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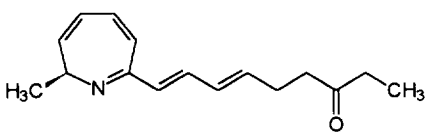
Optically Active 2*H*-Azepines: Synthesis and Rearrangement into their 3*H*-Isomers

Dieter Hamprecht, Jakob Josten and Wolfgang Steglich*

Institut für Organische Chemie der Universität, Karlstr. 23, D-80333 München, Germany

Abstract: A general synthesis of optically active 2*H*-azepines **12** starting from α-amino acids is described. The 2*H*-azepines easily rearrange into the corresponding 3*H*-isomers **18**. The pungent taste of chalciporone (**1**) and simple 2,7-dialkylsubstituted 2*H*-azepines is due to the 2*H*-azepine nucleus and is independent of the absolute configuration at C-2. Copyright © 1996 Elsevier Science Ltd

The pungent taste of the common mushroom *Chalciporus piperatus* (German: Pfefferröhrling) is caused by the 2*H*-azepine alkaloid chalciporone (**1**) and structurally related minor constituents.[1,2] In order to prove the structure and establish the absolute configuration of these unique alkaloids we became interested in synthetic approaches[3,4] to 2*H*-azepines.[5] Recently, we reported the first synthesis of the achiral 2*H*-azepine (**2**), the core structure of these heterocycles.[6] We herein describe the application of that methodology to the synthesis of a variety of optically active 2,7-disubstituted 2*H*-azepines.

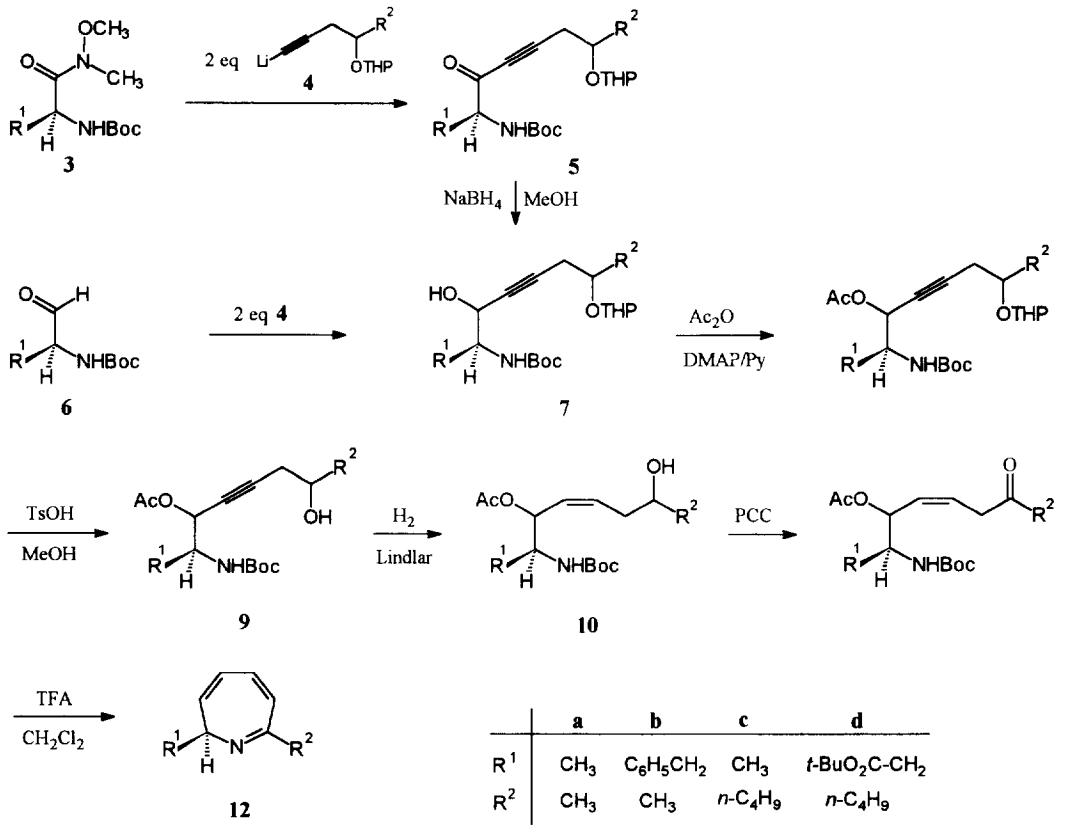


1

2

The high tendency of chalciporone (**1**) for rearrangement into its thermodynamically more stable 3*H*-isomer requires a synthetic route in which the heterocycle is formed in the last step. As shown in Scheme 1, suitable candidates for this ring closure can be obtained from α-amino acids in a short sequence. The linear precursors **7** are prepared either by reaction of an *N*-methoxy-*N*-methyl amide **3**[7,8] with a lithiated THP-protected homopropargylic alcohol **4**,[10,11] followed by reduction of the resulting ketone **5** with sodium borohydride or by addition of **4** to an *N*-Boc-α-aminoaldehyde **6**. Due to the latent instability of *N*-Boc-α-aminoaldehydes[12] and the higher overall yields obtained in the two step process the first pathway was preferred

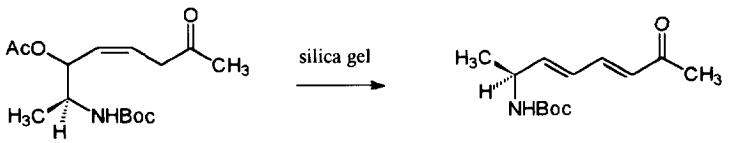
in most cases. The coupling reactions required two equivalents of the acetylide **4** to compensate for the acidic urethane NH group. The excess of reagent **4** was easily recovered.



Scheme 1

The intermediates **4**, **5** and **7** to **11** were obtained as complex mixtures of diastereomers due to the presence of up to four stereocenters. Since after the final ring closure only the stereogenic center derived from the amino acid is retained, we made no effort to control the stereochemistry of the other stereocenters. All syntheses were carried out with these mixtures without any adverse effects.

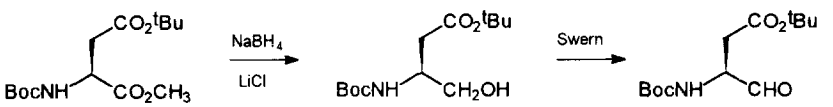
The mixture of the diastereomeric alcohols **7** was acetylated to yield the protected diols **8**. After acid catalyzed cleavage of the tetrahydropyranyl (THP) ether, the alkynols **9** were hydrogenated using Lindlar catalyst to afford the (*Z*)-homoallylic alcohols **10** in nearly quantitative yield. Hydrogenation of the THP ethers **8** usually proceeded less effectively. Oxidation of the alcohols **10** with pyridinium chlorochromate (PCC)[13] yielded the (*Z*)-alkenones **11**, which could be stored at -20 °C for several months. Chromatography on silica gel converts some of the oxidation products, e. g. **11a**, into the (*E,E*)-dienones **13** (Scheme 2).



11a **13**

Scheme 2

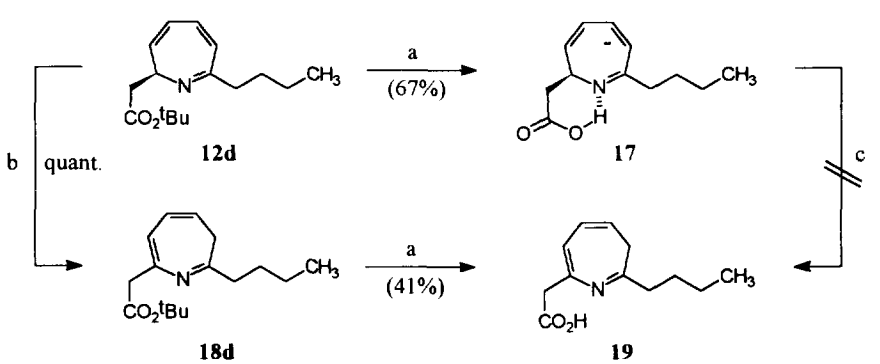
Upon treatment of the ketones **11** with trifluoroacetic acid in dichloromethane at or below room temperature the optically active 2*H*-azepines **12** were obtained in 45-72% yield. During this reaction, formation of the cyclic iminium salt,[6] cleavage of the urethane group and 1,4-elimination of acetic acid take place. The overall yields of 2*H*-azepines with respect to the amino acid derivatives **3** were approximately 30%.



14 **15** **16**

Scheme 3

The functionalized 2*H*-azepine **12d** was obtained in 21% overall yield from aldehyde **16**, which was prepared from 4-*tert*-butyl 1-methyl *N*-Boc-aspartate (**14**)[14] by selective reduction of the methoxycarbonyl group with sodium borohydride/LiCl[15] followed by Swern oxidation[16] of the resulting alcohol **15** (Scheme 3). On standing in *tert*-butyl methyl ether (*t*-BuOMe) **12d** rearranged into the thermodynamically more stable 3*H*-azepine derivative **18d** (Scheme 4). Conversion of the ester **12d** into the corresponding acid **17** was achieved with iodotrimethylsilane.[17] The low-field shifts of the azepine resonances in the ^{1}H NMR spectrum of **17** indicate the formation of a hydrogen bond between the carboxyl group and the nitrogen.[18] The partial positive charge of the azepine ring obviously stabilizes the 2*H*-structure, since carboxylic acid **17** shows no tendency to rearrange to its 3*H*-isomer **19**.[19] The latter compound can however be prepared by cleavage of ester **18d**.



Scheme 4: a) Me_3SiI, CH_2Cl_2, 0 °C, 15 min, then MeOH; b) *t*-BuOMe, r.t., 10 d (55% conversion); c) $CDCl_3$, r.t., 12 d.

We have recently used the chemistry described herein to synthesize chalciporone (**1**) from *L*-alanine, thus establishing the (2*S*)-configuration of this alkaloid.[2,4] These results will be reported in a separate communication.

The 2*H*-azepines **12** are slightly yellow liquids or oils which easily rearrange into the more stable 3*H*-isomers **18** (Scheme 5). This rearrangement occurs on standing in organic solvents at room temperature or on slightly warming them in chloroform for several hours (*vide supra*). The 2*H*- and 3*H*-isomers are easily separated by chromatography on silica gel, the more basic[5e] 2*H*-isomers showing lower R_f values. The structure of the 2*H*-azepines **12** and their 3*H*-isomers **18** is supported by the ^1H and ^{13}C NMR data. Thus, the azepine resonances of the 2,7-dimethyl derivatives **12a** and **18a** (Table 1) are in close agreement with those of chalciporone (**1**) and its 3*H*-isomer isochalciporone,[1] respectively. In the EI mass spectra 3*H*-azepines like **18a** and **18b** showed more intense molecular ions than the corresponding 2*H*-isomers.

12 **18**

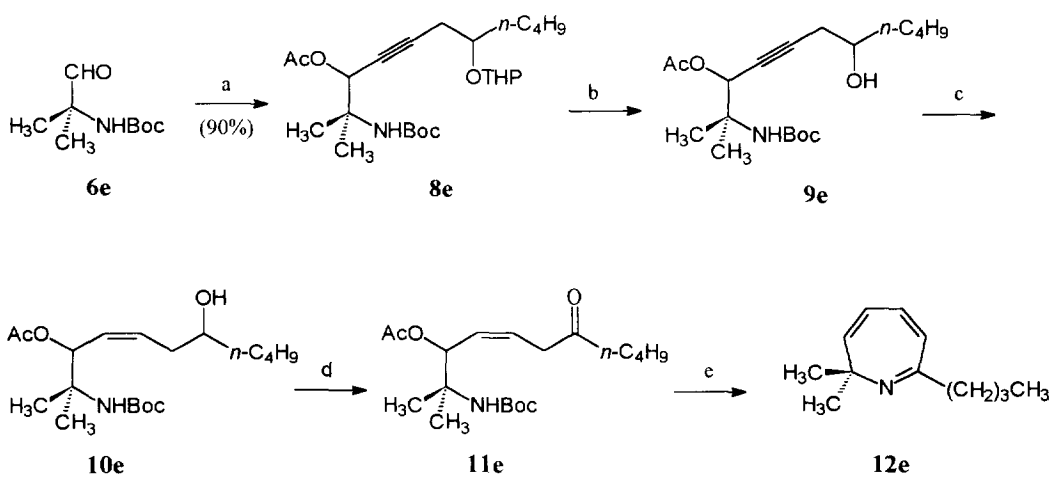
Scheme 5

Table 1. ^1H and ^{13}C NMR data of 2,7-dimethyl-2*H*-azepine (**12a**) and 2,7-dimethyl-3*H*-azepine (**18a**) (400 MHz, in $CDCl_3$ with TMS as internal standard)

H atom	**12a**	**18a**	C atom	**12a**	**18a**
2-H	δ 2.81, br dq, *J* = 6.6, 5.4 Hz		C-2	δ 54.83, Ddd *J* = 160, 12.0, 5.6 Hz	δ 147.11, tq *J* = 6.0, 6.0 Hz
3-H	δ 5.59, dd *J* = 9.4, 5.4 Hz	δ 2.15, coalesc. br s (ref. 26)	C-3	δ 135.49, Ddd *J* = 160, 12.0, 5.6 Hz	δ 37.78, Td, br *J* = 134, 7.0 Hz
4-H	δ 6.17, dddd *J* = 9.4, 4.8, 1.8, 1.8 Hz	δ 5.13, dt *J* = 8.7, 7.0 Hz	C-4	δ 126.16, Ddd *J* = 159, 10.0, 5.0 Hz	δ 112.77, Ddt *J* = 162.5, 6.5, 6.5 Hz
5-H	δ 6.68, dd *J* = 11.2, 4.8 Hz	δ 6.19, dd *J* = 8.7, 6.0 Hz	C-5	δ 135.67, Dddd *J* = 158, 10, 2, 2 Hz	δ 127.30, Dt *J* = 156, 7.0 Hz
6-H	δ 6.77, ddq *J* = 11.2, 1.8, 0.9 Hz	δ 5.96, d *J* = 6.0 Hz	C-6	δ 133.17, Dm *J* = 156 Hz	δ 113.20, Ddq *J* = 155, 10.0, 4.5 Hz
2-CH_3	δ 1.58, d *J* = 6.6 Hz	δ 2.14 or 2.12 s	C-7	δ 163.13, m	δ 149.26, dq *J* = 7.0, 6.0 Hz
7-CH_3	δ 2.10, d *J* = 0.9 Hz	δ 2.12 or 2.14 s	2-CH_3	δ 21.77, Qdd *J* = 127, 4.4, 1.6 Hz	δ 26.09, Qt *J* = 126, 2.0 Hz
			7-CH_3	δ 24.11, Q *J* = 127 Hz	δ 24.18, Qd *J* = 126, 4.0 Hz

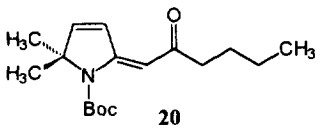
Vapors of volatile 2*H*-azepines like **12a** cause a painful sensation to the respiratory tract. Interestingly, the (*R*)-isomer of **12a** exhibits the same action as the (*S*)-compound. All 2,7-disubstituted 2*H*-azepines investigated so far resemble chalciporone (**1**)[1] in provoking a long lasting pungent sensation on the tongue. On rearrangement to the 3*H*-azepines the pungency is lost.

