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Total Synthesis of Epohelmin B and Its Analogues

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

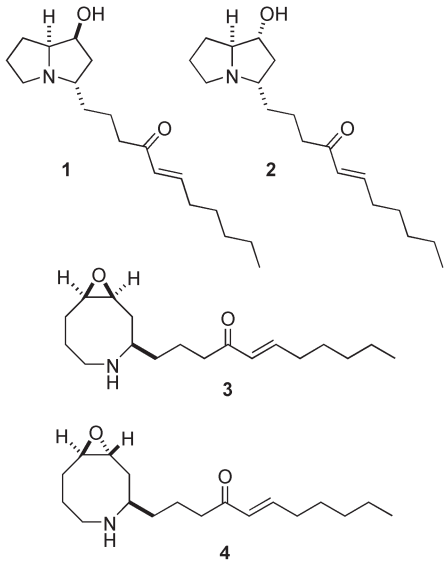
Abstract: A concise synthesis of the pyrrolizidine alkaloid epohelmin B (**1**) and a series of analogues is described. The key steps en route to this lanosterol synthase (oxidosqualene cyclase) inhibitor comprise a highly practical "azonia–Cope rearrangement", which sets the chiral amine center with excellent optical purity, a ring-closing metathesis (RCM) reaction catalyzed by a readily prepared and now also commercially available ruthenium–indenylidene complex, a manganese-catalyzed epoxidation of the resulting eight-membered cycloalkene derivative, and a nosyl-deprotection/transannular-epoxide-opening cascade to forge the pyrrolizidine core. Digression from the route leading to the natural product in the final stages allowed for the preparation of several "epohelmin-like" compounds with modified side chains, which is necessary for investigations into a possible functional relationship with other known lanosterol synthase inhibitors.

Keywords: alkaloids · epoxides · medium-ring compounds · metathesis · natural products

Introduction

Statins are a well-known class of compounds with pronounced inhibitory activity against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, and as such are currently the most successful of the clinically approved drugs used to control blood cholesterol level in humans. HMG-CoA reductase, however, acts in an early step of cholesterol biosynthesis; inhibition of this enzyme may, therefore, unintentionally affect the metabolism of other physiologically important non-sterol isoprenoids (e.g., ubiquinone, coenzyme Q, prenylated proteins).[1] In contrast, molecular targets in the pathway to cholesterol downstream of HMG-CoA reductase may allow improved selectivity in the treatment of cardiovascular diseases that result from hypercholesterolemia. Among them, lanosterol synthase (oxidosqualene cyclase, EC 5.4.99.7) appears particularly promising because higher organisms form the steroid nucleus exclusively by the cascade cyclization of 2,3-oxidosqualene catalyzed by this particular enzyme.[2] Selective inhibitors of lanosterol synthase may therefore qualify as anticholesteraemic drugs to complement or even substitute the now widely used members of the statin family.

In a search for natural products that may exert such function, Ebizuka and co-workers isolated two novel alkaloids from an unidentified fungus (strain FKI-0929), which inhibited recombinant lanosterol synthase with IC_{50} values of 10 and 6 μM. Called epohelmin A and B, the oxazabicyclo-[6.1.0]nonane structures **4** and **3**, respectively, were original-



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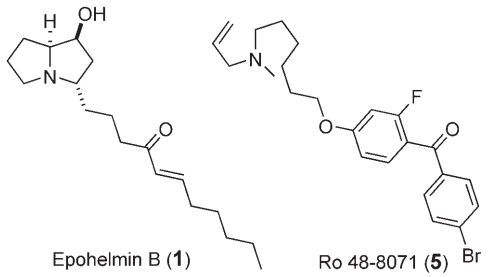
ly proposed to describe these secondary metabolites.[3] Subsequently, this assignment was questioned and totally revised by Snider and co-workers, who determined by an elegant synthesis that the epohelmins are in fact the pyrrolizidin-1-ol derivatives **2** and **1**, respectively.[4]

This structural issue notwithstanding, the epohelmins represent an interesting new lead in the quest for selective lanosterol synthase inhibitors. One may even see a certain relationship with some of the fully synthetic compounds known to affect the same enzyme target. Among them, Ro 48-8071 (**5**; Scheme 1) is particularly potent (IC_{50} ≈6.5 nM); it rivals simvastatin (Zocor) in its efficiency in reducing blood cholesterol levels in various animal models.[5–7] The basic nitrogen atom of **5** forms a charged hydrogen bond with Asp455 of human oxidosqualene cyclase, which is the decisive catalytic acid that triggers the cyclization of the natural substrate 2,3-oxidosqualene to the lanosterol skeleton. Equally important is the carbonyl group in **5**, which forms strong interactions with Ile338 through a water bridge supported by additional attractive forces between the adjacent electron-deficient arenes and the π-electron-rich binding pocket of the enzyme.[5,6] As one might expect, the distance between the amine nitrogen atom and the carbonyl group in **5** plays a vital role for effective binding.



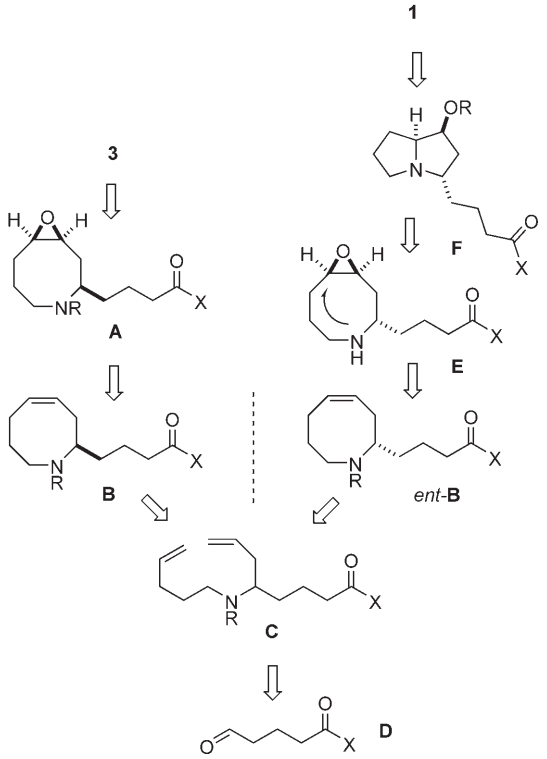
Scheme 1. Comparison of epohelmin B and and Ro 48-8071 (**5**), emphasizing the possible relationship between these lanosterol synthase inhibitors.

Although no biochemical or structural data are presently available, one might speculate about a possible functional relationship between the epohelmins and this benchmark synthetic inhibitor. As evident from Scheme 1, both compounds feature a basic nitrogen atom linked through a spacer of appropriate length to a carbonyl group flanked by a π system. Therefore, it may be worthwhile to investigate the mode of action of the epohelmins in more detail and to prepare analogues modeled around this putative "pharmacophore" model. To this end, we became interested in developing a concise and efficient access route to epohelmin B as the more potent of the two natural products, which should be flexible by design and accommodate substantial structural variations for future studies of structure–activity relationship. The results of the first round of investigations along these lines are summarized below.

Results and Discussion

Strategic Considerations

Our synthetic venture commenced before the constitution and stereochemistry of the epohelmins was corrected by Snider and co-workers.[4] Therefore, our initial target was the oxazabicyclononane **3**, which should be derived from olefin **B** by selective oxidation of the double bond (Scheme 2). This eight-membered cycloalkene could be accessible by ring-closing metathesis (RCM)[8,9] of an N-alkylated homoallylamine of type **C**, which, in turn, could originate from the simple carbonyl precursor **D** by suitable asymmetric allylation chemistry. The enone side chain of **3** can be conveniently installed in the final stage of the synthesis, which is advantageous in terms of structural modifications of this part of the molecule.



