{64}N_4O_4$ [M^+] 940.4928, found: 940.4930.

3.6.2. Tetra-*O*-benzylbisnorhalitulin tris-trifluoroacetate (24). Yield: 80–95%; TLC R_f=0.2 (EtOAc–hexanes, 3:1, v/v); HPLC R_t=58 min; UV λ_{max}(qual.): 263 nm (1.00), 341 (0.10), 412 (0.15); ^{1}H NMR (600 MHz, CD_3OD): δ 1.67–1.80 (m, 8H), 1.93–2.07 (m, 4H), 2.41–2.54 (m, 2H), 3.32–3.38 (m, 2H), 3.39–3.52 (m, 4H), 4.29 (t, J=7.0 Hz, 2H), 5.18 (s, 4H), 5.42 (s, 4H), 7.20–7.40 (m, 22H), 7.47 (s, 2H), 7.57 (dd, J=8.5, 5.4 Hz, 2H), 8.89 (dd, J=5.4, 1.4 Hz, 2H), 8.93 (dd, J=8.5, 1.4 Hz, 2H); ^{13}C NMR (151 MHz, CD_3OD): δ 23.2 (2×CH_2), 24.9 (2×CH_2), 25.5 (2×CH_2), 27.8 (CH_2), 48.4 (CH_2), 52.7 (2×CH_2), 55.5 (CH_2), 73.1 (2×CH_2), 76.8 (2×CH_2), 120.4 (2×CH), 120.8 (2×C_q), 121.6 (2×CH), 125.1 (2×C_q), 125.2 (2×CH), 128.7 (4×CH), 129.7 (4×CH), 129.9 (2×CH), 130.0 (2×CH), 130.1 (4×CH), 130.3 (4×CH), 132.9 (2×C_q), 135.7 (2×C_q), 136.7 (2×C_q), 137.2 (2×C_q), 137.7 (2×C_q), 146.2 (2×CH), 146.4 (2×CH), 154.9 (2×C_q); MS (ESI) m/z 913 [M^++H]; HRMS (ESI) calcd for $C_{61}H_{61}N_4O_4$ [M^++H] 913.4693, found 913.4708.

3.7. General procedure for benzyl deprotection by transfer hydrogenolysis

A solution of the relevant tetrabenzyl ether (10 mg,

0.01 mmol) in dry ethanol (5 mL) and TFA (0.1 mL) maintained under argon was treated with palladium on charcoal (5 mg, 10% Pd) and 1,4-cyclohexadiene (0.1 mL, 85 mg, 1.1 mmol). The resulting mixture was heated at reflux for 45 min then cooled to rt over 1 h. Filtration and removal of the solvents under reduced pressure gave the free quinolinediols as red oils and in good purity. Further purification was achieved by HPLC [solvent A: H_2O–CH_3CN (9:1)+0.05% TFA, solvent B: CH_3CN; gradient: start-10 min: 100% A, 50 min: 100% B, flow: 3 mL/min].

3.7.1. Bis-3,4-(7,8-dihydroxyquinolin-5-yl)pyrrole (22). Yield: 87%, red oil; UV λ_{max}(qual.): 205 nm (1.00), 252 (0.85), 360 (0.15); ^{1}H NMR (600 MHz, CD_3OD) δ 7.16 (s, 2H), 7.18 (s, 2H), 7.27 (dd, J=8.4, 4.8 Hz, 3-H, 2H), 8.59 (d, J=8.4 Hz, 4-H, 2H), 8.65 (d, J=4.8 Hz, 2-H, 2H); ^{13}C NMR (151 MHz, CD_3OD) δ 118.8 (2×CH), 120.8 (2×CH), 121.2 (2×C_q), 123.1 (2×CH), 124.3 (2×C_q), 128.3 (2×C_q), 135.3 (2×C_q), 136.3 (2×C_q), 142.0 (2×CH), 146.3 (2×CH), 147.0 (2×C_q); MS (EI) m/z (rel. int.): 386 (27, M^++H), 385 (100, M^+), 356 (12), 193 (3), 178 (5).

3.7.2. (*S*)-Halitulin tris-trifluoroacetate (1). Yield: >90%; orange–red oil, $[\alpha]_D$=−3.5 (c 0.25, MeOH); HPLC R_t=37 min; UV $\lambda_{max}(\varepsilon)$: 266 nm (67310), 351 (5070), 434 (7320); ^{1}H and ^{13}C NMR: see Table 1; MS (EI) m/z (rel. int.): 581 (12, M^++H), 580 (46, M^+), 424 (3), 399 (100), 398 (23), 385 (2), 235 (5), 169 (6), 168 (40), 152 (11), 126 (14), 124 (12), 110 (22), 98 (15), 91 (13), 86 (12), 82 (11), 70 (25), 58 (23), 55 (23); HRMS (EI) calcd for $C_{35}H_{40}N_4O_4$ [M^+] 580.3050, found 580.3052.