7-Butyl-2,2-dimethyl-2*H*-azepine (**12e**) should be more stable than the compounds **12a-d** due to the lack of a hydrogen atom that could migrate. In the course of the synthesis of **12e** we realized that some of the intermediates showed a pronounced tendency to undergo undesired cyclization reactions. Thus, we were unable to obtain the *N*-methoxy-*N*-methyl amide of *N*-Boc-α-aminoisobutyric acid because of competing *N*-carboxy anhydride formation. In an alternative approach the *N*-protected aminoaldehyde **6e**[20] was treated with the lithiated alkyne **4** (Scheme 6). Addition of acetic anhydride at low temperature to the reaction mixture gave the protected diols **8e** in excellent yield. Cleavage of the THP ether, Lindlar hydrogenation of the triple bond, Swern oxidation and treatment of the resulting Boc-protected amino enone **11e** with TFA at low temperature afforded 2*H*-azepine **12e**. This compound is stable in solution for several days after which it showed a tendency to form insoluble products. Dimethyl derivative **12e** and monomethyl azepine **12a** were of comparable pungency.



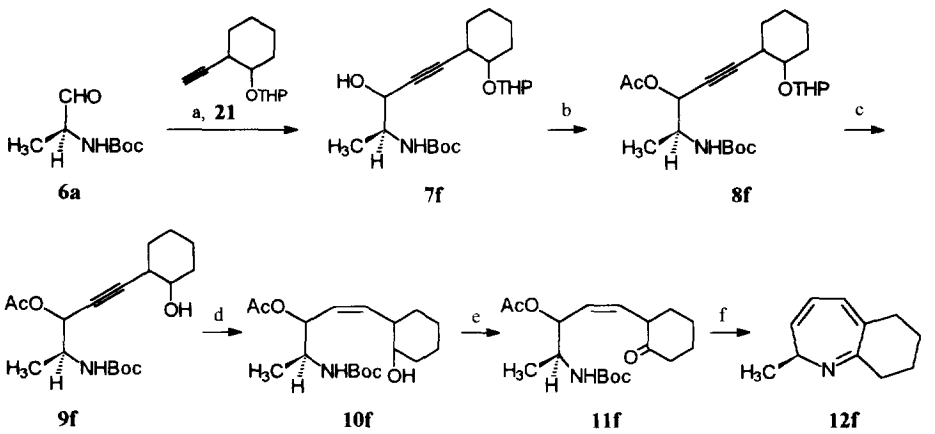
Scheme 6: a) **4** (2.2 eq), THF, -78 °C, 30 min; then Ac_2O, -78 °C → r.t.; b) MeOH, cat. PPTS, 50 °C, 165 min; c) H_2, Lindlar cat., quinoline (trace), THF-hexanes (1:1), r.t., 2 h; d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -63 °C; e) TFA/CH_2Cl_2 (1:2), -15 °C, 4 h.

Interestingly, a pyrroline derivative **20** was obtained in 11% yield besides ketone **11e** by oxidation of alcohol **10e** with PCC.



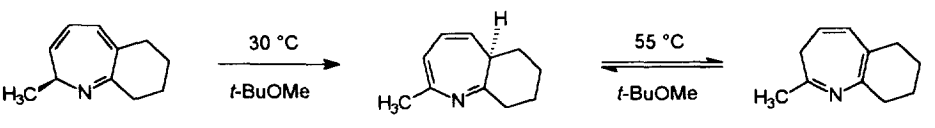
20

6,7-Substituted 2*H*-azepines can be assembled from 3,4-disubstituted 1-alkyn-4-ols. Thus, the protected aminoaldehyde **6a** was allowed to react with the lithium salt of alkyne **21**[21] to yield the alkynol **7f**. This intermediate gave rise to the bicyclic 2*H*-azepine **12f** in five steps with 66% overall yield (Scheme 7).



Scheme 7: a) 2.9 eq **21**, 2.9 eq BuLi, THF, -78 °C, 70 min; then **6a**, -78 °C → -10 °C, 3 h; b) Ac_2O, pyridine, cat. DMAP, CH_2Cl_2, r.t., 16 h; c) ethylene glycol, DME, cat. PPTS, 70 °C, 90 min; d) H_2, Lindlar cat., benzene, r.t., 3 h; e) PCC, CH_2Cl_2, r.t., 24 h; f) TFA, CH_2Cl_2, 18 °C, 285 min.

12f undergoes a thermally allowed suprafacial [1,5]-sigmatropic H-shift in *tert*-butyl methyl ether at 30 °C. The product is the optically active 3*H*-azepine **18f**. It exhibited a high optical rotation, thus supporting a stereoselective mechanism of the rearrangement. At elevated temperature a second, reversible hydrogen migration occurs which establishes an equilibrium with the optically inactive 3*H*-azepine **22** (Scheme 8).



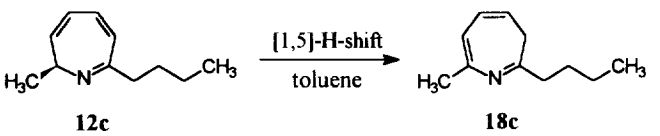
12f $[\alpha]_D^{22} = 23°$ ($c = 0.45$, Et_2O)

18f $[\alpha]_D^{22} = 481°$ ($c = 0.22$, *t*-BuOMe)

22

Scheme 8

The rearrangement of (*S*)-7-butyl-2-methyl-2*H*-azepine (**12c**) was studied in some detail. Measuring the decrease in optical activity is a convenient way to follow the rearrangement of the optically active 2*H*-azepine **12c** to the achiral 3*H*-tautomer **18c** (Scheme 9). The reaction follows first order kinetics, and the semi-logarithmic plot shows a linear correlation between ln $|\alpha_{436}{}^{T}|$ and *t* over several half-lifes. Observation of the rearrangement of **12c** to its 3*H*-isomer **18c** in toluene at different temperatures gave rise to the following activation parameters:



12c **18c**

E_a =	87 kJ mol^{-1}
ln A =	23
$\Delta H^{\neq}$ =	84 kJ mol^{-1}
$\Delta S^{\neq}$ =	-65 J K^{-1} mol^{-1}

Scheme 9

These parameters correlate well with those reported for [1,5]-sigmatropic hydrogen shifts in cycloheptatriene.[23] The negative entropy of activation $\Delta S^{\neq}$ is in accord with a rigid transition state. As expected for a sigmatropic rearrangement, the nature of the solvent has only a minor influence on the rate of this process (Table 2). Compared to apolar solvents the hydrogen shift is slightly accelerated in dipolar aprotic and somewhat retarded in polar protic solvents.

Table 2. Rate constants *k* and half-lifes $t_{½}$ for the rearrangement of (*S*)-7-butyl-2-methyl-2*H*-azepine (**12c**) in various solvents at the indicated temperatures *T*; *k* and $t_{½}$ were determined by plots of ln $|\alpha_{436}{}^{T}|$ *versus t*; *r* are the respective linear correlation coefficients.

solvent	*c* [g/100 ml]	*T* [°C]	*k* [10^{-5}s^{-1}]	$t_{½}$ [min]	*r*
toluene	2.8	25.0	0.45	2557	-0.99992
toluene	2.0	50.0	6.51	177	-0.99994
toluene	2.3	60.0	18.14	64	-0.99977
toluene/1% NEt_3	1.6	50.0	6.16	187	-0.99994
$CHCl_3$/0.1% NEt_3	1.6	50.0	7.73	149	-0.99944
acetone/0.1% NEt_3	2.1	50.0	6.27	184	-0.99983
DMSO/0.5% NEt_3	2.0	50.0	7.66	151	-0.99977
H_3CNO_2	2.0	50.0	8.98	129	-0.99989
EtOH/0.1% NEt_3	1.4	50.0	5.31	218	-0.99983

EXPERIMENTAL SECTION

General. Melting points were determined with a Reichert Thermovar hot-stage or a Büchi 530 and are uncorrected. NMR spectra were recorded on a Bruker ARX 300 (^{1}H: 300 MHz; ^{13}C: 75.47 MHz) and a Varian 400S (^{1}H: 400 MHz; ^{13}C: 100.58 MHz) in $CDCl_3$ with TMS as an internal standard, if not otherwise indicated. Infrared spectra were recorded on a Perkin-Elmer 1420 or a Bruker Aspect 1000 IR spectrometer. UV spectra were recorded on a Hewlett-Packard HP 8452 A photodiode array spectrometer or a Merck Hitachi L-3000 photodiode array detector. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Finnigan MAT 95Q. For analytical TLC silica gel 60 F_{254} on aluminum foil (Merck) was used. The R_F-values were determined in EtOAc/hexanes = 1:1 (system I), 1:2 (system II) or 1:3 (system III), if not otherwise indicated. For preparative TLC silica gel 60 F_{254} on glass (Merck) was used. Column chromatography was performed on silica gel 60 (40-63 μm; Merck) or, if indicated, neutral alumina (Woelm, 4% H_2O, activity 2-3) using EtOAc/hexanes if not otherwise indicated. For preparative HPLC a Knauer pre-packed HPLC column 250 x 16 mm, Merck Lichrosorb Si 60 7 μm (irr.), precolumn 30 x 16 mm, Merck Lichrosorb Si 60 10 μm (irr.) was used. All experiments using moisture sensitive reagents were performed under an argon atmosphere using dried glassware and dry solvents. All solvents were distilled before use.

General Procedure for the synthesis of alkynones 5

To a solution of alkyne **4**[10,11] (150 mmol) in THF (100 ml) was added dropwise a solution of *n*-BuLi in hexane (100 ml, 1.5 M, 150 mmol). The internal temperature of the reaction mixture was kept between -45 and -60 °C during the addition. After 15 min a solution of the *N*-methoxy-*N*-methyl amide **3a**[8] (60 mmol) in THF (500 ml) was added dropwise at -60 °C. The mixture was allowed to warm to 0 °C and then poured into 1 M aqueous KH_2PO_4. The aqueous layer was extracted twice with *t*-BuOMe. The combined organic layers were washed with 1 M aqueous KH_2PO_4 and brine, dried (Na_2SO_4) and concentrated. Chromatography (silica gel, ether/hexanes = 1:1) of the residue yielded the alkynones **5** as pale yellow oils. Excess **4** could be recovered in a separate fraction.

(2*S*)-2-*tert*-Butoxycarbonylamino-7-(tetrahydropyran-2-yloxy)-4-octyn-3-one (5a).* Yield 75%, R_F = 0.55 (system I); IR ($CHCl_3$): 3420 (m), 3320 (w), 3020 (sh), 3010 (m), 2990 (s), 2950 (s), 2890 (w), 2200 (s), 1750 (sh), 1700 (ss), 1670 (ss), 1560 (ss), 1450 (m), 1370 (m), 1340 (w), 1290 (w), 1250 (m), 1160 (ss), 1130 (m), 1080 (m), 1030 (m), 1000 (m), 960 (w), 900 (w), 860 (m), 810 (w), 720 cm^{-1} (w); ^{1}H NMR (200 MHz) δ 1.24 and 1.32 (each d, *J* = 6.2 Hz, 3H, 8-H), 1.40 and 1.42 (each d, *J* = 7.2 Hz, 3H, 1-H), 1.42 (s, 9H, $C(C\underline{H}_3)_3$), 1.85-1.93 (m, 6H, 3'-, 4'-, 5'-H), 2.51/2.61 and 2.58/2.73 (each dd, *J* = 16.8, 6.1 Hz, 2H, 6-H), 3.48 (dt, *J* = 11.2, 5.0 Hz, 1H, 6'$_{eq}$-H), 3.88 (ddd, *J* = 11.2, 11.2, 6.0, 1H, 6'$_{ax}$-H), 4.01 (tq, *J* = 6.1, 6.1 Hz, 1H, 7-H), 4.36 (dq, *J* = 8.0, 7.0 Hz, 1H, 2-H), 4.70 (m, 1H, 2'-H), 5.22 (br d, *J* = 8 Hz, 1H, NH); ^{13}C NMR (100.6 MHz) δ 1.24 17.36 (C-1), 21.15 (C-8), 25.17 (C-4'), 26.27 (C-5'), 27.62 (C-3'), 28.11[$C(\underline{C}H_3)_3$], 30.59 (C-6), 56.77 (C-2), 62.39 (C-6'), 70.11 (C-7), 79.68 ([$\underline{C}(CH_3)_3$], 81.99 (C-5), 94.31 (C-4), 96.97 (C-2'), 154.91 ($HN\underline{C}O_2$), 186.73 (C-3); FAB MS (*m*NBA matrix) *m/z* = 340.2 (9%) $[M+H]^+$, 284.2 (4), 240.2 (2), 200.1 (100), 182.1 (8), 154.1 (31), 136.1 (22), 107.1 (11); $C_{18}H_{29}NO_5$ (339.43).