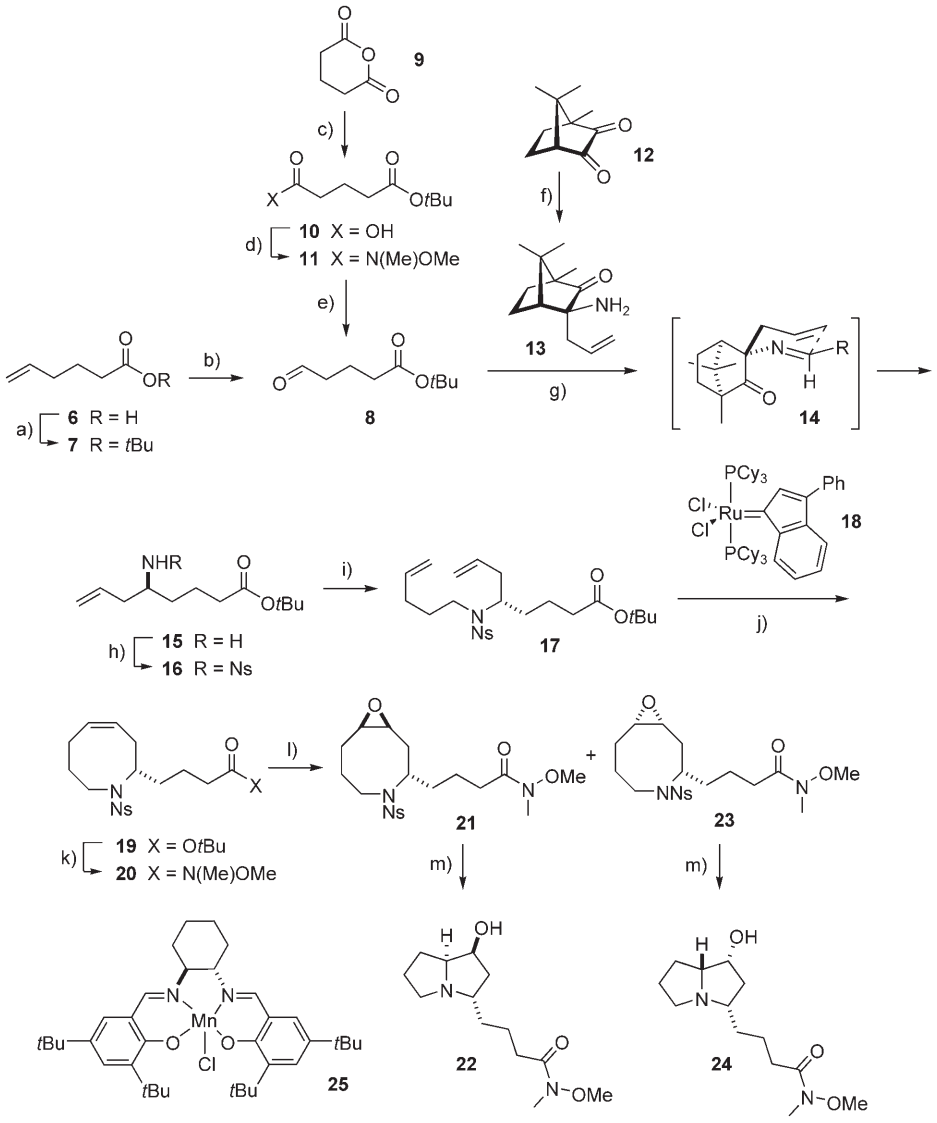
Scheme 2. Retrosynthetic analysis of the originally assigned (**3**) and the correct structure (**1**) of epohelmin B.

Gratifyingly, this original synthesis plan was flexible enough to accommodate the—at first sight—quite dramatic changes in the actual target structure implied by Snider's report.[4] Although the opposite enantiomer of **B** is needed owing to the concurrent misassignment of the configuration of the chiral center at C2 in the original isolation paper,[3] a straightforward transannular cyclization of **E** driven by release of the torsional strain inherent to the eight-membered ring should lead to the now required pyrrolizidine scaffold **F**, which can then be easily elaborated into the target.

Total Synthesis of Epohelmin B and Its Analogues

The required aldehyde component **8** can be prepared by converting commercially available 5-hexenoic acid (**6**) into the corresponding *tert*-butyl ester **7** followed by ozonolysis of the terminal alkene (Scheme 3). Although this method is fully satisfactory and high-yielding, 5-hexenoic acid is fairly expensive; therefore, the alternative route starting from cheap glutaric acid anhydride (**9**) is recommended for large-scale preparations.

Aldehyde **8** was then converted in a single operation into the required homoallylic amine **15** by application of the excellent "azonia–Cope rearrangement" methodology developed by Kobayashi and co-workers.[10] To this end, **8** was stirred with (1*S*)-(+)-camphorquinone-derived amine **13** in acidic medium at 0 °C overnight. Initial formation of imine **14** engendered a [3,3]-sigmatropic rearrangement, which set the new chiral center; hydrolytic workup released amine **15**, which was obtained in good chemical yield and with excellent optical purity (94 % *ee*) on the multigram scale. Amine **15** was then converted into the *N*-nosyl derivative **16** to ensure proper protection and concomitant activation toward N-alkylation.[11] In fact, treatment of **16** with 5-bromo-1-pentene and K_2CO_3 in DMF gave the expected diene **17** in high yield and set the stage for the subsequent formation of the medium-sized ring by RCM. This transformation was best effected with the aid of ruthenium indenylidene **18**,[12,13] which serves as a cheap, readily prepared, and now also commercially available substitute for the more common classical Grubbs catalyst $[(Ph_3P)_2Cl_2Ru{=}CHPh]$.[14] Although "second-generation" ruthenium carbene complexes endowed with an N-heterocyclic carbene as ancillary ligand reacted faster,[15] the use of **18** at ambient temperature consistently gave the best yields of the desired azacyclooctene derivative **19** (94 %). This result supports our earlier conclusion that complex **18** is particularly well-suited for the formation of medium rings, as was deduced from other applications to natural-product synthesis previously reported by our laboratory.[12,16]



Scheme 3. Synthesis of the pyrrolizidine nucleus **22** of epohelmin B and its stereoisomer **24**. Reaction conditions: a) *t*BuOH, *N*,*N*′-diisopropylcarbodiimide, DMAP (20 mol %), CH_2Cl_2, 73 %; b) O_3, CH_2Cl_2, −78 °C, then Me_2S, room temperature, 86 %; c) *t*BuOH, $ZnCl_2$ (2 mol %), 60 °C, 60 %; d) HN(OMe)Me·HCl, CDI, Et_3N, CH_2Cl_2, 84 %; e) $LiAlH_4$, Et_2O, 72 %; f) allylboronic acid pinacol ester, NH_3, MeOH, 80 % (*de* > 99 %), compare reference [10]; g) i) camphorsulfonic acid (10 mol %), 1,2-dichloroethane, 0 °C; ii) NH_2OH·HOAc, MeOH, 50 °C, 80 % (94 % *ee*); h) NsCl, K_2CO_3, CH_2Cl_2, 0 °C→room temperature, 84 %; i) 5-bromo-1-pentene, K_2CO_3, DMF, 60 °C, 95 %; j) **18** (10 mol %), CH_2Cl_2, room temperature, 94 %; k) i) trifluoroacetic acid, CH_2Cl_2; ii) HN(OMe)Me·HCl, Et_3N, DCC, DMAP (10 mol %), CH_2Cl_2, 96 %; l) see Table 1; m) $HSCH_2COOH$, LiOH, DMF, 96 % (**22**), 90 % (**24**), compare text. CDI = carbonyl diimidazole, Cy = cyclohexyl, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, Ns = *o*-nitrophenylsulfonyl.

To avoid any complications during the final elaboration of the enone side chain, the *tert*-butyl ester group of **19** was converted into the corresponding Weinreb amide **20** prior to oxidation of the double bond.[17] The structure of this compound in the solid state is depicted in Figure 1. Although

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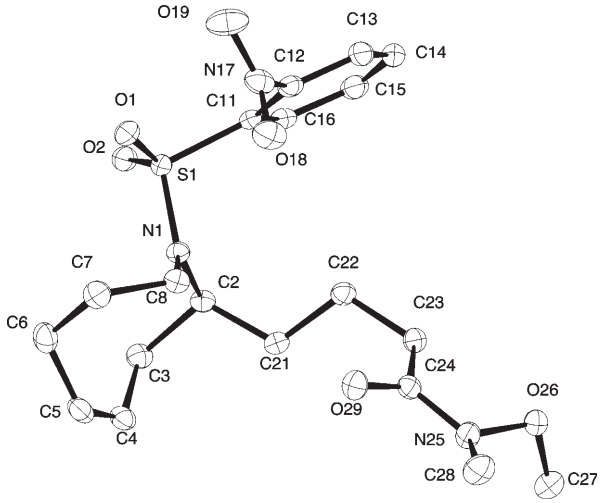


Figure 1. Molecular structure of compound **20** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

its conformation suggests that the β face of the olefin is more open and should therefore be preferentially attacked by an external oxidant, *meta*-chloroperbenzoic acid (*m*CPBA) as well as two different dioxiranes slightly favored the formation of epoxide **23** (Table 1).[18] Gratifyingly,

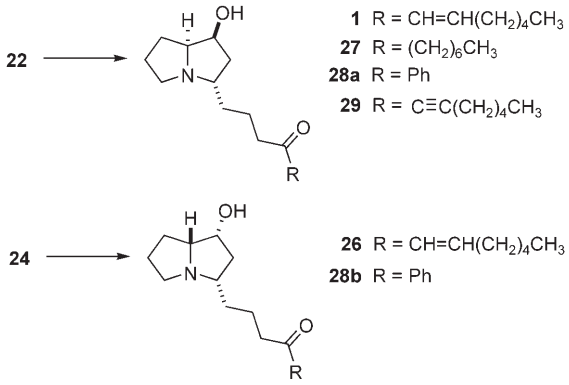
Table 1. Epoxidation of alkene **20** under different experimental conditions.