3.7.3. Bisnorhalitulin tris-trifluoroacetate (25). Yield: >90%, orange–red oil; HPLC R_t=37 min; UV λ_{max}(qual.): 264 nm (1.00), 336 (0.05), 423 (0.15); ^{1}H NMR (400 MHz, CD_3OD) δ 1.66–1.87 (m, 8H), 1.90–2.10 (m, 4H), 2.47–2.51 (m, 2H), 3.33–3.37 (m, 4H), 3.44–3.49 (m, 2H), 4.31 (t, J=7.0 Hz, 2H), 7.27 (s, 2H), 7.32 (s, 2H), 7.58 (dd, J=8.5, 5.6 Hz, 2H), 8.79 (dd, J=5.6, 1.5 Hz, 2H), 9.01 (dd, J=8.5, 1.5 Hz, 2H); ^{13}C NMR (151 MHz, CD_3OD): δ 23.2, 24.9, 25.5 (each 2×CH_2), 27.9, 48.3 (CH_2), 52.7 (2×CH_2), 55.6 (CH_2), 118.8 (2×CH), 120.9 (2×C_q), 124.3, 124.6 (each 2×CH), 124.8, 128.5, 132.3, 133.6 (each 2×C_q), 144.0 (2×CH), 146.8 (2×CH), 150.0 (2×C_q); MS (EI) m/z (rel. int.): 553 (19, M^++H), 552 (57, M^+), 400 (21), 399 (100), 398 (30), 371 (5), 276 (4), 140 (21); HRMS (EI) calcd for $C_{33}H_{36}N_4O_4$ [M^+] 552.2737, found 552.2719.

Acknowledgements

The authors are grateful to the Fonds der Chemischen Industrie and the Alexander von Humboldt foundation for financial support and to Mrs Sabine Voss and Ms Kathrin Hohnholt for skillful technical assistance.

References

1. Kashman, Y.; Koren-Goldshlager, G.; Garcia Gravalos, M. D.; Schleyer, M. *Tetrahedron Lett.* **1999**, *40*, 997–1000.
2. (a) Koren-Goldshlager, G.; Kashman, Y.; Schleyer, M. *J. Nat. Prod.* **1998**, *61*, 282–284. (b) Revision of structure: Heinrich, M. R.; Kashman, Y.; Spiteller, P.; Steglich, W. *Tetrahedron* **2001**, *57*, 9973–9978.
3. Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2001**, *42*, 3287–3289.
4. Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1347–1350.
5. Usuki, Y.; Hirakawa, H.; Goto, K.; Iio, H. *Tetrahedron: Asymmetry* **2001**, *12*, 3293–3296.
6. Fürstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373–6380.
7. Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1340–1343.
8. Heinrich, 8. M. R.; Steglich, W. *Tetrahedron* **2003**, *59*, 9231–9237.
9. Beckwith, A. L. J.; Meijs, G. F. *J. Org. Chem.* **1987**, *52*, 1922–1930.
10. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
11. Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168–9177.
12. Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888–2902.
13. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (b) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334–4344.
14. Syntheses of quinoline-7.8-diol: (a) Ohta, T.; Okuda, O. *J. Pharm. Soc., Jpn* **1951**, *71*, 784–786. (b) Ried, W.; Berg, A.; Schmidt, G. *Chem. Ber.* **1952**, *85*, 204–216. (c) Ohta, T.; Mori, Y.; Koike, K. *Chem. Ind.* **1957**, 1271. (d) 5-Bromo-7,8-dimethoxyquinoline: Trecourt, F.; Mallet, M.; Mongin, F.; Quéguiner, G. *Synthesis* **1995**, 1159–1162.
15. See, for example Dakin, H. D. *Am. Chem. J.* **1909**, *42*, 495.
16. (a) Shopova, M.; Vassileva, E.; Fugier, C.; Henry-Basch, E. *Synth. Commun.* **1997**, *27*, 1661–1667. (b) Horner, L.; Sturm, K. *Liebigs Ann. Chem.* **1957**, *608*, 128–139, and references cited therein.
17. Ogata, Y.; Kawasaki, A.; Suyama, S. *Tetrahedron* **1969**, *25*, 1361–1366.
18. With the corresponding triflate no coupling product could be obtained (see however Ref. 7).
19. Nakano, Y.; Imai, D. *Synthesis* **1997**, 1425–1428.
20. The tetraacetates were prepared by treatment of synthetic and natural halitulin, respectively, with Ac_2O, NEt_3 and cat. DMAP in dichloromethane. The resulting solutions were used directly for the $[\alpha]_D$ measurements.
21. Williams, D. E.; Craig, K. S.; Patrick, B.; Mc Hardy, L. M.; van Soest, R.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2002**, *67*, 245–258.