(2*S*)-2-*tert*-Butoxycarbonylamino-1-phenyl-7-(tetrahydropyran-2-yloxy)-4-octyn-3-one (5b). Yield 68%, R_F = 0.30 (system I); IR ($CHCl_3$): 3420 (m), 3000 (m), 2980 (s), 2940 (s), 2880 (m), 2720 (s), 1700 (ss), 1670 (ss), 1490 (ss), 1450 (m), 1370 (m), 1350 (m), 1240 (m), 1160 (ss), 1120 (m), 1075 (m), 1030 (m), 1020 (m), 995 (m), 910 (ss), 865 (m), 700 cm^{-1} (m); ^{1}H NMR (200 MHz) δ 1.26 and 1.33 (each d, *J* = 6.0 Hz, 3H), 1.42 (s, 9H), 1.45-1.90 (m, 6H), 2.53/2.62 and 2.60/2.75 (each dd, *J* = 16.8, 5.3 Hz, 2H), 3.20 (m, 2H), 3.49 (dt, *J* =11.2, 5.0 Hz, 1H), 3.88 (ddd, *J* = 11.2, 11.2, 6.0 Hz, 1H), 4.02 (tq, *J* = 6.0, 6.0 Hz, 1H), 4.66 (dt, *J* = 8.0, 7.2 Hz, 1H), 4.72 (m, 1H), 5.08 (br d, *J* = 8.0 Hz, 1H), 7.10-7.35 (m, 5H); ^{13}C NMR (100.6 MHz) δ

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* The compounds **5**, **7 - 11d** and **11f** are mixtures of diastereomers. Only the defined stereogenic centers are indicated in the names.

21.36, 25.31, 26.45, 27.84, 28.22, 30.91, 37.15, 62.64, 70.22, 79.81, 80.34, 95.54, 97.67, 126.95, 128.44 (2C), 129.44 (2C), 137.70, 154.98, 185.59; FAB MS (*m*NBA matrix) *m/z* = 416.2 (14%) $[M+H]^+$, 323.2 (50), 276.1 (100), 258.1 (6), 232.1 (99), 214.1 (13), 120.1 (84); $C_{24}H_{33}NO_5$ (415.53).

(2*S*)-2-(*tert*-Butoxycarbonylamino)-7-(tetrahydropyran-2-yloxy)-4-undecyn-3-one (5c). Yield 86%, R_F = 0.74 (system II); ^{1}H NMR δ 0.91 (m, 3H), 1.25-1.47 (m, 16H), 1.47-1.88 (m, 8H), 2.53-2.81 (m, 2H), 3.51 (m, 1H), 3.77 (m, 1H), 3.91 (m, 1H), 4.38 (m, 1H), 4.66 and 4.77 (each m, 1H), 5.33 and 5.39 (each br d, 1H); ^{13}C NMR δ 14.01, 14.04, 19.85, 19.87, 22.67, 22.69, 25.45, 25.47, 25.48, 26.27, 26.28, 27.40, 27.41, 27.63, 28.35, 31.04, 31.08, 33.78, 33.80, 34.82, 34.83, 62.88, 62.91, 75.83, 75.91, 76.89, 77.20, 79.91, 95.34, 95.41, 96.81, 99.61, 155.11, 186.92; $C_{21}H_{35}NO_5$ (381.51).

General procedure for the synthesis of alcohols 7 and acetates 8 from alkynones 5

To a solution of alkynone **5** (20 mmol) in methanol (100 ml) at 0 °C was added sodium borohydride (3 g, 80 mmol). The mixture was stirred at 0 °C for 1 h and then quenched with 2 M acetic acid. The solvent was removed *in vacuo* and the residue partitioned between EtOAc and brine. The aqueous layer was extracted twice with EtOAc, the extracts were washed with brine, dried ($MgSO_4$), and concentrated to yield the crude alcohol **7** as an oil. The products could be purified by chromatography (silica gel, ether/hexanes = 1:1) or were directly transformed into the acetates **8**.

(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxy-7-(tetrahydropyran-2-yloxy)-4-octyne (7a). Yield 98%, R_F = 0.34 (system I); IR ($CHCl_3$) 3530 (w), 3410 (m), 3300 (sh), 2990 (m), 2950 (s), 2910 (ss), 2850 (sh), 2830 (m), 1690 (ss), 1490 (s), 1450 (m), 1380 (m), 1360 (s), 1330 (w), 1240 (m), 1150 (s), 1120 (m), 1060 (m), 1020 (s), 990 (m), 940 (w), 890 (w), 860 (w), 800 cm^{-1} (w); ^{1}H NMR (200 MHz) δ 1.17 and 1.22 (each d, *J* = 6.4 Hz, 3H, 8-H), 1.23 and 1.30 (each d, *J* = 6.5 Hz, 3H, 1-H), 1.42 (s, 9H, $C(C\underline{H}_3)_3$), 1.43-1.85 (m, 6H, 3'-H, 4'-H, 5'-H), 2.25-2.60 (m, 2H, 6-H), 3.59 (m, 1H, 6'$_{eq}$-H), 3.68-4.07 (m, 3H, 6'$_{ax}$-H, 7-H, 2-H), 4.32 (m, 1H, 3-H), 4.65 and 4.75 (each m, 1H, 2'-H), 4.90 (br s, 1H, N<u>H</u>); ^{13}C NMR (100.6 MHz) δ 15.99 (C-1), 21.02 (C-8), 25.26 (C-4'), 25.82 (C-5'), 27.24 (C-3'), 28.23 [$C(\underline{C}H_3)_3$], 30.70 (C-6), 51.10 (C-2), 62.36 (C-6'), 66.10 (C-3), 70.78 (C-7), 79.53 [$\underline{C}(CH_3)_3$], 79.68 (C-5), 83.20 (C-4), 97.35 (C-2'), 155.65 (NCO_2); FAB MS (*m*NBA matrix) *m/z* = 342.3 (17%) $[M+H]^+$, 258.2 (53), 202.1 (100), 184.1 (33), 158.1 (42), 136.1 (18); $C_{18}H_{31}NO_5$ (341.45).

(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxy-1-phenyl-7-(tetrahydropyran-2-yloxy)-4-octyne (7b). Yield 98%, R_F = 0.23 (system I); IR ($CHCl_3$) 3420 (m), 3000 (m), 2970 (s), 2930 (s), 2860 (w), 1700 (ss), 1490 (s), 1445 (m), 1380 (m), 1360 (s), 1240 (m), 1160 (s), 1130 (m), 1070 (m), 1020 (s), 995 (m), 950 (w), 900 (w), 870 (w), 700 cm^{-1} (w); ^{1}H NMR (200 MHz) δ 1.22 and 1.33 (each d, *J* = 6.5 Hz, 3H), 1.40 (s, 9H), 1.45-1.90 (m, 6H), 2.30-2.60 (m, 2H, 6-H), 2.85 (m, 2H, 1-H), 3.50 (m, 1H, 6'$_{eq}$-H), 3.80-4.15 (m, 3H), 4.35 (m, 1H), 4.65 and 4.85 (each m, 1H), 4.90 and 5.10 (each br d, 1H, N<u>H</u>), 7.15-7.33 (m, 5H); ^{13}C NMR (100.6 MHz) δ 21.06, 25.24, 25.79, 27.25, 28.14, 30.91, 37.31 (C-1), 56.66 (C-2), 62.27, 64.48, 70.68, 79.41, 80.37, 84.22, 97.10, 126.26, 128.25 (2C), 129.03 (2C), 137.58, 155.79; FAB MS (*m*NBA matrix) *m/z* = 418.2 (13%) $[M+H]^+$, 369.1 (1), 334.2 (24), 307.1 (14), 278.1 (38), 260.1 (14), 234.1 (17), 199.1 (4), 120.1 (51); $C_{24}H_{35}NO_5$ (417.55).

(2*S*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)-7-(tetrahydropyran-2-yloxy)-4-undecyne (8c). Crude alcohol **7c** [R_F = 0.22, EtOAc/hexanes = 1:4] obtained from 7.6 mmol **5c** was dissolved in THF and treated with pyridine (1.1 ml, 14 mmol), DMAP (0.11 g, 0.9 mmol) and Ac_2O (1.3 ml, 14 mmol). After 19 h at r.t. the mixture was partitioned between EtOAc and 10% H_3PO_4. The aqueous layer was extracted with EtOAc, and the combined organic layers were then washed with 10% H_3PO_4, saturated aqueous $NaHCO_3$ and brine. After drying (Na_2SO_4) and evaporation of the solvent the crude product was purified by column chromatography (silica gel) to yield **8c** (2.86 g, 88%) as an oil: R_F = 0.35 (EtOAc/hexanes = 1:4); IR (film) 3350 (br, m), 2250 (w), 1745 (s), 1715 (s), 1505 (s), 1455 (m), 1370 (s), 1170 (s), 790 cm^{-1} (s); ^{1}H NMR δ 0.92 (m, 3H), 1.20 (m, 3H), 1.27-1.40 (m, 4H), 1.44 (s, 9H), 1.47-1.63 (m, 6H), 1.68 and 1.83 (each br m, 2H), 2.05 (m, 3H), 2.31-

2.52 (m, 2H), 3.48 (br m, 1H), 3.66-3.87 (m, 2H), 3.87-4.07 (m, 1H), 4.58-5.06 (m, 2H), 5.31 (br m, 1H); $C_{23}H_{39}NO_6$ (425.57).

Synthesis of alcohols 7 and acetates 8 from aldehydes 6 and 16

***tert*-Butyl (3*S*)-3-(*tert*-Butoxycarbonylamino)-4-hydroxy-8-(tetrahydropyran-2-yloxy)-5-dodecynoate (7d).** To a solution of alkyne **4**[10,11] (6.90 g, 32.8 mmol, 2.49 eq) in absolute THF (20 ml) *n*-BuLi (20.6 ml, 1.6 M in hexane, 33.0 mmol, 2.50 eq) was added dropwise over 20 min at -100 °C. The addition was controlled at such a rate that the inner temperature of the flask did not exceed -78° C. After a further 10 min a solution of freshly prepared aldehyde **6d** (3.60 g, 13.2 mmol, 1.00 eq) in THF (40 ml) was added over 15 min. After 30 min at -78 °C the mixture was warmed to 0 °C and quenched by addition of 3.5% aqueous ammonium chloride (100 ml) and ether. The aqueous phase was extracted twice with ether and the combined organic phases were dried ($MgSO_4$). **7d** was separated from excess **4** by chromatography (silica gel). **7d**: 4.28 g (67%), R_F = 0.54 (system I); IR (film) 3400 (br, m), 2920 (s), 2740 (w), 1720 (s), 1580 (m), 1320 (s), 1240 (m), 1180 (s), 1100 cm^{-1} (m); ^1H NMR δ 0.91 (m, 3H), 1.23-1.36 (m, 4H), 1.44 and 1.45 (each s, 18H), 1.48-1.64 (m, 6H), 1.68-1.86 (m, 3H), 2.36-2.60 (m, 3H), 2.67-2.77 (m, 1H), 3.44-3.53 (m, 1H), 3.68-3.88 and 3.98-4.13 (m, 3H), 4.48 (br s, 1H), 4.57-4.62 and 4.75-4.84 (m, 1H), 5.05-5.40 (m, 1H). Anal. Calcd. for $C_{26}H_{45}NO_7$ (483.64): C 64.57, H 9.38, N 2.90. Found: C 64.92, H 9.42, N 3.04.