Entry	Oxidant	Solvent	*T* [°C]	Yield [%][a]	**21/23**
1	*m*CBPA	CH_2Cl_2	20	83	26:74
2	*m*CBPA	CH_2Cl_2	−30	82	30:70
3	dimethyldioxirane	acetone	20	93	27:73
4	oxone, hexafluoroacetone, $NaHCO_3$, Na–EDTA	MeCN	20	99	29:71
5	MeC(O)OOH, $Mn(OAc)_2\cdot 4H_2O$ (2%), ppei (5%)	MeCN	20	83	46:54
6	MeC(O)OOH, $Mn(OAc)_2\cdot 4H_2O$ (2%), ppei (5%)	MeCN/ CH_2Cl_2	−78	–[b]	51:49
7	*m*CBPA, salen **25** (50%), NMO	CH_2Cl_2	−78	n.d.	65:35
8	*m*CBPA, salen **25** (50%), NMO, $AgPF_6$ (50%)	CH_2Cl_2	−78	83	64:36

[a] Yield of isolated product, unless otherwise stated. [b] Complete conversion by HPLC. EDTA = ethylenediamine tetraacetate, n.d. = not determined, NMO = *N*-methylmorpholine-*N*-oxide, ppei = (pyridine-2-carbaldehyde)-1-phenylethylimine,[21] salen = *N*,*N*′-ethylenebis(salicylideneiminato).

however, this outcome could be rectified by recourse to metal-catalyzed oxidation. Among the various protocols tested, a modification of the low-temperature variant of the manganese–salen-catalyzed, *m*CPBA-mediated epoxidation reported by Jacobsen and co-workers was the best compromise between yield, selectivity, and practicality.[19] In contrast to the literature procedure, however, the precatalyst **25** had to be ionized in situ with $AgPF_6$ to reach full conversion at −78°C; neutral **25** itself was found to be insufficiently active.[20] Interestingly, the stereochemical course of the reaction remains substrate-controlled as either enantiomer of **25** as well as *rac*-**25** led to exactly the same product distribution.

The isomeric epoxides **21** and **23** were not readily separable at this stage; therefore, they were carried through as a mixture until the last step of the sequence, in which routine chromatography sufficed to obtain the individual products in analytically pure form. To this end, it was necessary to remove the nosyl group[11] from the endocyclic nitrogen atom without affecting the somewhat labile oxirane to trigger the envisaged transannular cyclization. After some experimentation, it was found that treatment of **21/23** with thioglycolic acid and powdered LiOH in anhydrous DMF at ambient temperature served this purpose well. Under these conditions, a fully chemoselective cleavage of the *N*-Ns substituent was reached without any noticeable attack of the thiol on the epoxide moiety; gratifyingly though, the basic nitrogen atom, once released from the sulfonamide precursor, engaged in a spontaneous and essentially quantitative opening of the oxirane held in transannular proximity[18] to provide the required pyrrolizidine nucleus **22** of epohelmin B and its stereoisomer **24** in excellent yield. As the latter compound turned out to be highly sensitive and rapidly decomposed during flash chromatography on silica gel,[22] the crude material was engaged in the final step of the sequence without delay to instal the enone moiety of the natural product (Scheme 4). This was achieved upon treatment



Scheme 4. Final step in the preparation of epohelmin B and its analogues. Reaction conditions: 1-Iodo-1-heptene, *t*BuLi (>3 equiv), THF, −78→−40°C, 78% (**1**, over two steps), 65% (**26**, over two steps); or: heptylmagnesium bromide, THF, 0°C→room temperature, 60% (**27**, over two steps); or: PhMgBr, THF, −20°C→room temperature, 68% (**28a**, over two steps), 60% (**28b**, over two steps); or: 1-heptynyllithium, THF, −78→−20°C, 65% (**29**, over two steps).

of the crude mixture of Weinreb amides **22** and **24** with an excess of 1-lithio-1-heptene generated from 1-iodo-1-heptene and *t*BuLi in THF at low temperature immediately prior to use. As mentioned above, the resulting products could be separated and purified by flash chromatography. Alternatively, epoxides **21** and **23** can be separated by preparative HPLC and processed individually to give the final products as described. In any case, the analytical and spectroscopic data of the synthetic samples of epohelmin B (free

base; **1**) thus formed are in excellent agreement with those of the natural product reported in the literature.[3,4] Likewise, all data of the accompanying product *epi*-epohelmin A (**26**) are in full accord with the proposed structure.

The effectiveness of the end game, which requires a single chromatographic separation over the last three synthetic operations, was demonstrated by the preparation of a small collection of "epohelmin-like" compounds, which differ from the natural product in their lateral chains (Scheme 4). The isomeric phenyl derivatives **28a/b** were inspired by the possible functional analogy to Ro 48-8071 (**5**), whereas the need for any π system within the pharmacophore can be probed with the saturated analogues **27**. To complete the overview of the correlation between the oxidation state and lanosterol synthase inhibitory activity, the alkynylogous epohelmin analogue **29** was also prepared. All compounds of this series were obtained in respectable yields upon reaction of the required organolithium or -magnesium reagent with Weinreb amides **22** and **24** as described above. This set of epohelmin-type pyrrolizidines should allow us to gain first insight into pertinent structure–activity relationships in this series and to establish or disprove any functional relationship with Ro 48-8071 (**5**), which represents the standard in this field. Investigations along these lines are underway and will be reported in due course.

Conclusions

A concise, productive, and largely reagent-controlled total synthesis of the lanosterol synthase inhibitor epohelmin B and its analogues was established. The synthesis comprises no more than 11 steps in the longest linear sequence and provides an overall yield of 28%. The key operations consist of an "azonia–Cope rearrangement" to set the chiral amine center with high optical purity, a ring-closing metathesis reaction catalyzed by the readily available ruthenium indenylidene complex **18**, and a strain-driven N-deprotection/transannular cyclization cascade. Due to the flexibility inherent in this route, a systematic structural editing of the natural product should be possible. As a first step along this line, an assortment of "epohelmin-like" compounds with modified side chains was produced that will be used for biochemical investigations and a first round of structure–activity profiling of these alkaloids.[23]

Experimental Section

General

All reactions were carried out in flame-dried glassware under Ar. The solvents used were purified by distillation over the drying agents indicated in parentheses and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2 (P_4O_{10}), 1,2-dichloroethane (P_4O_{10}), MeCN, Et_3N (CaH_2), MeOH (Mg), DMF (Desmodur, dibutyltin dilaurate), hexanes, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a Bruker DPX 300, AMX 300, AV 400, or DMX 600 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS), coupling constants (J) are in Hz. The solvent signals were used as references ($CDCl_3$: $\delta_C = 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H = 7.26$ ppm; CD_2Cl_2: $\delta_C = 53.1$ ppm; residual $CDHCl_2$ in CD_2Cl_2: $\delta_H = 5.32$ ppm). IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) are in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV) spectrometer; MS (ESI): Finnigan MAT 95 spectrometer; accurate mass determinations: Bruker APEX III FT-MS (7-T magnet) spectrometer. Melting points: Büchi B-540 melting-point apparatus (corrected). Elemental analysis: performed by H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich, Acros) were used as received.

Syntheses

10:[24] A suspension of glutaric acid anhydride (**9**; 57.00 g, 0.50 mol) and $ZnCl_2$ (1.00 g, 0.01 mol) in *tert*-butanol (284 mL, 3.00 mol) was stirred at 60 °C for 9 days. For workup, NaOH (0.5 M, 400 mL) was added, and stirring continued at ambient temperature for 30 min. The aqueous phase was extracted with *tert*-butyl methyl ether (4×400 mL), and the combined organic layers were washed with water (3×500 mL), dried over Na_2SO_4, filtered, and evaporated to give 5-*tert*-butoxy-5-oxopentanoic acid (**10**; 56.47 g, 60%) as a pale-yellow oil. The crude product contained about 15% of the di-*tert*-butyl ester and was used in the next step without any further purification. An analytically pure sample of **10** was obtained by flash chromatography (hexanes/EtOAc = 2:1). IR (film): $\tilde{\nu}$ = 2979, 2936, 2673, 1729, 1711, 1479, 1456, 1417, 1393, 1368, 1320, 1289, 1254, 1151, 1056, 1005, 954, 937, 845, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (t, J = 7.3 Hz, 2H), 2.30 (t, J = 7.3 Hz, 2H), 1.91 (quint, J = 7.3 Hz, 2H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9 (C), 172.3 (C), 80.5 (C), 34.5 (CH_2), 33.0 (CH_2), 28.1 (CH_3), 20.0 ppm (CH_2); MS (EI): m/z (%) = 133 (10), 115 (70), 87 (26), 59 (7), 57 (100), 56 (17), 55 (7), 45 (11), 43 (19), 42 (11), 41 (31), 29 (15); HRMS (ESI): m/z calcd for $C_9H_{16}O_4$ + H: 189.1127; found: 189.1125.

11: Carbonyl diimidazole (40.55 g, 250.10 mmol) was added to a solution of **10** (≈85%, 36.21 g, 192.40 mmol) in CH_2Cl_2 (930 mL) at 0 °C. The ice bath was removed, and the mixture was stirred for 10 min at ambient temperature. The resulting colorless solution was cooled to 0 °C before Et_3N (62.2 mL, 250.10 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (25.15 g, 250.10 mmol) were introduced. The mixture was then stirred for 14 h at ambient temperature before it was diluted with CH_2Cl_2 (500 mL). The organic phase was washed with HCl (1 M, 600 mL) and saturated aqueous $NaHCO_3$ (500 mL), dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc = 2:1) to give *tert*-butyl 5-(methoxy(methyl)amino)-5-oxopentanoate (**11**; 44.50 g, 84%) as a colorless liquid. IR (film): $\tilde{\nu}$ = 2977, 2938, 1728, 1668, 1459, 1417, 1389, 1367, 1317, 1254, 1229, 1151, 1108, 995, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H), 3.18 (s, 3H), 2.47 (t, J = 7.3 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 1.97–1.88 (m, 2H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (C), 172.6 (C), 80.2 (C), 61.2 (CH_3), 34.9 (CH_2), 32.2 (CH_3), 30.9 (CH_2), 28.1 (CH_3), 20.1 ppm (CH_2); MS (EI): m/z (%) = 171 (21), 158 (58), 130 (16), 115 (100), 87 (32), 61 (52), 57 (98), 55 (15), 43 (15), 42 (22), 41 (29), 29 (14); HRMS (ESI): m/z calcd for $C_{11}H_{21}NO_4$ + Na: 254.1363; found: 254.1363.

8:[24] $LiAlH_4$ (3.80 g, 100.0 mmol) was added in small portions to a vigorously stirred solution of **11** (18.50 g, 80.0 mmol) in Et_2O (200 mL), and the resulting mixture was stirred for 60 min. After the mixture was cooled to 0 °C, the suspension was hydrolyzed by dropwise addition of aqueous $KHSO_4$ (20% *w/w*, 100 mL). The mixture was diluted with Et_2O (50 mL), the aqueous phase was repeatedly extracted with Et_2O (3×50 mL), and the combined organic layers were consecutively washed with HCl (3 M, 3×50 mL), saturated aqueous $KHCO_3$ (3×50 mL), and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by distillation (b.p. 92–93 °C, 6 mbar) to give *tert*-butyl 5-oxopentanoate (**8**; 9.92 g, 72%) as a colorless liquid. IR (film): $\tilde{\nu}$ = 3111, 2978, 2937, 2722, 1728, 1479, 1457, 1418, 1393, 1368, 1319, 1255, 1152, 1076, 1055, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.78 (t, J = 1.4 Hz, 1H), 2.51 (dt, J = 7.2, 1.4 Hz, 2H), 2.28 (t, J = 7.3 Hz, 2H), 1.98–1.85 (m, 2H), 1.45 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.7 (CH), 172.2 (C), 80.5 (C), 43.0 (CH_2), 34.4 (CH_2), 28.1 (CH_3), 17.5 ppm (CH_2); MS (EI):

m/*z* (%) = 117 (10), 116 (11), 99 (54), 71 (26), 57 (100), 56 (12), 55 (10), 43 (18), 42 (10), 41 (33), 29 (18), 27 (8). HRMS (ESI): *m*/*z* calcd for $C_9H_{16}O_3$+H: 173.1178; found: 173.1176.

15: (±)-Camphorsulfonic acid (0.30 g, 1.63 mmol) was added to a solution of **13** (3.37 g, 16.27 mmol) and **8** (2.90 g, 16.27 mmol) in 1,2-dichloroethane (34 mL) at 0 °C, and the resulting mixture was stirred for 24 h at this temperature. A solution of $HONH_2$·AcOH (0.5 M, prepared from $HONH_2$·HCl (2.36 g, 34.0 mmol), NaOH (solid, 1.36 g, 34.0 mol), and AcOH (1.96 mL, 34.0 mmol) in MeOH (68 mL)) was added, and the mixture was stirred at 50 °C for 1.5 h. For workup, the solvent was evaporated, and the remaining supernatant oil was decanted from the solid, which was extracted with hexanes (3×20 mL). The organic phases were evaporated, the residue was combined with the supernatant oil, and the resulting crude material was purified by flash chromatography (CH_2Cl_2/MeOH = 20:1 + 2% *v*/*v* NEt_3) to give (−)-(*S*)-*tert*-butyl 5-amino-oct-7-enoate (**15**; 2.78 g, 80%, 94% *ee*, determined at the stage of **17**) as a colorless liquid. $[\alpha]_D^{20} = -7.3$ (*c* = 1.0, CH_2Cl_2); IR (film): $\tilde{\nu}$ = 3075, 3003, 2977, 2931, 2871, 1729, 1640, 1457, 1392, 1367, 1256, 1154, 914, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.84–5.71 (m, 1H), 5.13–5.04 (m, 2H), 2.79 (tt, *J* = 7.8, 4.9 Hz, 1H), 2.28–2.21 (m, 1H), 2.22 (t, *J* = 7.4 Hz, 2H), 2.05–1.95 (m, 1H), 1.75–1.55 (m, 4H), 1.50–1.38 (m, 1H), 1.43 (s, 9H), 1.36–1.25 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (C), 135.5 (CH), 117.5 (CH_2), 80.1 (C), 50.4 (CH), 42.3 (CH_2), 36.8 (CH_2), 35.5 (CH_2), 28.1 (CH_3), 21.7 ppm (CH_2); MS (EI): *m*/*z* (%) = 172 (12), 140 (16), 117 (6), 116 (100), 98 (59), 70 (25), 57 (27), 56 (18), 55 (24), 43 (14), 41 (16), 29 (7); HRMS (ESI): *m*/*z* calcd for $C_{12}H_{23}NO_2$+Na: 236.1621; found: 236.1622; elemental analysis: calcd (%) for $C_{12}H_{23}NO_2$ (213.32): C 67.57, H 10.87, N 6.57; found: C 67.50, H 10.78, N 6.52.

16: 2-Nitrobenzene sulfonyl chloride (4.79 g, 21.60 mmol) was added to a stirred supension of **15** (2.30 g, 10.80 mmol) and K_2CO_3 (5.97 g, 43.20 mmol) in CH_2Cl_2 (85 mL) at 0 °C. Stirring was continued for 14 h at ambient temperature before the mixture was diluted with CH_2Cl_2 (80 mL) and water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3×80 mL), the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2→CH_2Cl_2/MeOH = 20:1) to give (−)-(*S*)-*tert*-butyl 5-(2-nitrophenylsulfonamido)oct-7-enoate (**16**; 3.61 g, 84%) as a colorless oil. $[\alpha]_D^{20} = -65.1$ (*c* = 1.03, CH_2Cl_2); IR (film): $\tilde{\nu}$ = 3337, 3002, 2978, 2933, 1724, 1542, 1442, 1420, 1392, 1366, 1300, 1256, 1166, 1126, 1087, 1061, 998, 921, 854, 784, 742, 731, 655, 597, 568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.11 (m, 1H), 7.88–7.83 (m, 1H), 7.76–7.68 (m, 2H), 5.64–5.55 (m, 1H), 5.25 (d, *J* = 8.1 Hz, 1H), 5.00–4.88 (m, 2H), 3.60–3.45 (m, 1H), 2.24–2.12 (m, 4H), 1.70–1.43 (m, 4H), 1.42 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (C), 147.7 (C), 135.2 (C), 133.3 (CH), 132.8 (CH), 132.7 (CH), 130.4 (CH), 125.3 (CH), 119.0 (CH_2), 80.3 (C), 54.7 (CH), 39.3 (CH_2), 34.9 (CH_2), 34.2 (CH_2), 28.1 (CH_3), 21.0 ppm (CH_2); MS (EI): *m*/*z* (%) = 325 (21), 302 (12), 301 (90), 284 (9), 283 (67), 255 (7), 241 (7), 187 (8), 186 (100), 57 (33), 55 (12), 41 (11); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}N_2O_6S$+Na: 421.1404; found: 421.1408; elemental analysis: calcd (%) for $C_{18}H_{26}N_2O_6S$ (398.47): C 54.26, H 6.58, N 7.03; found: C 54.34, H 6.52, N 6.96.