3-Acetoxy-2-(*tert*-butoxycarbonylamino)-2-methyl-7-(tetrahydropyran-2-yloxy)-4-undecyne (8e). Alkyne **4** (9.25 g, 44.0 mmol) was dissolved in THF (30 ml). Over 20 min a solution of *n*-BuLi in hexane (1.6 M, 27.5 ml, 44.0 mmol) was added at -78 °C. After an additional 10 min aldehyde **6e**[20] (3.75 g, 20.0 mmol) in THF (60 ml) was added over 15 min. The solution was left for 30 min. Then Ac_2O (12.5 ml, 132 mmol) was added dropwise. After an additional 45 min the mixture was allowed to warm to r.t. Water was added, and the layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated and chromatographed (silica gel) to yield **8e** (7.92 g, 90%) as a colorless oil: R_F = 0.43 (EtOAc/hexanes = 1:3); IR (film) 3360 (m), 2240 (w), 1745 (s), 1720 (s), 1370 (s), 1235 (s), 1165 (s), 1080 (s), 1025 cm^{-1} (s); ^1H NMR δ 0.88-0.93 (m, 3H), 1.28-1.45 (m, 18H), 1.48-1.75 (m, 8H), 1.78-1.85 (m, 1H), 2.09 and 2.23 (each s, 3H), 2.39-2.64 (m, 2H), 3.45-3.52 (m, 1H), 3.65-3.79 (m, 2H), 4.63-4.78 (m, 2H), 5.69 (br s, 1H); ^{13}C NMR δ 14.01, 20.90, 22.71, 25.50, 27.27, 27.57, 28.39, 30.98, 31.08, 34.68, 55.17, 62.55, 68.56, 73.81, 76.25, 84.44, 96.86, 99.07, 154.43, 169.53; FAB MS (*m*-NBA matrix) *m/z* = 440 (3.3%) $[M+H]^+$, 356 (22), 256 (76), 240 (75), 196 (33), 102 (44), 85 (100), 57 (82); Anal. Calcd. for $C_{24}H_{41}NO_6$ (439.59): C 65.58, H 9.40, N 3.19. Found: C 65.71, H 9.45, N 3.35.

2-[(4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-1-pentyn-1-yl]-1-(tetrahydropyran-2-yloxy)cyclohexane (7f). 2-Ethynyl-1-(tetrahydropyran-2-yloxy)cyclohexane **21**[21] (9.30 g, 44.6 mmol) was dissolved in THF (70 ml) and cooled to -78 °C. A solution of *n*-BuLi in hexane (1.6 M, 27.9 ml, 44.6 mmol) was added over 30 min. After 70 min freshly prepared **6a** (2.64 g, 15.2 mmol) in THF (70 ml) was added dropwise over a period of 30 min. The solution was then allowed to warm to -10 °C over 3 h. Aqueous NH_4Cl and Et_2O were added. The organic layer was separated and washed twice with brine. Drying (Na_2SO_4), concentration and chromatographic separation (silica gel) from excess **21** (7.10 g, 71%) yielded **7f** (3.99 g, 69%) as a colorless viscous oil: R_F = 0.31 (system II); ^1H NMR δ 1.15-1.90 (m, 25H), 1.92-2.08 (m, 2H), 2.37-2.50 (m, 1H), 3.44-3.67 (m, 2H), 3.74-4.16 (m, 2H), 4.30-4.43 (m, 1H), 4.59-4.81 (m, 1H), 4.88-4.92 and 5.00-5.07 (m, 1H); IR (film) 3420 (m, br), 2240 (w), 1690 (s), 1495 (s), 1160 (m), 1025 cm^{-1} (m); $C_{21}H_{35}NO_5$ (381.51).

General procedure for the synthesis of acetates 8

To a solution of the alkynol **7** (20mmol), pyridine (1.78 ml, 22 mmol), and DMAP (10 mg) in CH_2Cl_2 (30 ml) was added acetic anhydride (2.07 ml) and the mixture was kept at r.t. for 16 h. The solvent was then removed *in vacuo* and the residue chromatographed (silica gel) to yield acetates **8** as colorless viscous oils.

(2*S*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)-7-(tetrahydropyran-2-yloxy)-4-octyne (8a). Yield 93%, R_F = 0.52 (system I); IR ($CHCl_3$) 3420 (w), 2990 (sh), 2980 (m), 2940 (m), 2880 (w), 2240 (w), 1730 (ss), 1700 (ss), 1500 (s), 1450 (m), 1370 (s), 1240 (ss), 1160 (s), 1130 (m), 1070 (m), 1020 (s), 1000 (m), 950 (w), 900 (w), 810 cm^{-1} (w); ^1H NMR δ 1.19 (d, J = 6.2 Hz, 3H, 8-H), 1.28 (d, J = 6.4 Hz, 3H, 1-H), 1.42 (s, 9H, $C(C\underline{H}_3)_3$), 1.43-1.90 (m, 6H, 3'-H, 4'-H, 5'-H), 2.03 (s, 3H, $C\underline{H}_3CO$), 2.25-2.60 (m, 2H, 6-H), 3.40-3.60 (m, 1H, $6'_{eq}$-H), 3.80-4.13 (m, 3H, $6'_{ax}$-H, 7-H, 2-H), 4.65 and 4.75 (each m, 1H, 2'-H), 5.00 (br s, 1H, N<u>H</u>), 5.33 (m, 1H, 3-H); ^{13}C NMR δ 16.61 (C-1), 20.80 (C-8), 21.17 ($\underline{C}H_3CO$), 25.32 (C-4'), 25.99 (C-5'), 27.30 (C-3'), 28.24 [$C(\underline{C}H_3)_3$], 30.78 (C-6), 48.28 (C-2), 62.46 (C-6'), 67.48 (C-3), 70.28 (C-7), 75.69 (C-5), 79.25 [$\underline{C}(CH_3)_3$], 84.80 (C-4), 97.62 (C-2'), 155.35 (NCO_2), 169.71 ($CH_3\underline{C}O$); FAB MS (*m*NBA matrix) *m/z* = 384.3 (19%) $[M+H]^+$, 300.2 (64), 244.1 (72), 226.1 (11), 200.1 (72), 184.1 (100), 140.1 (48), 123.1 (28); $C_{20}H_{33}NO_6$ (383.49).

(2*S*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)-1-phenyl-7-(tetrahydropyran-2-yloxy)-4-octyne (8b). Yield 89%, R_F = 0.38 (system I); IR ($CHCl_3$) 3460 (w), 3020 (m), 3000 (s), 2960 (s), 2880 (w), 2260 (w), 1750 (ss), 1720 (ss), 1510 (ss), 1460 (m), 1380 (s), 1300 (w), 1250 (ss), 1180 (s), 1150 (m), 1090 (m), 1040 (s), 1010 (m), 930 (w), 890 (w), 720 cm^{-1} (w); ^1H NMR (200 MHz) δ 1.21 and 1.31 (each d, J = 6.7 Hz, 3H), 1.41 (s, 9H), 1.43-1.92 (m, 6H), 2.03 (s, 3H), 2.30-2.58 (m, 2H), 2.87 (m, 2H), 3.49 (m, 1H), 3.80-4.17 (m, 2H), 4.28 (m, 1H), 4.68 and 4.78 (each m, 1H), 4.87 (br d, 1H, N<u>H</u>), 5.31 (m, 1H), 7.12-7.35 (m, 5H); ^{13}C NMR (100.6 MHz) δ 20.53, 21.06, 25.17, 25.79, 27.15, 28.02, 30.60, 37.41 (C-1), 53.38 (C-2), 62.14, 66.11, 70.39, 75.29, 79.00, 85.58, 97.22, 126.34, 128.20 (2C), 128.75 (2C), 136.92, 155.33, 169.28; FAB MS (*m*NBA matrix) *m/z* = 460.2 (39%) $[M+H]^+$, 376.2 (82), 320.1 (52), 302.1 (8), 276.1 (100), 260.1 (83), 242.1 (13), 216.1 (59), 181.1 (26); $C_{26}H_{37}NO_6$ (459.58).

***tert*-Butyl (3*S*)-4-Acetoxy-3-(*tert*-butoxycarbonylamino)-8-(tetrahydropyran-2-yloxy)-5-dodecynoate (8d).** Yield 98%, yellowish oil, R_F = 0.56 (system III); IR (film) 3420 (br, m), 2940 (s), 2240 (w), 1720 (s), 1500 (m), 1360 (s), 1160 (m), 1020 (s), 910 (m), 740 cm^{-1} (s); NMR δ 0.92 (m, 3H), 1.30-1.37 (m, 4H), 1.41-1.47 (m, 18H), 1.55-1.60 (m, 6H), 1.70-1.76 (m, 1H), 1.80-1.84 (m, 1H), 2.05-2.08 (m, 3H), 2.35-2.65 (m, 4H), 3.45-3.55 (m, 1H), 3.62-4.00 (m, 3H), 4.59-4.62 (m, 1H), 4.74-4.82 (m, 1H), 5.42-5.48 (m, 1H). Anal. Calcd. for $C_{28}H_{47}NO_8$ (525.68): C 63.98, H 9.01, N 2.66. Found: C 63.90, H 8.86, N 2.68.

2-[(4*S*)-3-Acetoxy-4-(*tert*-butoxycarbonylamino)-1-pentyn-1-yl]-1-(tetrahydropyran-2-yloxy)cyclohexane (8f). Yield 98%, R_F = 0.25 (EtOAc/hexanes = 1:5); IR (film) 3330 (m, br), 2925 (s), 2220 (w), 1740 (s), 1705 (s), 1225 cm^{-1} (s); ^1H NMR δ 1.19-1.27 (m, 3H), 1.32-1.88 (m, 21H), 1.92-2.09 (m, 5H), 2.34-2.50 (m, 1H), 3.42-3.73 (m, 2H), 3.89-4.16 (m, 2H), 4.52-4.73 (m, 1H), 4.84-4.90 and 5.06-5.52 (m, 2H); Anal. Calcd. for $C_{13}H_{37}NO_6$ (303.44): C 65.22, H 8.81, N 3.31. Found: C 65.19, H 9.07, N 3.46.

General procedure for the cleavage of the THP ethers 8

Method A: A solution of THP ether **8** (20 mmol) and *p*-toluenesulfonic acid (35 mg, 0.2 mmol) in methanol (80 ml) was stirred for 12 h at r.t. The reaction mixture was partitioned between EtOAc and aqueous $NaHCO_3$ and the aqueous layer extracted with EtOAc. The combined organic extracts were then washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The crude alcohols **9** were purified by chromatography on silica gel (ether/hexane = 2:1).

Method B[24]: A solution of THP ether **8** (20 mmol) and pyridinium *p*-toluenesulfonate (0.49 g, 2.0 mmol) in absolute ethanol (100 ml) was stirred for 3.5 h at 55 °C. The crude alcohols **9** were obtained as described above and were purified by chromatography on silica gel (ether/hexane = 2:1).

Method C: A solution of THP ether **8** (10 mmol) and pyridinium *p*-toluenesulfonate (0.25 g) in dimethoxyethane (25 ml) and glycol (40 ml) was warmed to 70 °C for 3 h. The mixture was cooled to r.t. over 90 min and ether was added. Workup as described above and chromatographic purification yielded alcohols **9**. In comparison to method B this procedure allowed a more selective removal of the THP protecting group.

(2*S*)-3-Acetoxy-(2-*tert*-butoxycarbonylamino)-4-octyn-7-ol (9a). Yield 82% (method A), 53% (B), colorless oil, R_F = 0.33 (ether/hexanes = 2:1); IR ($CHCl_3$) 3440 (w), 2990 (w), 2980 (m), 2940 (m), 2880 (w), 1740 (ss), 1710 (ss), 1500 (s), 1450 (w), 1370 (m), 1240 (ss), 1210 (ss), 1170 (s), 1060 (m), 980 (w), 950 (w), 850 cm^{-1} (w); ^1H NMR (200 MHz) δ 1.18 (d, J = 6.7 Hz, 3H, 8-H), 1.23 (d, J = 6.4 Hz, 3H, 1-H), 1.42 (s, 9H, [C(CH_3)$_3$]), 2.03 (s, 3H, CH_3CO), 2.20-2.50 (m, 2H, 6-H), 3.95 (m, 2H, 2-H, 7-H), 4.72 (br d, 1H, NH), 5.30 (m, 1H, 3-H); ^{13}C NMR (100.6 MHz) δ 16.57 (C-1), 20.86 (CH_3CO), 22.36 (C-8), 28.25 [C(CH_3)$_3$], 29.04 (C-6), 48.43 (C-2), 66.02 (C-7), 67.30 (C-3), 79.46 [$C(CH_3)_3$], 84.00 (C-5), 84.53 (C-4), 155.28 (NCO_2), 169.98 (CH_3CO); FAB MS (*m*NBA matrix) *m/z* = 300.3 (24%) $[M + H]^+$, 244.2 (42), 200.2 (69), 184.2 (100), 154.1 (33), 140.1 (73), 107.1 (20); $C_{15}H_{25}NO_5$ (299.37).

(2*S*)-3-Acetoxy-(2-*tert*-butoxycarbonylamino)-1-phenyl-4-octyn-7-ol (9b). Yield 79% (method A), colorless oil, R_F = 0.27 (ether/hexanes = 2:1); IR ($CHCl_3$) 3440 (m), 3010 (m), 2980 (s), 2930 (m), 2870 (w), 2220 (w), 1735 (ss), 1700 (ss), 1500 (ss), 1450 (w), 1370 (m), 1240 (ss), 1210 (ss), 1160 (s), 1110 (w), 1030 (m), 980 (w), 940 (w), 850 (w), 700 cm^{-1} (w); ^1H NMR (200 MHz) δ 1.28 (d, J = 6.1 Hz, 3H), 1.40 (s, 9H), 2.05 (s, 3H), 2.25-2.48 (m, 2H, 6-H), 2.85 (m, 2H), 3.97 (m, 1H), 4.25 (m, 1H), 4.75 (br d, 1H, NH), 5.29 (m, 1H), 7.12-7.35 (m, 5H); ^{13}C NMR (100.6 MHz) δ 20.99, 22.58, 28.32, 29.30, 37.74 (C-1), 53.68 (C-2), 66.25, 79.73, 84.12, 85.21, 126.77, 128.61 (2C), 129.14 (2C), 136.93, 155.49, 169.91; FAB MS (*m*NBA matrix) *m/z* = 376.2 (26%) $[M + H]^+$, 320.1 (20), 260.1 (57), 216.1 (53), 199.1 (17), 181.1 (11); $C_{21}H_{29}NO_5$ (375.47).