17: 5-Bromo-1-pentene (2.30 mL, 22.60 mmol) was added to a suspension of **16** (3.00 g, 7.54 mmol) and K_2CO_3 (5.21 g, 67.6 mmol) in DMF (65 mL), and the resulting mixture was stirred for 2 h at 60 °C. For workup, the DMF was distilled off under reduced pressure, the residue was dissolved in CH_2Cl_2 (80 mL), the resulting organic phase was washed with brine (30 mL), dried (Na_2SO_4), and evaporated, and the crude product was purified by flash chromatography (hexanes/EtOAc = 6:1) to give (+)-(*S*)-*tert*-butyl 5-(2-nitro-*N*-(pent-4-enyl)phenylsulfonamido)oct-7-enoate (**17**; 3.35 g, 95%, 94% *ee*) as a pale-yellow syrup (*ee* determined by HPLC: 250 mm Chiracel OD-H: $t_r(S)$ = 19.7 min (97.2%), $t_r(R)$ = 21.7 min (2.8%), *n*-heptane/2-propanol = 95:5, 0.5 mL min^{-1}, *p* = 2.3 MPa, *T* = 298 K). $[\alpha]_D^{20} = +3.4$ (*c* = 1.00, CH_2Cl_2); IR (film): $\tilde{\nu}$ = 2978, 2934, 1725, 1546, 1371, 1350, 1256, 1160, 1126, 918, 852, 747, 588, 566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.99 (m, 1H), 7.70–7.62 (m, 2H), 7.59–7.53 (m, 1H), 5.78 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.61 (ddt, *J* = 17.2, 10.0, 7.1 Hz, 1H), 5.08–4.85 (m, 4H), 3.84–3.72 (m, 1H), 3.32–3.13 (m, 2H), 2.30–2.18 (m, 2H), 2.15 (t, *J* = 6.4 Hz, 2H), 2.07 (q, *J* = 7.3 Hz, 2H), 1.87–1.66 (m, 2H), 1.66–1.40 (m, 4H), 1.42 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C), 148.0 (C), 137.3 (CH), 134.5 (CH), 133.9 (C), 133.3 (CH), 131.3 (CH), 131.1 (CH), 123.9 (CH), 117.6 (CH_2), 115.4 (CH_2), 80.2 (C), 58.4 (CH), 43.7 (CH_2), 38.7 (CH_2), 35.1 (CH_2), 32.5 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 28.1 (CH_3), 22.0 ppm (CH_2); MS (EI): *m*/*z* (%) = 393 (12), 371 (7), 370 (19), 369 (100), 309 (9), 186 (30), 183 (6), 83 (9), 69 (7), 57 (13), 55 (8), 41 (13); HRMS (ESI): *m*/*z* calcd for $C_{23}H_{34}N_2O_6S$+Na: 489.2030; found: 489.2036; elemental analysis: calcd (%) for $C_{23}H_{34}N_2O_6S$ (466.59): C 59.21, H 7.34, N 6.00; found: C 59.16, H 7.31; N 6.08.

19: A solution of **18** (0.59 g, 0.64 mmol) and **17** (3.00 g, 6.44 mmol) in CH_2Cl_2 (270 mL) was stirred at ambient temperature for 1 h. For workup, the solvent was evaporated, and the residue was purified by flash chromatography (hexanes→hexanes/EtOAc = 6:1) to afford (+)-(*S*,*Z*)-*tert*-butyl 4-(1-(2-nitrophenylsulfonyl)-1,2,3,6,7,8-hexahydroazocin-2-yl)butanoate (**19**; 2.67 g, 94%, 93% *ee*) as a syrup (*ee* determined by HPLC: 250 mm Chiracel OD-H: $t_R(S)$ = 20.2 min (96.4%), $t_R(R)$ = 22.2 min (3.6%), *n*-heptane/2-propanol = 90:10, 0.5 mL min^{-1}, *p* = 2.3 MPa, *T* = 298 K). $[\alpha]_D^{20} = +148.2$ (*c* = 1.40, CH_2Cl_2); IR (film): $\tilde{\nu}$ = 2975, 2935, 1725, 1545, 1371, 1345, 1159, 1126, 852, 746, 593, 581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.01 (m, 1H), 7.69–7.63 (m, 2H), 7.58–7.52 (m, 1H), 5.82–5.63 (m, 2H), 3.96 (dq, *J* = 6.8, 3.7 Hz, 1H), 3.67 (ddd, *J* = 15.3, 4.3, 1.5 Hz, 1H), 2.93 (ddd, *J* = 15.8, 12.4, 3.8 Hz, 1H), 2.56 (ddd, *J* = 13.8, 7.4, 3.5 Hz, 1H), 2.36–2.24 (m, 1H), 2.21–1.95 (m, 5H), 1.59–1.13 (m, 5H), 1.39 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C), 148.0 (C), 133.9 (C), 133.2 (CH), 132.8 (CH), 131.3 (CH), 131.1 (CH), 126.7 (CH), 123.8 (CH), 80.2 (C), 58.0 (CH), 42.1 (CH_2), 35.1 (CH_2), 31.2 (CH_2), 30.9 (CH_2), 30.6 (CH_2), 28.0 (CH_3), 23.7 (CH_2), 21.7 ppm (CH_2); MS (EI): *m*/*z* (%) = 365 (24), 315 (17), 296 (16), 295 (100), 282 (16), 252 (22), 196 (27), 186 (30), 109 (13), 81 (16), 57 (19), 41 (9); HRMS (ESI): *m*/*z* calcd for $C_{21}H_{30}N_2O_6S$+Na: 461.1717; found: 461.1719; elemental analysis: calcd (%) for $C_{21}H_{30}N_2O_6S$ (438.54): C 57.51, H 6.90, N 6.39; found: C 57.41, H 6.83, N 6.31.

19a (X = OH): A solution of **19** (3.71 g, 8.43 mmol) in CH_2Cl_2 (84 mL) and trifluoroacetic acid (13.0 mL, 168.60 mmol) was stirred for 1 h before toluene (80 mL) was added, and all volatile materials were removed under reduced pressure. The residue was dissolved in toluene (2×80 mL), which was evaporated to remove traces of the acid azeotropically. The crude product was dried in high vacuum to afford (+)-(*S*,*Z*)-4-(1-(2-nitrophenylsulfonyl)-1,2,3,6,7,8-hexahydroazocin-2-yl)butanoic acid (**19a**; 3.24 g, quant.) as a colorless syrup. $[\alpha]_D^{20} = +99.5$ (*c* = 0.42, CH_2Cl_2); IR (film): $\tilde{\nu}$ = 3094, 3022, 2938, 2863, 1707, 1544, 1463, 1438, 1411, 1374, 1343, 1298, 1267, 1236, 1202, 1161, 1126, 1002, 984, 852, 777, 745, 732, 653, 633, 595, 580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.18 (br s, 1H), 8.07–8.00 (m, 1H), 7.71–7.62 (m, 2H), 7.59–7.51 (m, 1H), 5.82–5.62 (m, 2H), 4.03–3.92 (m, 1H), 3.69 (dd, *J* = 15.3, 2.5, 1H), 2.93 (ddd, *J* = 15.4, 12.2, 3.2 Hz, 1H), 2.61–2.49 (m, 1H), 2.39–1.98 (m, 6H), 1.62–1.14 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9 (C), 147.9 (C), 133.8 (C), 133.4 (CH), 132.9 (CH), 131.3 (CH), 131.0 (CH), 126.6 (CH), 123.9 (CH), 57.8 (CH), 42.1 (CH_2), 33.4 (CH_2), 31.2 (CH_2), 30.8 (CH_2), 30.4 (CH_2), 23.7 (CH_2), 21.1 ppm (CH_2); MS (EI): *m*/*z* (%) = 315 (15), 295 (100), 282 (15), 212 (9), 196 (20), 186 (40), 109 (19), 108 (9), 81 (25), 55 (12), 54 (12), 41 (12); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{22}N_2O_6S$+Na: 405.1091; found: 405.1092; elemental analysis: calcd (%) for $C_{17}H_{22}N_2O_6S$ (382.43): C 53.39, H 5.80, N 7.30; found: C 53.46, H 5.75, N 7.27.

20: A solution containing **19a** (600 mg, 1.56 mmol), DMAP (0.209 g, 1.70 mmol), *N*,*N*′-dicyclohexylcarbodiimide (351 mg, 1.70 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (161 mg, 1.65 mmol) in CH_2Cl_2 (15 mL) was stirred at ambient temperature for 2 h. The suspension was diluted with EtOAc (30 mL), and the mixture was stirred for 5 min before stirring was stopped to allow *N*,*N*′-dicyclohexylurea to crystallize over a period of about 30 min. The precipitate was filtered off through a small pad of celite, the filtrate was evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc = 1:1→1:2) to give (+)-(*S*,*Z*)-*N*-methoxy-*N*-methyl-4-(1-(2-nitrophenylsulfonyl)-1,2,3,6,7,8-hexahydroazocin-2-yl)butanamide (**20**; 642 mg, 96%) as a colorless solid. Recrystallization from CH_2Cl_2/*n*-heptane afforded colorless

crystals suitable for X-ray structure analysis. $[\alpha]_D^{20} = +133.7$ ($c = 1.04$, CH_2Cl_2); m.p.: 88–89 °C; IR (KBr): $\tilde{\nu} = 2933$, 1655, 1628, 1539, 1463, 1437, 1374, 1335, 1161, 1125, 1093, 1064, 1026, 999, 971, 902, 787, 770, 749, 732, 654, 634, 581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.06$–8.00 (m, 1H), 7.68–7.62 (m, 2H), 7.57–7.50 (m, 1H), 5.80–5.61 (m, 2H), 3.98 (dq, $J = 6.6$, 3.7 Hz, 1H), 3.68 (ddd, $J = 15.4$, 4.3, 1.7 Hz, 1H), 3.62 (s, 3H), 3.11 (s, 3H), 2.96 (ddd, $J = 15.7$, 12.3, 3.8 Hz, 1H), 2.55 (ddd, $J = 13.8$, 7.2, 3.6 Hz, 1H), 2.36–1.98 (m, 5H), 1.70–1.21 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.8$ (C), 148.0 (C), 133.9 (C), 133.2 (CH), 132.7 (CH), 131.3 (CH), 131.1 (CH), 126.8 (CH), 123.7 (CH), 61.1 (CH_3), 58.1 (CH), 42.1 (CH_2), 32.2 (CH_3), 31.4 (CH_2), 31.22 (CH_2), 31.18 (CH_2), 30.5 (CH_2), 23.8 (CH_2), 20.9 ppm (CH_2); MS (EI): m/z (%) = 365 (23), 295 (15), 240 (15), 239 (100), 186 (38), 179 (9), 178 (28), 136 (19), 110 (8), 109 (8), 81 (13), 55 (15); HRMS (ESI): m/z calcd for $C_{19}H_{27}N_3O_6S$: 448.1513; found: 448.1514; elemental analysis: calcd (%) for $C_{19}H_{27}N_3O_6S$ (425.50): C 53.63, H 6.40, N 9.88; found: C 53.60, H 6.42, N 9.81.

21 and **23**: Method A: A suspension of **25** (148 mg, 0.24 mmol) and $AgSbF_6$ (61 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was stirred for 10 min at ambient temperature before **20** (200 mg, 0.47 mmol) and NMO (551 mg, 4.70 mmol) were added. The resulting yellow-brown suspension was cooled to −78 °C, and *m*CPBA (324 mg, 1.88 mmol) was introduced in small portions. The mixture was stirred for 2 h at −78 °C before it was allowed to reach ambient temperature. Evaporation of the solvent followed by purification of the brown residue by flash chromatography (EtOAc) yielded a mixture of (+)-*N*-methoxy-*N*-methyl-4-((1*S*,3*S*,8*R*)-4-(2-nitrophenylsulfonyl)-9-oxa-4-azabicyclo[6.1.0]nonan-3-yl)butanamide (**21**) and (+)-*N*-methoxy-*N*-methyl-4-((1*R*,3*S*,8*S*)-4-(2-nitrophenylsulfonyl)-9-oxa-4-azabicyclo[6.1.0]nonan-3-yl)butanamide (**23**) as a colorless syrup (173 mg, 83%). The diastereomer ratio (d.r. = 64:36) was determined by HPLC: t_r(**23**) = 41.8 min, t_r(**21**) = 44.6 min; 125 mm YMC Pro C18, 120 A, 2.1 mm; MeCN/water (25:75); 0.2 mL min^{-1}; $T = 308$ K, $p = 6.3$ MPa.

Method B: *m*CPBA (77% *w/w*, 1.686 g, 7.52 mmol) was added to a solution of **20** (0.800 g, 1.88 mmol) in CH_2Cl_2 (24 mL) at 0 °C. The ice bath was removed, and the mixture was stirred for 0.5 h at ambient temperature. For workup, the suspension was diluted with CH_2Cl_2 (25 mL) and successively washed with $NaHSO_3$ (2 M, 15 mL) and aqueous $NaHCO_3$ (10% *w/w*, 15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (EtOAc) to give a mixture of **21** and **23** as a colorless syrup (0.688 g, 83%, d.r. = 26:74). The diastereomers were separated by preparative HPLC (Shimadzu LC-8A, Nucleodur 100-10-C18A, NW 50, 198 × 48 mm, 06/01; MeCN/water (30:70); 35.0 mL min^{-1}; $T = 308$ K, $p = 2.8$ MPa). **21**: $[\alpha]_D^{20} = +116.2$ ($c = 0.59$, CH_2Cl_2); IR (film): $\tilde{\nu} = 2928$, 1658, 1544, 1462, 1441, 1416, 1375, 1343, 1165, 1124, 1065, 992, 778, 745, 730, 580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$–8.01 (m, 1H), 7.73–7.63 (m, 2H), 7.62–7.54 (m, 1H), 4.09–3.97 (m, 1H), 3.82 (dd, $J = 15.5$, 5.2 Hz, 1H), 3.63 (s, 3H), 3.24 (ddd, $J = 15.7$, 13.1, 4.3 Hz, 1H), 3.14–3.05 (m, 1H), 3.12 (s, 3H), 2.91 (dt, $J = 10.9$, 3.9 Hz, 1H), 2.46–2.04 (m, 5H), 1.79 (ddd, $J = 14.8$, 10.0, 3.2 Hz, 1H), 1.71–1.58 (m, 2H), 1.56–1.35 (m, 2H), 1.35–1.16 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.5$ (C), 148.0 (C), 133.5 (CH), 133.4 (C), 131.4 (CH), 131.1 (CH), 124.1 (CH), 61.2 (CH_3), 55.4 (CH), 55.0 (CH), 51.4 (CH), 41.9 (CH_2), 33.1 (CH_2), 32.2 (CH_3), 31.1 (CH_2), 29.9 (CH_2), 25.0 (CH_2), 22.9 (CH_2), 20.9 ppm (CH_2); MS (EI): m/z (%) = 381 (24), 311 (26), 256 (11), 255 (72), 194 (29), 186 (100), 139 (11), 96 (12), 81 (20), 61 (11), 55 (30), 41 (18); HRMS (ESI): m/z calcd for $C_{19}H_{27}N_3O_7S$+Na: 464.1462; found: 464.1461; elemental analysis: calcd (%) for $C_{19}H_{27}N_3O_7S$ (441.50): C 51.69, H 6.16, N 9.52; found: C 51.62, H 6.12, N 9.46.

23: $[\alpha]_D^{20} = +130.9$ ($c = 1.47$, CH_2Cl_2); IR (film): $\tilde{\nu} = 2938$, 1658, 1545, 1465, 1439, 1417, 1374, 1344, 1163, 1126, 1110, 989, 852, 780, 765, 745, 745, 729, 593, 569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.09$–8.02 (m, 1H), 7.72–7.64 (m, 2H), 7.59–7.52 (m, 1H), 4.11–4.01 (m, 1H), 3.92–3.82 (m, 1H), 3.61 (s, 3H), 3.10 (s, 3H), 3.09–3.04 (m, 1H), 2.99 (dt, $J = 9.4$, 4.6 Hz, 1H), 2.90–2.79 (m, 1H), 2.38 (dt, $J = 14.1$, 4.1 Hz, 1H), 2.33–2.16 (m, 3H), 2.04 (br q, $J = 13.8$ Hz, 1H), 1.71–1.60 (m, 1H), 1.52–1.33 (m, 3H), 1.33–1.15 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.4$ (C), 148.0 (C), 133.9 (C), 133.5 (CH), 131.5 (CH), 130.9 (CH), 123.8 (CH), 61.1 (CH_3), 54.9 (CH), 54.8 (CH), 54.3 (CH), 44.7 (CH_2), 33.0 (CH_2), 32.1 (CH_3), 31.4 (CH_2), 31.3 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 20.9 ppm (CH_2); MS (EI): m/z (%) = 381 (34), 311 (22), 256 (13), 255 (85), 194 (22), 186 (100), 138 (12), 96 (13), 81 (14), 61 (13), 55 (30), 41 (18); HRMS (ESI): m/z calc. for $C_{19}H_{27}N_3O_7S$+Na: 464.1462; found: 464.1460.

22: Mercaptoacetic acid (10 μL, 0.15 mmol) and powdered anhydrous LiOH (17 mg, 0.69 mmol) were added to a solution of **21** (50 mg, 0.11 mmol) in DMF (1.1 mL), and the resulting mixture was stirred for 1.5 h. The red-orange suspension was evaporated at 50 °C under high vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and NaOH (6 M, 2 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over anhydrous Na_2CO_3 and evaporated to give (+)-4-((1*S*,3*S*,7a*S*)-1-hydroxyhexahydro-1*H*-pyrrolizin-3-yl)-*N*-methoxy-*N*-methylbutanamide (**22**; 27 mg, 96%), which was pure enough for further use. An analytically pure sample was obtained by flash chromatography (CH_2Cl_2/MeOH = 1:1 + 2% *v/v* NH_4OH) as a colorless syrup (22 mg, 78%). $[\alpha]_D^{20} = +10$ ($c = 0.23$, CH_2Cl_2); IR (film): $\tilde{\nu} = 3375$, 2930, 2869, 1660, 1459, 1416, 1385, 1352, 1327, 1162, 1094, 1015, 996 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.19$ (br t, $J = 3.8$ Hz, 1H), 3.82–3.72 (m, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 3.17–3.06 (m, 1H), 3.04–2.90 (m, 1H), 2.70–2.58 (m, 1H), 2.45 (br t, $J = 5.9$ Hz, 2H), 2.13 (ddd, $J = 13.2$, 5.2, 0.8 Hz, 1H), 2.01–1.85 (m, 3H), 1.83–1.49 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 71.7$ (C), 70.1 (C), 65.1 (CH), 61.3 (CH_3), 54.9 (CH_2), 43.8 (CH_2), 35.8 (CH_2), 31.9 (CH_2), 27.6 (CH_2), 24.3 (CH_2), 22.3 ppm (CH_2); the signals for the carboxy and *N*-methyl carbon atoms of the Weinreb amide were not detected; MS (EI): m/z (%) = 256 (4) $[M]^+$, 225 (9), 196 (8), 181 (15), 152 (8), 127 (9), 126 (100), 110 (13), 108 (12), 97 (12), 96 (62), 70 (18), 41 (14); HRMS (ESI): m/z calcd for $C_{13}H_{24}N_2O_3$+H: 257.1860; found: 257.1859; elemental analysis: calcd (%) for $C_{13}H_{24}N_2O_3$ (256.34): C 60.91, H 9.44, N 10.93; found: C 61.05, H 9.42, N 10.85.