(10*S*)-9-Acetoxy-10-(*tert*-butoxycarbonylamino)-7-undecyn-5-ol (9c). Yield 69% (method B), oil: R_F = 0.33 (system II); IR (film) 3370 (br, s), 2225 (m), 1700 (s), 1520 (s), 1455 (m), 1240 (s), 1170 (s), 740 cm^{-1} (s); ^1H NMR δ 0.91 (m, 3H), 1.20 (m, 3H), 1.27-1.40 (m, 4H), 1.45 (s, 9H), 1.53 (br m, 2H), 2.08 (m, 3H), 2.28-2.49 (m, 2H), 2.59 (br s, 1H), 3.75 (m, 1H), 4.05 (br s, 1H), 4.82 (br m, 1H), 5.34 (m, 1H); $C_{18}H_{31}NO_5$ (341.45).

***tert*-Butyl (3*S*)-4-Acetoxy-3-(*tert*-butoxycarbonylamino)-8-hydroxy-5-dodecynoate (9d).** Yield 89% (method C), oil, R_F = 0.55 (system I); IR (film) 3440 (br, m), 2960 (m), 2920 (m), 2240 (w), 1720 (s), 1500 (m), 1360 (s), 1260 (m), 1160 (s), 1040 (s), 910 (m), 740 cm^{-1} (s); ^1H NMR δ 0.91 (m, 3H), 1.28-1.38 (m, 4H), 1.45 (s, 18H), 1.48-1.55 (m, 3H), 2.07-2.10 (m, 3H), 2.25-2.62 (m, 4H), 3.68-3.74 (m, 1H), 4.10-4.45 (m, 1H), 5.03-5.09 (m, 1H), 5.40-5.50 (m, 1H); ^{13}C NMR δ 13.93, 20.78, 21.01, 22.53, 27.66, 27.74, 27.93, 28.22, 28.27, 36.00, 36.04, 37.47, 37.70, 50.20, 50.53, 50.71, 65.47, 65.55, 69.69, 69.86, 79.75, 79.82, 81.39, 84.67, 155.29, 169.67, 169.7; Anal. Calcd. for $C_{23}H_{39}NO_7$ (441.57): C 62.56, H 8.90, N 3.17. Found: C 63.13, H 9.28, N 3.12.

9-Acetoxy-10-(*tert*-butoxycarbonylamino)-10-methyl-7-undecyn-5-ol (9e). Yield 89% (method B), oil, R_F = 0.28 (system III); ^1H NMR δ 0.91 (t, J = 7.1 Hz, 3H), 1.30-1.42 (m, 10H), 1.43 (s, 9H), 1.48-1.56 (m, 2H), 2.10 (s, 3H), 2.20 (dd, J = 9.9, 5.3 Hz, 1H), 2.30-2.48 (m, 2H), 3.69-3.77 (m, 1H), 4.61 (br s, 1H), 5.66 and 5.69 (each t, J = 2.0 Hz, 1H); ^{13}C NMR δ 14.00, 20.92, 22.61, 27.75, 28.39, 36.05, 36.08, 55.10, 68.66, 68.75, 69.95, 69.97, 77.95, 77.97, 79.90, 83.91, 154.47, 169.63, 169.66; IR (film) 3330 (m, br), 2220 (w), 1730 (s), 1230 (s), 1160 cm^{-1} (s); Anal. Calcd. for $C_{19}H_{33}NO_5$ (355.47): C 64.20, H 9.36, N 3.94. Found: C 64.34, H 9.18, N 3.99.

2-[(4*S*)-3-Acetoxy-4-(*tert*-butoxycarbonylamino)-1-pentyn-1-yl]cyclohexanol (9f). Yield 97% (method C), viscous colorless oil, R_F = 0.29 (system II); IR (film) 3360 (m, br), 2220 (w), 1700 (s), 1505 (m), 1365 (m), 1230 cm^{-1} (s); ^1H NMR δ 1.05-1.41 (m, 8H), 1.45 and 1.46 (each s, 9H), 1.60-1.69 (m, 1H), 1.72-1.78 (m, 1H), 1.93-2.04 (m, 2H), 2.08 and 2.10 (each s, 3H), 2.16-2.20 (m, 1H), 3.36-3.50 (m, 1H), 3.98-4.14 (m, 1H), 4.60-4.77 (m, 1H), 5.30-5.39 (m, 1H); ^{13}C NMR δ 16.78, 20.87, 20.95, 24.14, 24.72, 24.75, 28.32, 28.36, 30.78, 33.20, 38.96, 49.09, 66.71, 67.27, 73.19, 79.78, 155.24, 169.71, 169.88; $C_{18}H_{29}NO_5$ (339.43).

General procedure for the synthesis of the (*Z*)-alkenes 10

To a solution of alkyne **9** (20 mmol) in either *n*-hexane/ether = 5:1 (**9a**, **9b**), THF/*n*-hexane = 1:1 (**9c**, **9e**) or benzene (**9d**, **9f**) were added Lindlar catalyst[25] (0.75 g, in the case of **9e** 2 g) and freshly distilled quinoline (0.15 g, resp. 0.3 g). The mixture was vigorously shaken and the hydrogen uptake monitored by a gas burette. After the hydrogen uptake had ceased the mixture was filtered through celite and the residue washed with EtOAc. The organic phases were washed with 10% H_3PO_4 and brine and dried ($MgSO_4$). Evaporation of the solvent and chromatography (silica gel) of the residue gave the (*Z*)-alkenes **10**.

(2*S*,4*Z*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)-4-octen-7-ol (10a). Yield 95%, colorless oil, R_F = 0.33 (ether/hexanes = 2:1); IR ($CHCl_3$) 3440 (m), 3000 (m), 2980 (s), 2920 (m), 2880 (w), 1730 (ss), 1700 (ss), 1500 (s), 1450 (w), 1390 (sh), 1360 (m), 1240 (s), 1200 (s), 1160 (s), 1050 (m), 1020 (w), 980 (w), 940 (w), 750 cm^{-1} (m); ^1H NMR (200 MHz) δ 1.14 (d, J = 6.9 Hz, 3H, 8-H), 1.23 (d, J = 6.4 Hz, 3H, 1-H), 1.42 (s, 9H, [C(C<u>H</u>$_3$)$_3$]), 2.03 (s, 3H, C<u>H</u>$_3$CO), 2.15-2.60 (m, 2H, 6-H), 3.87 (m, 2H, 2-H, 7-H), 4.70 (br d, 1H, N<u>H</u>), 5.44 (m, 2H, 3-H, 4-H), 5.70 (m, 1H, 5-H); ^{13}C NMR (100.6 MHz) δ 15.64 (C-1), 20.95 (<u>C</u>H$_3$CO), 22.96 (C-8), 28.18 [C(<u>C</u>H$_3$)$_3$], 37.29 (C-6), 48.83 (C-2), 66.82 (C-7), 72.68 (C-3), 79.16 [<u>C</u>(CH$_3$)$_3$], 126.98 (C-5), 132.19 (C-4), 155.23 (N<u>C</u>O$_2$), 170.57 (CH$_3$<u>C</u>O); $C_{15}H_{27}NO_5$ (301.38).

(2*S*,4*Z*)-3-Acetoxy-(2-*tert*-butoxycarbonylamino)-1-phenyl-4-octen-7-ol (10b). Yield 98%, colorless oil, R_F = 0.27 (ether/hexanes = 2:1); IR ($CHCl_3$) 3430 (m), 3000 (m), 2970 (s), 2930 (m), 2870 (w), 1730 (ss), 1700 (ss), 1500 (s), 1450 (m), 1390 (m), 1365 (s), 1240 (ss), 1200 (s), 1160 (s), 1020 (m), 970 (w), 840 (m), 700 cm^{-1} (m); ^1H NMR (200 MHz) δ 1.22 (d, J = 6.3 Hz, 3H), 1.37 (s, 9H), 2.06 (s, 3H), 2.10-2.47 (m, 2H, 6-H), 2.60-3.00 (m, 2H), 3.84 (m, 1H), 4.12 (m, 1H), 4.68 (br d, J = 9.6 Hz, 1H, N<u>H</u>), 5.48 (m, 2H), 5.76 (m, 1H), 7.12-7.35 (m, 5H); ^{13}C NMR (100.6 MHz) δ 21.30, 23.37, 28.34, 37.75 (C-1), 37.82 (C-6), 53.80 (C-2), 67.28, 72.20, 79.61, 126.55, 127.51, 128.48 (2C), 129.30 (2C), 131.93, 137.49, 155.36, 170.13; FAB MS (*m*NBA matrix) *m*/z = 378.2 (18%) $[M+H]^+$, 307.1 (16), 262.1 (36), 218.1 (75). $C_{21}H_{31}NO_5$ (377.48).

(7*Z*,10*S*)-9-Acetoxy-10-(*tert*-butoxycarbonylamino)-7-undecen-5-ol (10c). Yield 91%, oil, R_F = 0.32 (system II); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H), 1.13 (m, 3H), 1.25-1.38 (m, 4H), 1.45 (s, 9H), 1.48 (m, 2H), 2.05 (s, 3H), 2.22-2.41 (m, 2H), 2.79 (br s, 1H), 3.66 (m, 1H), 3.88 (br s, 1H), 4.69 (d) and 4.87 (br d, 1H), 5.38-5.57 (m, 2H), 5.73 (m, 1H); IR (film) 3360 (br, m), 1710 (s), 1240 cm^{-1} (s); Anal. Calcd. for $C_{18}H_{33}NO_5$ (343.46): C 62.95, H 9.68, N 4.08. Found: C 62.91, H 9.85, N 3.73.

***tert*-Butyl (3*S*,5*Z*)-3-(*tert*-Butoxycarbonylamino)-8-hydroxy-5-dodecenoate (10d).** Yield 98%, oil, R_F = 0.39 (system II); IR (film) 3360 (br, m), 3320 (sh), 1720 (s), 1500 (m), 1360 (s), 1230 (s), 1160 (s), 1020 cm^{-1} (m). Anal. Calcd. for $C_{23}H_{41}NO_7$ (443.58): C 62.28, H 9.32, N 3.16. Found: C 62.57, H 9.16, N 3.05.

(*Z*)-9-Acetoxy-10-(*tert*-butoxycarbonylamino)-10-methyl-7-undecen-5-ol (10e). Yield 93%, colorless oil, R_F = 0.39 (system II); ^1H NMR δ 0.88-0.93 (m, 3H), 1.28-1.55 (m, 21H), 2.05 (s, 3H), 2.20-2.63 (m, 3H), 3.57-3.75 (m, 1H), 4.55 and 4.73 (each s, 1H), 5.38-5.47 (m, 1H), 5.71-5.86 (m, 2H); ^{13}C NMR δ 14.05, 14.08, 21.18, 21.19, 22.70, 22.73, 27.87, 28.02, 28.42, 28.44, 35.57, 36.29, 36.60, 37.67, 54.84, 54.97, 70.96, 71.04, 73.51, 73.93, 133.06, 133.11, 154.30, 170.14, 170.66; IR (film) 3453 (m), 3368 (m), 1725 (s), 1248 (s) cm^{-1}; Anal. Calcd. for $C_{19}H_{35}NO_5$ (357.49): C 63.84, H 9.87, N 3.92. Found: C 64.02, H 9.69, N 4.07.

(*Z*)-2-[(4*S*)-3-Acetoxy-4-(*tert*-butoxycarbonylamino)-1-penten-1-yl]cyclohexanol (10f). Chromatography of the crude product yielded two fractions of diastereomers with different polarity. The less polar fraction (1.38 g, 47%) was a viscous colorless oil, R_F = 0.43 (system I); IR (film) 3340 (m), 1690 (s), 1520 (m), 1370 (m), 1235 cm^{-1} (s); ^1H NMR δ 1.06-1.16 (m, 4H), 1.23-1.32 (m, 3H), 1.44 (s, 9H), 1.60-1.68 (m, 1H), 1.71-1.79 (m, 2H), 2.02-2.07 (m, 4H), 2.25-2.35 (m, 1H), 2.42-2.65 and 2.83-2.94 (m, 1H), 3.14-3.30 (m, 1H), 3.76-4.15 (m, 1H), 4.89-5.06 (m, 1H), 5.32-5.64 (m, 3H); ^{13}C NMR δ 16.98, 21.11, 21.18, 24.94, 28.40, 31.25, 34.40, 46.19, 49.26, 72.68, 73.56, 79.59, 126.64, 137.41, 155.46, 169.96. The more polar fraction (1.48 g, 50%) was a material which slowly crystallized during drying *in vacuo*, m.p. 99-101 °C (hexane); R_F = 0.32

(system I); IR (film) 3505 (m), 3315 (m), 1715 (s), 1515 (m), 1365 (m), 1245 (s), 1170 cm^{-1} (s); ^1H NMR δ 1.14 (2 x d, J = 7.0 Hz, 3H), 1.18-1.30 (m, 4H), 1.45 (s, 9H), 1.60-1.69 (m, 2H), 1.73-1.80 (m, 1H), 2.03-2.08 (m, 4H), 2.32-2.43 (m, 1H), 2.78-2.94 (m, 1H), 3.15-3.26 (m, 1H), 3.89 (br s, 1H), 4.47-4.71 (m, 1H), 5.27-5.43 (m, 2H), 5.47-5.58 (m, 1H); ^{13}C NMR δ 16.23, 16.77, 21.10, 21.14, 24.68, 24.94, 25.01, 28.32, 28.36, 31.61, 31.65, 34.52, 34.69, 45.57, 48.54, 73.33, 73.42, 79.42, 125.74, 139.12, 155.06, 171.08; Anal. Calcd. for $C_{18}H_{31}NO_5$ (341.45): C 63.32, H 9.15, N 4.10; Found: C 63.11, H 9.17, N 3.84.

General procedure for the synthesis of ketones 11[13]

Alcohol **10** (15 mmol) was added at 0 °C to pyridinium chlorochromate (PCC) (6.65 g, 30.8 mmol) and CH_2Cl_2 (60 ml). After 2.5 h at r.t. TLC analysis indicated almost complete consumption of **10**. Et_2O (50 ml) was added and the mixture was filtered through a pad of Florisil (5 cm). The residue was washed with Et_2O. Evaporation of the solvent yielded the crude oily ketones **11** which were used in the next step without further purification. Chromatography on silica gel led to elimination of acetic acid and the formation of dienones (see compound **13**).

(4*Z*,7*S*)-6-Acetoxy-7-(*tert*-butoxycarbonylamino)-4-octen-2-one (11a). Yield 85%; IR ($CHCl_3$) 3420 (m), 2990 (m), 2970 (m), 2920 (w), 1710 (ss), 1500 (ss), 1460 (w), 1360 (m), 1260 (ss), 1240 (s), 1160 (s), 1050 (w), 1020 (m), 970 (w), 910 (m), 850 (w), 710 cm^{-1} (s); ^1H NMR δ 1.05 (d, J = 6.9 Hz, 3H, 8-H), 1.42 (s, 9H, [C(C$\underline{H}_3$)$_3$]), 1.97 (s, 3H, C$\underline{H}_3$CO), 2.12 (s, 3H, 1-H), 3.21 (ddd, J = 18.0, 7.0, 2.0 Hz, 1H, 3-H), 3.39 (ddd, J = 18.0, 7.0, 1.0 Hz, 1H, 3-H), 3.74 (m, 1H, 7-H), 4.53 (br s, 1H, N$\underline{H}$), 5.30 (dd, J = 9.0, 4.5 Hz, 1H, 6-H), 5.42 (ddt, J = 11.0, 9.0, 1.5 Hz, 1H, 5-H), 5.79 (dtd, J = 11.0, 7.0, 1.0 Hz, 1H, 4-H); ^{13}C NMR δ 15.79 (C-8), 20.97 (C$\underline{H}_3$CO), 28.29 [C(C$\underline{H}_3$)$_3$], 30.80 (C-1), 42.26 (C-3), 48.71 (C-7), 72.47 (C-6), 79.37 [$\underline{C}$(CH$_3$)$_3$], 126.92 (C-4), 127.84 (C-5), 155.08 (N$\underline{C}$O$_2$), 170.15 (CH$_3\underline{C}$O), 205.97 (C-2); FAB MS (*m*NBA matrix) *m*/z = 300.2 (29%) $[M + H]^+$, 289.1 (71), 273.1 (22), 258.1 (44), 242.1 (53), 202.1 (56), 184.1 (100), 165.1 (49); $C_{15}H_{25}NO_5$ (299.37).

(4*Z*,7*S*)-6-Acetoxy-7-(*tert*-butoxycarbonylamino)-8-phenyl-4-octen-2-one (11b). Yield 78%, colorless oil, R_F = 0.50 (ether/hexanes = 2:1); IR ($CHCl_3$) 3430 (w), 2980 (w), 2930 (w), 1710 (ss), 1500 (s), 1450 (w), 1370 (s), 1240 (ss), 1230 (s), 1160 (s), 1020 (m), 970 (w), 860 (m), 700 cm^{-1} (m); ^1H NMR (200 MHz) δ 1.35 (s, 9H), 2.15 (s, 3H), 2.06 (s, 3H, CH_3CO), 2.75 and 2.88 (each dd, J = 14.5, 5.3 Hz, 2H), 3.27 and 3.41 (each dd, J = 18.7, 7.0, 2H), 4.07 (m, 1H), 4.60 (br d, J = 9.6 Hz, 1H, N$\underline{H}$), 5.38 (dd, J = 9.6, 6.0 Hz, 1H), 5.52 (dd, J = 11.0, 9.2 Hz, 1H), 5.87 (dt, J = 11.0, 7.2 Hz, 1H, 4-H), 7.10-7.37 (m, 5H); ^{13}C NMR (100.6 MHz) δ 20.79, 28.27, 30.00, 36.55, 43.00, 53.32, 71.79, 78.86, 126.50, 127.03, 128.47 (2C), 128.59, 129.48 (2C), 137.79, 155.45, 170.84, 205.66; FAB MS (*m*NBA matrix) *m*/z = 376.2 (24%) $[M + H]^+$, 350.1 (7), 334.1 (47), 320.1 (33);. $C_{21}H_{29}NO_5$ (375.46).

(7*Z*,10*S*)-9-Acetoxy-10-(*tert*-butoxycarbonylamino)-7-undecen-5-one (11c). R_F = 0.57 (system II); IR (film) 3360 (br, m), 1710 (s), 1520 (s), 1450 (m), 1365 (s), 1240 (s), 1170 cm^{-1} (s); ^1H NMR δ 0.91 (t, 3H), 1.13 (m, 3H), 1.32 (m, 2H), 1.45 (s, 9H), 1.58 (m, 2H), 2.05 (2 x s, 3H), 2.47 (q, 2H), 3.23-3.49 (m, 2H), 3.86 (br s, 1H), 4.66 and 4.79 (each d, 1H), 5.42 (m, 1H), 5.52 (m, 1H), 5.88 (m, 1H); $C_{18}H_{31}NO_5$ (341.45).

***tert*-Butyl (3*S*,5*Z*)-4-Acetoxy-3-(*tert*-butoxycarbonylamino)-8-oxo-5-dodecenoate (11d).** Yield 84%, yellowish oil, R_F = 0.33 (system III); IR (film) 3360 (br, m), 2960 (m), 1740 (s), 1500 (m), 1370 (s), 1230 (s), 1160 (s), 1045 (m), 1020 cm^{-1} (m); ^1H NMR δ 0.87-0.94 (m, 3H), 1.22-1.64 (m, 22H), 2.04 (s, 3H), 2.30-2.62 (m, 4H), 3.20-3.53 (m, 2H), 4.04-4.18 (m, 1H), 4.90-4.98 and 5.20-5.25 (m, 1H), 5.40-5.60 (m, 2H), 5.85-5.93 (m, 1H); ^{13}C NMR δ 13.83, 21.04, 22.30, 22.41, 22.49, 25.80, 28.01, 28.07, 28.16, 28.33, 37.31, 41.30, 42.56, 42.62, 50.39, 70.60, 71.07, 79.55, 81.28, 81.34, 127.05, 127.49, 128.06, 128.48, 155.22, 169.88, 170.00, 170.09, 207.89; $C_{23}H_{39}NO_7$ (441.57).

(*Z*)-9-Acetoxy-10-(*tert*-butoxycarbonylamino)-10-methyl-7-undecen-5-one (11e). DMSO (2.66 ml, 37.5 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of $(COCl)_2$ (2.42 ml, 28.2 mmol) in CH_2Cl_2

(20 ml) at -63 °C.[16] **10e** (6.70 g, 18.7 mmol) in CH_2Cl_2 (130 ml) was added over 30 min. The resulting suspension was stirred for an additional 30 min at -63 °C followed by the dropwise addition of NEt_3 (10.5 ml, 75.0 mmol) in CH_2Cl_2 (20 ml) over 15 min. After 20 min H_2O (28 ml) was added. The mixture was then partitioned between ether/hexanes = 1:1 and $KHSO_4$ (9.1 g) in H_2O (90 ml). The organic layer was separated and washed sequentially with saturated aqueous $NaHCO_3$, H_2O and brine. After drying ($MgSO_4$) a small amount (0.46 g, 7%) of unreacted **10e** was separated from ketone **11e** (5.62 g, 91% at 93% conversion). Yellow oil, R_F = 0.41 (system III); ^{1}H NMR δ 0.90 (t, J = 7.3 Hz, 3H), 1.24-1.33 (m, 8H), 1.42 (s, 9H), 1.50-1.61 (m, 2H), 2.04 (s, 3H), 2.46 (td, J = 7.2, 2.0 Hz, 2H), 3.30 (ddd, J = 18.7, 6.3, 2.0 Hz, 1H), 3.60 (ddd, J = 18.7, 7.5, 1.6 Hz, 1H), 4.58 (br s, 1H), 5.45-5.52 (m, 1H), 5.81 (d, J = 10.2 Hz, 1H), 5.96 (dt, J = 13.8, 5.8 Hz, 1H); ^{13}C NMR δ 13.83, 21.05, 22.30, 23.26, 25.82, 28.39, 41.34, 42.59, 54.73, 72.78, 79.30, 126.22, 128.93, 154.46, 169.77, 208.30; IR (film) 3369 (w), 1739 (s), 1717 (s), 1367 (s), 1241 (s), 1173 cm^{-1} (s); Anal. Calcd. for $C_{19}H_{33}NO_5$ (355.47): C 64.20, H 9.36, N 3.94. Found: C 64.33, H 9.41, N 3.60.

(*Z*)-2-[(4*S*)-3-Acetoxy-4-(*tert*-butoxycarbonylamino)-1-penten-1-yl]cyclohexanone (11f).

The less polar fraction of **10f** (1.35 g, 3.95 mmol) was treated with pyridinium chlorochromate (2.88 g, 10.6 mmol) in CH_2Cl_2 (20 ml) and stirred at r.t. for 24 h. TLC analysis indicated complete consumption of the starting material. Et_2O (40 ml) was added, the mixture was filtered through a pad of Florisil (7 cm) and the residue was washed well with Et_2O. Evaporation of the solvent yielded diastereomer **11f** (1.30 g, 97%) as a colorless oil, which was sufficiently pure for further transformation without additional purification, R_F = 0.49 (system I); ^{1}H NMR δ 1.10 (2 x d, J = 7.1 Hz, 3H), 1.41 and 1.42 (each s, 9H), 1.57-1.80 (m, 3H), 1.85-1.92 (m, 1H), 2.02-2.20 (m, 5H), 2.29-2.47 (m, 2H), 3.40-3.59 (m, 1H), 3.74-3.92 (m, 1H), 4.47-4.76 (m, 1H), 5.28-5.31 (m, 1H), 5.42-5.52 (m, 1H), 5.67-5.75 (m, 1H); ^{13}C NMR δ 21.10, 21.15, 24.34, 24.43, 27.56, 28.38, 28.40, 28.44, 28.45, 34.43, 34.55, 41.87, 41.94, 50.02, 50.31, 71.90, 79.29, 126.06, 132.57, 155.16, 170.14, 210.73.

The more polar fraction of **10f** (1.39 g, 4.07 mmol) was treated as above to yield diastereomer **11f** (1.24 g, 90%): yellowish oil, R_F = 0.46 (system I); IR (film) 3360 (br, w), 1715 (s), 1510 (s), 1370 (s), 1240 (s), 1170 (s), 690 cm^{-1} (s); ^{1}H NMR δ 1.13 (2 x d, J = 6.8 Hz, 3H), 1.45 (s, 9H), 1.54-2.13 (m, 9H), 2.30-2.43 (m, 2H), 3.50-3.63 (m, 1H), 3.85 (br s, 1H), 4.54 (br s, 1H), 5.32-5.58 (m, 2H), 5.82-5.92 (m, 1H); ^{13}C NMR δ 17.48, 20.94, 24.78, 27.68, 28.27, 28.36, 35.28, 41.85, 48.92, 49.62, 71.35, 72.26, 79.44, 125.62, 133.26, 133.85, 155.18, 170.05, 210.21, 210.34; Anal. Calcd. for $C_{18}H_{29}NO_5$ (339.43): C 63.69, H 8.61, N 4.13. Found: C 64.10, H 8.90, N 3.73.

General procedure for the synthesis of the 2*H*-azepines 12

Ketone **11** (1 mmol) in CH_2Cl_2 (5 ml) was added over 15 min to a mixture of trifluoroacetic acid (0.77 ml, 10 mmol) and CH_2Cl_2 (20 ml) at 0 °C. The mixture was stirred for 18 h at r.t. and then treated with triethylamine (1.39 ml, 10 mmol). The solution was washed twice with water, the aqueous layers extracted with CH_2Cl_2 and the combined organic phases dried (Na_2SO_4). The solvent was carefully removed under reduced pressure, whereby the bath temperature should not exceed 5 °C because of the high volatility of simple 2*H*-azepines. The product was purified by flash-chromatography on silica gel.