24: (+)-4-((1*R*,3*S*,7a*R*)-1-Hydroxyhexahydro-1*H*-pyrrolizin-3-yl)-*N*-methoxy-*N*-methylbutanamide: Prepared analogously from **23** (26 mg, 0.10 mmol) as a colorless syrup (23 mg, 90%). $[\alpha]_D^{20} = +14$ ($c = 0.26$, CH_2Cl_2); IR (film): $\tilde{\nu} = 3399$, 2926, 2866, 1662, 1460, 1446, 1415, 1385, 1354, 1327, 1178, 1160, 1095, 1014, 996 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.15$ (q, $J = 6.1$ Hz, 1H), 3.63 (s, 3H), 3.21–3.11 (m, 1H), 3.12 (s, 3H), 2.87–2.73 (m, 1H), 2.73–2.62 (m, 1H), 2.62–2.52 (m, 1H), 2.41 (t, $J = 6.9$ Hz, 2H), 2.23 (dt, $J = 13.3$, 6.7 Hz, 1H), 1.98–1.40 ppm (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.1$ (C), 71.3 (C), 69.8 (C), 61.1 (CH_3), 58.9 (CH), 46.6 (CH_2), 40.7 (CH_2), 32.2 (CH_2), 32.1 (CH_3), 31.8 (CH_2), 26.3 (CH_2), 22.6 (CH_2), 22.4 ppm (CH_2); MS (EI): m/z (%) = 256 (6) $[M]^+$, 225 (8), 212 (6), 196 (7), 181 (12), 152 (6), 126 (100), 110 (11), 108 (11), 97 (9), 96 (46), 70 (11), 41 (12); HRMS (ESI): m/z calcd for $C_{13}H_{24}N_2O_3$+H: 257.1860; found: 257.1859.

(*E*)-1-Iodohept-1-ene: Diisobutylaluminum hydride (Dibal-H; 1.0 M in hexane, 25.0 mL, 25.00 mmol) was added dropwise to a vigorously stirred solution of 1-heptyne (3.28 mL, 25.00 mmol) in hexane (25 mL) over 5 min at ambient temperature. The resulting mixture was then stirred at 50 °C for 4 h before the solvent was evaporated. The residue was dissolved in THF (20 mL) before a solution of iodine (6.35 g, 25.00 mmol) in THF (20 mL) was slowly added at −50 °C. Once the addition was complete, the mixture was allowed to reach ambient temperature before the reaction was quenched with H_2SO_4 (20%, 1 mL). The resulting suspension was poured into a mixture of ice and 20% H_2SO_4, the aqueous phase was extracted with pentanes (3 × 50 mL), and the combined organic layers were successively washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), dried over Na_2SO_4, and evaporated to give (*E*)-1-iodohept-1-ene as a colorless liquid (4.98 g, 89%, d.r. > 99:1). IR (film): $\tilde{\nu} = 2956$, 2927, 2870, 2856, 1606, 1465, 1436, 1209, 1174, 940, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.51$ (dt, $J = 14.3$, 7.2 Hz, 1H), 5.97 (dt, $J = 14.3$, 1.4 Hz, 1H), 2.05 (dq, $J = 7.2$, 1.4 Hz, 2H), 1.45–1.22 (m, 6H), 0.89 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.8$ (CH), 74.2 (CH), 36.0 (CH_2), 31.1 (CH_2), 28.0 (CH_2), 22.4 (CH_2), 14.0 ppm (CH_3); MS (EI): m/z (%) = 224 (25) $[M]^+$, 167 (10), 154 (16), 57 (11), 55 (100), 53 (7), 43 (11), 42 (11), 41 (53), 39 (26), 29 (28), 27 (14); HRMS (EI): m/z calcd for $C_7H_{13}I$: 224.0062; found:

224.0059; elemental analysis: calcd for $C_7H_{13}I$ (224.08): C 37.52, H 5.85; found: C 37.50, H 5.77.

1: *t*BuLi (1.7 M in pentane, 287 μL, 0.489 mmol) was added dropwise to a stirred solution of (*E*)-1-iodohept-1-ene (56 mg, 0.248 mmol) in THF (1.0 mL) at −78 °C, and the resulting suspension was stirred at that temperature for 20 min. A solution of **22** (16 mg, 0.062 mmol) in THF (1.0 mL) was then added over a period of 5 min, and stirring was continued for 1 h at −78 °C. The suspension was warmed to −40 °C over 2 h before the reaction was carefully quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture warmed to ambient temperature. The mixture was diluted with CH_2Cl_2 (5 mL), dried over Na_2SO_4, filtered, and evaporated, and the residue was purified by flash chromatography (SiO_2 deactivated with 1% *v*/*v* NEt_3; CH_2Cl_2/MeOH = 10:1 + 2% *v*/*v* NH_4OH) to give (+)-(*E*)-1-((1*S*,3*S*,7a*S*)-1-hydroxyhexahydro-1*H*-pyrrolizin-3-yl)-undec-5-en-4-one (epohelmin B, **1**; 14 mg, 78% over 2 steps) as a pale-yellow oil. $[\alpha]_D^{20} = +5.3$ ($c = 0.67$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3346$, 2924, 2855, 1667, 1627, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; free base): $\delta = 6.83$ (dt, $J = 15.9$, 6.9 Hz, 1H), 6.08 (dt, $J = 15.9$, 1.5 Hz, 1H), 4.17 (br t, $J = 3.5$ Hz, 1H), 3.74–3.64 (m, 1H), 3.10–3.01 (m, 1H), 2.95–2.83 (m, 1H), 2.64–2.51 (m, 3H), 2.20 (dq, $J = 7.0$, 1.5 Hz, 2H), 2.10 (ddd, $J = 13.1$, 5.3, 0.9 Hz, 1H), 1.95–1.85 (m, 3H), 1.78–1.56 (m, 5H), 1.51–1.40 (m, 3H), 1.35–1.25 (m, 4H), 0.89 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; free base): $\delta = 200.5$ (C), 147.5 (CH), 130.3 (CH), 72.0 (CH), 70.0 (CH), 64.9 (CH), 55.0 (CH_2), 43.9 (CH_2), 40.1 (CH_2), 36.2 (CH_2), 32.4 (CH_2), 31.4 (CH_2), 27.79 (CH_2), 27.64 (CH_2), 24.3 (CH_2), 22.4 (CH_2), 21.9 (CH_2), 13.9 ppm (CH_3); MS (EI): *m*/*z* (%) = 293 (11) $[M]^+$, 152 (12), 127 (8), 126 (100), 124 (6), 110 (7), 109 (9), 108 (9), 97 (7), 96 (27), 70 (13), 55 (9), 41 (8); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{31}NO_2$+Na: 316.2247; found: 316.2251. The recorded data are in good agreement with those reported for the free base in the literature.[3,4]

26: (*E*)-1-((1*R*,3*S*,7*aR*)-1-Hydroxyhexahydro-1*H*-pyrrolizin-3-yl)undec-5-en-4-one: Prepared analogously from **24** (12 mg, 0.047 mmol) as a pale-yellow syrup (9 mg, 65%). IR (film): $\tilde{\nu} = 2953$, 2928, 2858, 1696, 1670, 1629, 1457, 1375, 1346, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.82$ (dt, $J = 15.8$, 6.9 Hz, 1H), 6.08 (dt, $J = 15.9$, 1.4 Hz, 1H), 4.18 (br q, $J = 5.8$ Hz, 1H), 3.17–3.11 (m, 1H), 2.78–2.70 (m, 2H), 2.60–2.52 (m, 3H), 2.35 (dt, $J = 13.6$ Hz, 6.8 Hz, 1H), 2.20 (dq, $J = 7.0$, 1.3 Hz, 2H), 2.06–1.82 (m, 3H), 1.80–1.55 (m, 5H), 1.53–1.40 (m, 3H), 1.37–1.24 ppm (m, 4H), 0.89 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 200.0$ (C), 147.9 (CH), 130.1 (CH), 70.14 (CH), 70.10 (CH), 59.3 (CH), 47.0 (CH_2), 40.0 (CH_2), 39.5 (CH_2), 32.4 (CH_2), 31.32 (CH_2), 31.30 (CH_2), 27.7 (CH_2), 26.2 (CH_2), 22.8 (CH_2), 22.4 (CH_2), 21.7 (CH_2), 13.9 ppm (CH_3); MS (EI): *m*/*z* (%) = 293 (8) $[M]^+$, 152 (13), 139 (4), 127 (8), 126 (100), 124 (6), 109 (9), 108 (6), 97 (7), 96 (30), 70 (14), 55 (11), 41 (7); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{31}NO_2$+Na: 316.2247; found: 316.2247.