(*S*)- and (*R*)-2,7-Dimethyl-2*H*-azepine (12a). Yield 56%, aggressive smelling liquid, R_F = 0.23 (ether/hexanes = 5:1); (*S*)-**12a**: $[\alpha]_D^{24}$ = -36.5° (*c* = 1.0, Et_2O), (*R*)-**12a**: $[\alpha]_D^{24}$ = +34.0° (*c* = 0.05, Et_2O); (*S*)-**12a**: CD (EtOH) $\Delta\varepsilon_{235}$ = +6.38, $\Delta\varepsilon_{264}$ = 0, $\Delta\varepsilon_{295}$ = -5.31, (*R*)-**12a**: $\Delta\varepsilon_{235}$ = -6.38, $\Delta\varepsilon_{264}$ = 0, $\Delta\varepsilon_{295}$ = +5.31; UV (EtOH) λ_{max} = 237, 285 (sh), 315 nm (sh); IR ($CHCl_3$) 3200 (br), 3000 (sh), 2960 (ss), 2910 (ss), 2860 (m), 2820 (w), 1710 (ss), 1600 (s), 1530 (m), 1490 (w), 1430 (s), 1370 (ss), 1240 (s), 1160 (m), 1070 (m), 1020 (m), 910 (m), 850 (w), 800 (w), 660 (m), 610 cm^{-1} (m); ^{1}H and ^{13}C NMR, see Table 1. EI-MS (DE, 180 °C) *m/z* 121 (48%, M^+), 80 (71), 71 (8), 69 (8), 57 (20), 52 (100), 51 (31); HRMS calcd for $C_8H_{11}N$ 121.0892, found 121.0894.

(*S*)-2-Benzyl-7-methyl-2H-azepine (12b). Yield 63%, aggressive smelling liquid, R_F = 0.34 (ether/hexanes = 3:2); $[\alpha]_D^{24}$ = -101.7° (*c* = 0.70, Et_2O); CD (EtOH) $\Delta\varepsilon_{235}$ = +15.64, $\Delta\varepsilon_{295}$ = -11.82; UV

(EtOH) λ_{max} = 235 nm (log ε = 3.60), 295 (3.09), 325 (2.65); IR ($CHCl_3$) 3200 (br), 3080 (w), 3050 (w), 3000 (m), 2920 (ss), 2840 (m), 1680 (m), 1600 (ss), 1530 (m), 1490 (m), 1445 (m), 1425 (ss), 1370 (m), 1240 (m), 1090 (m), 1030 (w), 970 (m), 910 (m), 700 (ss), 660 (m), 630 cm^{-1} (m); ^1H NMR (200 MHz): δ 2.13 (s, 3H, CH_3), 2.97 (ddt, *J* = 8.6, 6.5, 5.3 Hz, 1H, 2-H), 3.22 (dd, *J* = 13.7, 8.6 Hz, 1H, 8-H), 3.42 (dd, *J* = 13.7, 6.5, 1H, 8'-H), 5.72 (ddt, *J* = 9.4, 5.3, 0.9 Hz, 1H, 3-H), 6.17 (dddd, *J* = 9.4, 4.8, 1.8, 1.8 Hz, 1H, 4 H), 6.67 (dd, *J* = 11.5, 4.8 Hz, 1H, 5-H), 6.67 (ddq, *J* = 11.5, 1.8, 0.9 Hz, 1H, 6-H), 7.15-7.33 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz) δ 24.12 (Q, *J* = 128 Hz, C-13), 42.00 (T, *J* = 128 Hz, C-8), 60.83 (Dddt, *J* = 134, 9.0, 4.0, 4.0 Hz, C-2), 126.07 (Dddd, *J* = 160, 6.0, 6.0, 2.0 Hz, C-12), 126.66 (Ddd, *J* = 159, 10.0, 5.0 Hz, C-4), 128.22 (Dd, *J* = 159, 6.0 Hz, C-11, C-11'), 129.33 (Dddt, *J* = 158, 5.0, 5.0, 4.8 Hz, C-10, C-10'), 133.00 (Dm, *J* = 159 Hz, C-6), 133.48 (Ddt, *J* = 161, 9.0, 5.0 Hz, C-3), 135.65 (Dddd, *J* = 158, 10.0, 1.8, 1.8 Hz, C-5), 139.30 (m, C-9), 163.46 (m, C-7); EI-MS (DE, 180 °C) *m/z* 198 (9%), 197 (88, M^+), 196 (72), 182 (21), 157 (15), 141 (18), 128 (10), 115 (18), 106 (100), 104 (55), 92 (59), 79 (15), 78 (13), 77 (19), 65 (24), 57 (51), 41 (13), 39 (8), 32 (71); HRMS calcd for $C_{14}H_{15}N$ 197.1204, found 197.1203.

(*S*)-7-Butyl-2-methyl-2*H*-azepine (12c). Crude ketone **11c** (0.49 g, 1.4 mmol) was dissolved in CH_2Cl_2 (20 ml) and treated with TFA (1.1 ml, 14 mmol). The mixture turned from yellow to orange. After 160 min at r.t. CH_2Cl_2 (30 ml) was added and the solution was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (silica gel) afforded the pure azepine **12c** (0.15 g, 64%) as a slightly yellow oil with strongly pungent smell and taste, R_F = 0.35 (system III); $[\alpha]_D^{24}$ = -103° (*c* = 1.0, $CHCl_3$); UV (EtOH) λ_{max} = 287 nm (lg ε = 2.87), 310 (sh), 320 (sh); IR (film) 3020 (m), 1620 (sh), 1600 (s), 1450 (s), 1430 (s), 1375 (s), 1060 (s), 735 cm^{-1} (s); ^1H NMR δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.29 (m, 2H), 1.49 (m, 2H), 1.59 (d, *J* = 6.5 Hz, 3H), 2.37 (m, 2H), 2.79 (quintet, *J* = 6.5 Hz, 1H), 5.60 (ddt, *J* = 9.3, 5.4, 0.9 Hz, 1H), 6.18 (ddt, *J* = 9.3, 5.4, 1.6 Hz, 1H), 6.70-6.80 (m, 2H); ^{13}C NMR δ 13.94, 21.92, 22.56, 30.84, 37.93, 54.99, 126.17, 132.75, 135.66, 136.11, 166.77; $C_{11}H_{17}N$ (163.26).

***tert*-Butyl (*S*)-(7-Butyl-2*H*-azepin-2-yl)acetate (12d).** Ketone **11d** (0.45 g, 1.0 mmol) in CH_2Cl_2 (10 ml) was treated with TFA (1.56 ml, 20.2 mmol). The solution first turned to red, later to brown. After 2 h at r.t. the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated and chromatographed (silica gel) to give **12d** (120 mg, 45%) as a yellow oil, R_F = 0.49 (system II); $[\alpha]_D^{24}$ = -70° (*c* = 0.25, *t*-BuOMe); UV (*t*-BuOMe) λ_{max} = 204 nm (lg ε = 3.61), 224 (3.66), 312 (2.97); IR (film) 3010 (sh), 2960 (m), 1735 (s), 1610 (w), 1540 (w), 1460 (w), 1370 (m), 1260 (m), 1155 (s), 955 (w), 855 (w), 760 cm^{-1} (w); ^1H NMR δ 0.84 (t, *J* = 7.3 Hz, 3H), 1.17-1.30 (m, 2H), 1.38-1.50 and 1.41 (m and s, 11H), 2.23-2.39 (m, 2H), 2.79 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.94 (dd, *J* = 15.1, 7.1 Hz, 1H), 3.03-3.11 (m, 1H), 5.62 (dd, *J* = 9.4, 5.4 Hz, 1H), 6.19 (ddt, *J* = 9.4, 4.7, 1.8 Hz, 1H), 6.66-6.78 (m, 2H); ^{13}C NMR δ 13.86, 22.37, 28.09, 30.52, 37.54, 42.00, 56.77, 80.32, 126.61, 132.72, 132.75, 136.03, 167.27, 171.33; Anal. Calcd. for $C_{16}H_{25}NO_2$ (263.38): C 72.97, H 9.57, N 5.32. Found: C 73.09, H 9.57, N 5.44.

7-Butyl-2,2-dimethyl-2*H*-azepine (12e). **11e** (0.36 g, 1.0 mmol) in CH_2Cl_2 (15 ml) was cooled to -15 °C and treated with TFA (7.50 ml, 97 mmol). After 4 h saturated aqueous Na_2CO_3 (50 ml) was added and the mixture extracted twice with CH_2Cl_2. Drying ($MgSO_4$), concentration *in vacuo* and chromatography (silica gel) afforded 82 mg (46%) of **12e** as a yellowish oil with strongly pungent taste, R_F = 0.37 (hexanes/acetone/EtOAc = 10:1:1); IR (film) 3019 (w), 1631 (w), 1613 cm^{-1} (m); ^1H NMR δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.31 and 1.31 (s and sextet, *J* = 7.3 Hz, 8H), 1.47-1.55 (m, 2H), 2.32-2.39 (m, 2H), 5.49 (dt, *J* = 10.2, 0.9 Hz, 1H), 6.04 (ddd, *J* = 10.2, 5.8, 1.3 Hz, 1H), 6.55 (ddd, *J* = 11.5, 5.8, 0.8 Hz, 1H), 6.61 (dt, *J* = 11.4, 1.1 Hz, 1H); ^{13}C NMR δ 14.00, 22.51, 26.66, 31.04, 39.82, 56.20, 124.76, 132.33, 134.76, 139.39, 165.62; MS (EI, 25 °C) *m/z* = 177 (5.0%, M^+), 162 (62), 148 (70), 120 (60), 106 (100); Anal. Calcd. for $C_{12}H_{19}N$ (177.29): C 81.30, H 10.80, N 7.90. Found: C 80.77, H 10.67, N 7.52.

(*S*)-2-Methyl-6,7,8,9-tetrahydro-2*H*-1-benzazepine (12f). **11f** (0.22 g, 0.65 mmol) was added to TFA (1.0 ml, 13 mmol) in CH_2Cl_2 (10 ml) and kept at 18 °C for 4.75 h. At that point the yellow-orange solution contained no more of the starting material (TLC analysis). Saturated aqueous $NaHCO_3$ was added and the mix-

ture was extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Chromatography yielded **12f** (75 mg, 72%) as a yellowish oil, R_F = 0.25 (system I); $[\alpha]_D^{22}$ = 23° (*c* = 0.45, ether); UV (*t*-BuOMe) λ_{max} = 204 nm (lg ε = 3.86), 230 (sh, 3.77), 242 (3.79), 300 (2.78); IR (film) 3020 (m), 1615 (m), 1560 (m), 1445 (m), 1375 (m), 750 cm^{-1} (s); ^1H NMR δ 1.56 (d, *J* = 6.7 Hz, 3H), 1.57-1.82 (m, 2H), 1.91-1.99 (m, 2H), 2.22-2.41 (m, 1H), 2.48-2.56 (m, 2H), 2.62-2.70 (m, 1H), 2.78-2.86 (m, 1H), 5.56 (dd, *J* = 9.2, 5.3, 1H), 6.11 (ddd, *J* = 9.2, 5.4, 1.6, 1H), 6.42 (d, *J* = 5.4, 1H); ^{13}C NMR δ 21.45, 21.59, 26.29, 36.00, 36.85, 54.47, 126.56, 130.04, 133.99, 144.56, 164.79; Anal. Calcd. for $C_{11}H_{15}N$ (161.25): C 81.94, H 9.38, N 8.69. Found: C 81.76, H 9.42, N 8.69.

(3*E*,5*E*,7*S*)-7-(*tert*-Butoxycarbonylamino)-3,5-octadien-2-one (13). The crude product from the oxidation of alcohol **10a** with pyridinium chlorochromate was purified by chromatography on a silica gel column (ether/hexanes = 2:1) and yielded the elimination product **13** in 79% yield. Colorless oil, R_F = 0.47 (ether/hexanes = 2:1); IR ($CHCl_3$) 3420 (m), 3000 (s), 2990 (sh), 2970 (s), 2920 (m), 1700 (ss), 1490 (m), 1450 (w), 1390 (m), 1360 (s), 1240 (s), 1160 (s), 1050 (m), 980 (w), 860 (w), 690 cm^{-1} (w); ^1H NMR (200 MHz) δ 1.25 (d, *J* = 7.2 Hz, 3H, 8-H), 1.42 (s, 9H, *t*-Bu-H), 2.25 (s, 3H, 1-H), 4.32 (ddq, *J* = 8.0, 7.2, 5.2 Hz, 1H, 7-H), 4.54 (br d, *J* = 8.0 Hz, 1H, NH), 6.08 (dd, *J* = 15.4, 5.2 Hz, 1H, 6-H), 6.11 (d, *J* = 15.6 Hz, 1H, 3-H), 6.25 (dddd, *J* = 15.4, 10.2, 0.6, 0.6 Hz, 1H, 5-H), 7.08 (dd, *J* = 15.6, 10.2 Hz, 1H, 4-H); EI MS (DE, 180 °C) *m/z* 239 (4%, M^+), 215 (3), 195 (4), 166 (4), 140 (7), 138 (9), 122 (8), 96 (30), 95 (14), 81 (13), 66 (8), 57 (100), 54 (14), 43 (62). HRMS calcd for $C_{13}H_{21}NO_3$ 239.1521, found 239.1502.

***tert*-Butyl (*S*)-3-(*tert*-Butoxycarbonylamino)-4-hydroxybutanoate (15).** To a solution of lithium chloride (1.83 g, 43.1 mmol) and 4-*tert*-butyl 1-methyl L-*N*-(*tert*-butoxycarbonyl)aspartate (**14**)[14] (31.1 g, 43.1 mmol) in THF (65 ml) sodium borohydride (1.63 g, 43.1 mmol) was added portionwise at -5 °C. After 4 h the mixture was neutralized with acetic acid and extracted (2 x) with *t*-BuOMe. Workup as usual and purification by column chromatography (silica gel) yielded **15** (11.4 g, 96%) as a slightly yellow oil, R_F = 0.34 (system I); IR (film) 3360 (br, m), 2980 (s), 1750 (s), 1500 (m), 1355 (s), 1160 (s), 1055 cm^{-1} (m); ^1H NMR (80 MHz) δ 1.38 (s, 18H), 2.50 (d, *J* = 6 Hz, 1H), 3.23 (m, 1H), 3.60 (t, *J* = 4.8 Hz, 2H), 5.25 (m, 1H); Anal. Calcd. for $C_{13}H_{23}NO_5$ (275.34): C 56.71, H 9.15, N 5.09. Found: C 56.25, H 9.04, N 5.02.