27: (+)-1-((1*S*,3*S*,7a*S*)-1-Hydroxyhexahydro-1*H*-pyrrolizin-3-yl)undecan-4-one: Prepared analogously from **22** (14 mg, 0.055 mmol) and 1-heptylmagnesium bromide (1.0 M in hexane, 165 μL, 0.165 mmol) as a colorless syrup (10 mg, 60%). $[\alpha]_D^{20} = +14.8$ ($c = 0.31$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3336$, 2925, 2856, 1709, 1456, 1410, 1375, 1209, 1156, 1094, 1014 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 4.15$ (br t, $J = 3.8$ Hz, 1H), 3.75–3.67 (m, 1H), 3.08–3.00 (m, 1H), 2.95–2.86 (m, 1H), 2.64–2.56 (m, 1H), 2.41 (t, $J = 7.1$ Hz, 2H), 2.40–2.34 (m, 1H), 2.37 (t, $J = 7.5$ Hz, 2H), 2.07 (ddd, $J = 13.0$, 5.2, 0.7 Hz, 1H), 1.97–1.79 (m, 3H), 1.77–1.64 (m, 2H), 1.64–1.47 (m, 5H), 1.33–1.22 (m, 8H), 0.88 ppm (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 210.5$ (C), 71.3 (CH), 69.7 (CH), 64.7 (CH), 54.4 (CH_2), 43.3 (CH_2), 42.4 (CH_2), 42.3 (CH_2), 35.0 (CH_2), 31.4 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 27.2 (CH_2), 23.9 (CH_2), 23.5 (CH_2), 22.3 (CH_2), 21.0 (CH_2), 13.5 ppm (CH_3); MS (EI): *m*/*z* (%) = 295 (6) $[M]^+$, 251 (6), 211 (5), 168 (5), 126 (100), 124 (9), 124 (9), 110 (7), 109 (5), 108 (5), 97 (10), 96 (30), 70 (9), 41 (6); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{33}NO_2$+H: 296.25840; found: 296.25840.

28a: (+)-4-((1*S*,3*S*,7a*S*)-1-Hydroxyhexahydro-1*H*-pyrrolizin-3-yl)-1-phenylbutan-1-one: Prepared analogously from **22** (14 mg, 0.055 mmol) and phenylmagnesium bromide (1.8 M in hexane, 122 μL, 0.220 mmol) as a colorless syrup (10 mg, 68%). $[\alpha]_D^{20} = +15.0$ ($c = 0.50$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3345$, 2922, 2867, 1681, 1597, 1580, 1448, 1408, 1355, 1323, 1259, 1201, 1179, 1157, 1136, 1088, 1016, 974, 753, 735, 690 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 7.98$–7.92 (m, 2H), 7.60–7.54 (m, 1H), 7.50–7.44 (m, 2H), 4.25 (br t, $J = 3.9$ Hz, 1H), 3.97–3.90 (m, 1H), 3.25–3.10 (m, 2H), 3.04 (dt, $J = 6.9$, 2.3 Hz, 2H), 2.74 (dt, $J = 10.4$, 6.5 Hz, 1H), 2.18 (ddd, $J = 13.3$, 5.2, 0.7 Hz, 1H), 2.09–1.90 (m, 3H), 1.89–1.61 ppm (m, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 199.3$ (C), 136.7 (C), 132.6 (CH), 128.2 (CH), 127.6 (CH), 70.7 (CH), 70.4 (CH), 65.5 (CH), 54.0 (CH_2), 43.1 (CH_2), 38.1 (CH_2), 33.6 (CH_2), 27.0 (CH_2), 23.8 (CH_2), 21.3 ppm (CH_2); MS (EI): *m*/*z* (%) = 273 (14) $[M]^+$, 229 (8), 160 (7), 126 (100), 124 (9), 110 (7), 109 (18), 108 (11), 105 (11), 97 (10), 96 (36), 77 (11), 70 (10); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{23}NO_2$+H: 274.1802; found: 274.1800.

28b: 4-((1*R*,3S,7a*R*)-1-Hydroxyhexahydro-1*H*-pyrrolizin-3-yl)-1-phenylbutan-1-one: Prepared analogously from **24** (14 mg, 0.055 mmol) and phenylmagnesium bromide (1.8 M in hexane, 122 μL, 0.220 mmol) as a colorless syrup (9 mg, 60%). IR (neat): $\tilde{\nu} = 3298$, 2925, 1681, 1596, 1579, 1448, 1371, 1264, 1233, 1207, 1180, 1158, 1075, 1033, 1001, 973, 865, 755, 737, 690, 658 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 8.01$–7.91 (m, 2H), 7.62–7.54 (m, 1H), 7.52–7.43 (m, 2H), 4.53 (q, $J = 7.3$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 1H), 3.73–3.56 (m, 1H), 3.51–3.38 (m, 1H), 3.25–2.92 (m, 4H), 2.49 (dt, $J = 13.3$, 6.5 Hz, 1H), 2.42–1.61 ppm (m, 8H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 198.8$ (C), 136.5 (C), 132.7 (CH), 128.3 (CH), 127.5 (CH), 68.9 (CH), 68.1 (CH), 59.4 (CH), 47.1 (CH_2), 37.3 (CH_2), 36.8 (CH_2), 28.9 (CH_2), 25.3 (CH_2), 23.5 (CH_2), 20.8 ppm (CH_2); MS (EI): *m*/*z* (%) = 273 (10) $[M]^+$, 229 (8), 160 (8), 126 (100), 124 (10), 110 (8), 109 (21), 108 (9), 105 (12), 97 (11), 96 (45), 77 (12), 70 (15); HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}NO_2$: 273.1729; found: 273.1726.

29: (+)-1-((1*S*,3*S*,7a*S*)-1-Hydroxyhexahydro-1*H*-pyrrolizin-3-yl)undec-5-in-4-one: Prepared analogously from **22** (12 mg, 0.047 mmol) and 1-heptynyllithium (freshly prepared from 1-heptyne (25 μL, 0.188 mmol) and *n*BuLi (1.6 M in hexane, 114 μL, 0.183 mmol) in THF (1.0 mL)) as a colorless syrup (9 mg, 65%). $[\alpha]_D^{20} = +13.0$ ($c = 0.37$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3323$, 2929, 2862, 2208, 1668, 1456, 1327, 1211, 1157, 1096, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.27$ (br t, $J = 3.9$ Hz, 1H), 4.13–3.91 (m, 1H), 3.30–3.09 (m, 2H), 2.77 (dt, $J = 10.3$, 6.3 Hz, 1H), 2.59 (dt, $J = 7.0$, 1.5 Hz, 2H), 2.37 (t, $J = 7.1$ Hz, 2H), 2.18 (dd, $J = 13.1$, 5.2 Hz, 1H), 2.13–1.91 (m, 3H), 1.90–1.63 (m, 6H), 1.58 (dt, $J = 14.6$, 7.2 Hz, 2H), 1.44–1.26 (m, 4H), 0.91 ppm (t, $^3J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 187.0$ (C), 94.2 (C), 80.3 (C), 70.6 (CH), 70.3 (CH), 65.5 (CH), 53.8 (CH_2), 44.9 (CH_2), 42.8 (CH_2), 32.5 (CH_2), 30.7 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 23.8 (CH_2) 21.8 (CH_2) 21.0 (CH_2), 18.5 (CH_2), 13.3 ppm (CH_3); MS (EI): *m*/*z* (%) = 291 (8) $[M]^+$, 204 (6), 190 (6), 176 (8), 162 (5), 152 (13), 127 (8), 126 (100), 108 (9), 96 (19), 70 (13), 55 (4), 41 (7); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{29}NO_2$+H: 292.2271; found: 292.2271.

X-ray Crystal-Structure Analysis

20: $C_{19}H_{27}N_3O_6S$, $M_r = 425.50$, colorless plate, crystal size $0.32 \times 0.23 \times 0.07$ mm^3, orthorhombic, space group $P2_12_12_1$, $a = 8.2668(2)$, $b = 11.0950(2)$, $c = 22.3426(5)$ Å, $V = 2049.27(8)$ $Å^3$, $T = 100$ K, $Z = 4$, $D_{calcd} = 1.379$ $g\,cm^3$, $\lambda = 1.54178$ Å, $\mu(Cu_{K\alpha}) = 1.764$ mm^{-1}, empirical absorption correction, absolute structure parameter 0.010(12), Bruker AXS Proteum X8 diffractometer, $3.96 < \theta < 63.43$, 16347 measured reflections, 3286 independent reflections, 3265 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least squares against F^2 to $R1 = 0.024$ ($I > 2\sigma(I)$), $wR2 = 0.062$, 264 parameters, H atoms refined riding, $S = 1.109$, residual electron density = +0.2/−0.3 e $Å^{-3}$. CCDC-658678 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

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