***tert*-Butyl (*S*)-3-(*tert*-Butoxycarbonylamino)-4-oxobutanoate (16).** Oxidation of alcohol **15** (3.70 g, 13.4 mmol) using $(COCl)_2$/DMSO/NEt_3 as described for compound **11e** yielded crude aldehyde **16** (3.60 g, 98%), R_F = 0.56 (system I), which was used immediately for further transformation.

Rearrangement of the 2*H*-azepines 12 into their 3*H*-isomers 18

2*H*-azepine **12** (1 mmol) was refluxed in chloroform (10 ml) for 2-3 h after which time the rearrangement was found to be completed (TLC analysis). The 3*H*-azepines **18** were purified by flash chromatography (silica gel).

2,7-Dimethyl-3*H*-azepine (18a). Yield 71%, liquid, R_F = 0.65 (ether/hexanes = 5:1); UV (EtOH) λ_{max} = 244 nm, 300 (sh), 324 (sh); IR ($CHCl_3$) 3010 (m), 2950 (s), 2940 (sh), 2900 (s), 2870 (m), 2830 (sh), 1650 (w), 1610 (ss), 1530 (m), 1420 (s), 1390 (w), 1360 (m), 1330 (m), 1280 (s), 1190 (s), 1070 (w), 1030 (w), 980 (m), 920 (w), 890 (m), 825 (m), 750 (s), 710 (m), 630 cm^{-1} (m); ^1H and ^{13}C NMR, see Table 1. EI MS (Hotbox, 180 °C) *m/z* 122 (17%) $[M+1]^+$, 121 (98, M^+), 120 (50), 106 (18), 103 (9), 80 (25), 79 (100), 78 (10), 77 (43), 65 (10), 53 (8), 52 (9), 51 (7), 42 (6), 41 (4), 39 (14); HRMS calcd for $C_8H_{11}N$ 121.0892, found 121.0871.

7-Benzyl-2-methyl-3*H*-azepine (18b). Yield 78%, liquid, R_F = 0.74 (ether/hexanes = 3:2); IR ($CHCl_3$) 3230 (br), 3000 (m), 2930 (s), 2850 (m), 1680 (w), 1610 (ss), 1540 (m), 1490 (m), 1450 (m), 1430 (ss), 1380 (w), 1370 (w), 1250 (w), 1100 (w), 1030 (w), 970 (m), 910 (ss), 700 (ss), 650 cm^{-1} (m); ^1H NMR (200 MHz) δ 2.12 (s, 3H, CH_3), 3.77 (s, 2H, 8-H), 5.16 (dt, *J* = 8.8, 7.2 Hz, 1H, 4-H), 5.75 (d, *J* = 6.0 Hz, 1H, 6-H), 6.23 (dd, *J* = 8.8, 6.0 Hz, 1H, 5-H), 7.10-7.40 (m, 5H, C_6H_5); ^{13}C NMR (100.6 MHz) δ 26.17 (Qt, *J* = 127, 2.0 Hz,

6.4, 6.4 Hz, C-4), 113.81 (Ddt, J = 155, 9.0, 4.4 Hz, C-6), 126.02 (Ddd, J = 160, 7.0, 7.0 Hz, C-12), 127.24 (Ddd, J = 155, 7.0, 7.0 Hz, C-5), 128.23 (Dd, J = 159, 7.2 Hz, C-11, C-11'), 129.00 (Dddt, J = 157, 6,2, 6.2, 6.0 Hz, C-10, C-10'), 139.94 (tdd, J = 9.0, 9.0, 9.0 Hz, C-9), 147.82 (tq, J = 6.0, 6.0 Hz, C-2), 152.64 (dt, J = 7.0, 7.0 Hz, C-3); EI-MS (DE, 180 °C) *m/z* 198 (12%) $[M+1]^+$, 197 (100, M^+), 196 (78), 182 (22), 155 (20), 153 (8), 141 (25), 129 (6), 128 (10), 120 (3), 118 (6), 115 (20), 106 (5), 91 (55), 79 (9), 78 (7), 77 (11), 65 (8), 57 (3), 39 (2); HRMS calcd for $C_{14}H_{15}N$ 197.1204, found 197.1211.

2-Butyl-7-methyl-3*H*-azepine (18c). The 3*H*-azepine **18c** was formed when keeping a solution of **12c** at r.t. or slightly elevated temperature, see Table 2. Chromatography (silica gel) afforded pure **18c** as a yellowish oil, R_F = 0.62 (system III); UV (EtOH) λ_{max} = 278 nm (lg ε = 3.41), 340 (sh); ^{1}H NMR δ 0.90 (t, J = 7.4 Hz, 3H), 1.33 (m, 2H), 1.54 (m, 2H), 2.16 (s, 3H), 2.36 (m, 2H), *ca.* 2.4-2.9 (br, 2H, see ref.[26]), 5.09 (dt, J = 8.7, 6.7 Hz, 1H), 5.98 (d, J = 6.0 Hz, 1H), 6.20 (dd, J = 8.7, 6.0 Hz, 1H); ^{13}C NMR δ 13.89, 22.58, 24.35, 30.28, 36.65, 39.54, 112.70, 113.14, 127.13, 149.34, 151.54; Anal. Calcd. for $C_{11}H_{17}N$ (163.26): C 80.93, H 10.50, N 8.58. Found: C 81.16, H 10.76, N 8.52.

Kinetic studies of the rearrangement of 12c to 18c. The rearrangement of (*S*)-7-butyl-2-methyl-2*H*-azepine (**12c**) to the 3*H*-azepine **18c** was monitored by the decrease of the optical rotation of solutions of **12c** at λ = 436 nm (Carl Zeiss Lichtelektrisches Präzisionspolarimeter 0.005 °). Table 2 summarizes the results and conditions of these experiments. To avoid the formation of highly colored by-products it was necessary to add small amounts of NEt_3 to some of the solvents.

***tert*-Butyl (2-Butyl-3*H*-azepin-7-yl)acetate (18d).** The 2*H*-azepine **12d** (0.27 g, 1.03 mmol) was kept in *t*-BuOMe (30 ml) at r.t. for 10 d. Residual **12d** (0.12 g, 45%) was separated by column chromatography from **18d** (0.15 g, 55%): yellow oil, R_F = 0.77 (system II); UV (*t*-BuOMe) λ_{max} = 204 nm (lg ε = 3.90), 246 (3.74), 264 (3.71); IR (film) 1735 (s), 1620 (m), 1150 cm^{-1} (s); ^{1}H NMR δ 0.89 (t, J = 7.4 Hz, 3H), 1.25-1.39 (m, 2H), 1.41 (s, 9H), 1.46-1.63 (m, 2H), ca. 1.8-3.2 (br, 2H, see ref.[26]), 2.33-2.39 (m, 2H), 3.40 (br s, 2H), 5.17 (dt, J = 8.8, 6.8 Hz, 1H), 6.03 (d, J = 5.9 Hz, 1H), 6.23 (dd, J = 8.8, 5.9 Hz, 1H); ^{13}C NMR δ 13.88, 22.46, 28.04, 29.97, 36.73, 39.32, 45.24, 80.47, 114.52, 114.97, 126.71, 146.99, 152.71, 170.59; $C_{16}H_{25}NO_2$ (263.38).

(*R*)-2-Methyl-6,7,8,9-tetrahydro-5a*H*-1-benzazepine (18f). 12f (75 mg, 0.47 mmol) was dissolved in *t*-BuOMe (25 ml) and kept for 9 days at 30.0 °C. The mixture turned brown and some insoluble material deposited. The mixture was concentrated and chromatographed (silica gel) to yield starting material (6.8 mg, 9%), azepine **22** (0.8 mg, 1%), and **18f** (13.0 mg, 18%) as a yellow oil, R_F = 0.61 (system I); $[\alpha]_D^{22}$ = 481° (*c* = 0.22, *t*-BuOMe); UV (*t*-BuOMe) λ_{max} = 206 nm (lg ε = 3.89), 242 (3.70), 270 (3.57); ^{1}H NMR δ = 1.26-1.33 (m, 1H), 1.52-2.25 and 2.16 (m and s, 10H), 2.45-2.57 (m, 1H), 4.96 (dd, J = 8.5, 5.9 Hz, 1H), 5.98 (d, J = 6.0, 1H), 6.21 (m, 1H); ^{13}C NMR δ = 21.72, 24.15, 24.76, 27.84, 32.57, 43.26, 112.42, 118.03, 125.56, 147.92, 148.28; IR (film) 3020 (w), 1605 (s), 1450 (m), 1230 (m), 740 cm^{-1} (s); $C_{11}H_{15}N$ (161.25).

(*S*)-(7-Butyl-2*H*-azepin-2-yl)acetic Acid (17). Ester **12d** (130 mg, 0.43 mmol) was treated with Me_3SiI (0.15 ml, 1.05 mmol) in CH_2Cl_2 (5 ml) at 0 °C. After 15 min MeOH (1 ml) was added and the solvent was removed *in vacuo*. The procedure was repeated with benzene. Chromatography (CH_2Cl_2 → CH_2Cl_2/EtOH = 5:1 → CH_2Cl_2/EtOH = 2:1) on a small amount of silica gel (*ca.* 20 ml) afforded **17** (60 mg, 67%, yellow film), R_F = 0.50 (MeOH/$CHCl_3$ = 1:1); $[\alpha]_D^{22}$ = -60° (*c* = 0.67, EtOH); UV (EtOH) λ_{max} = 206 nm (sh, lg ε = 3.80), 218 (3.92), 288 (3.16); IR (film) 3380 (br, m), 1590 (br, s), 1435 (br, s), 1345 (m), 1315 (m), 1235 (m), 760 cm^{-1} (s); ^{1}H NMR (CD_3OD) δ 0.95 (t, J = 7.2 Hz, 3H), 1.22-1.44 (m, 2H), 1.54-1.70 (m, 2H), 2.60-2.68 (m, 2H), 3.02 (dd, J = 16.5, 6.2 Hz, 1H), 3.14 (dd, J = 16.6, 7.9 Hz, 1H), 3.44-3.54 (m, 1H), 5.96 (dd, J = 9.4, 5.7 Hz, 1H), 6.62 (dd, J = 9.2, 5.7 Hz, 1H), 7.11 (d, J = 11.4 Hz, 1H), 7.31 (dd, J = 11.4 Hz, 5.5, 1H); ^{13}C NMR (CD_3OD) δ 14.34, 23.54, 31.59, 31.67, 31.74, 37.22, 39.43, 56.52, 130.21, 131.23, 135.46, 143.71, 174.83, 175.40; FAB MS (*m* NBA matrix) *m/z* = 208 (100%), $[M+H]^+$; $C_{12}H_{17}NO_2$ (207.27).

(2-Butyl-3*H*-azepin-7-yl)acetic Acid (19). A solution of **18d** (0.14 g, 0.53 mmol) in CH_2Cl_2 (5.5 ml) was treated with Me_3SiI (0.15 ml, 1.05 mmol) at 0 °C. After 10 min MeOH (1 ml) was added and the solvent was removed. The procedure was repeated with $CHCl_3$. The residue was chromatographed ($CHCl_3 \rightarrow$ $CHCl_3$/EtOH = 1:10; *ca.* 30 ml silica gel) to yield **19** (45 mg, 41%) as a yellow-brown film, R_F = 0.59 ($CHCl_3$/MeOH = 1:1); UV (EtOH) λ_{max} = 206 nm (lg ε = 3.91), 244 (3.72), 262 (sh, 3.68); IR (film) 3200 (br, w), 3020 (w), 1625 (m), 1430 (m), 1375 (m), 1280 (m), 725 cm^{-1} (m); ^1H NMR δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.26-1.39 (m, 2H), 1.47-1.63 (m, 2H), 2.50 and 2.53 (t, *J* = 7.6 Hz and br s, 4H), 3.42 (s, 2H), 5.23 (dt, *J* = 8.8, 6.7 Hz, 1H), 6.21 (d, *J* = 6.0 Hz, 1H), 6.31 (dd, *J* = 8.8, 6.0 Hz, 1H), 11.35 (br s, 1H); ^{13}C NMR δ 13.76, 22.20, 29.12, 36.70, 39.21, 42.79, 114.88, 116.97, 127.44, 143.25, 155.70, 171.25; $C_{12}H_{17}NO_2$ (207.27).

***N*-(*tert*-Butoxycarbonyl)-5,5-dimethyl-2-(2-oxohexylidene)-2,5-dihydropyrrole (20).** The mixture obtained from the oxidation of alcohol **10e** (1.7 g, 4.8 mmol) with pyridinium chlorochromate (3.1 g, 14 mmol) in CH_2Cl_2 (20 ml) at r.t. yielded after chromatography (silica gel) unreacted **10e** (0.40 g, 24%), the expected ketone **11e** (0.78 g, 46%) and the pyrroline **20** (0.15 g, 11%). **20**: Colorless crystals, mp 88-90 °C (EtOAc-hexane), R_F = 0.57 (system III); IR (KBr) 3340 (m, br), 2967 (m), 1718 (s), 1662 (m), 1608 (m), 1561 (s), 1382 (m), 1368 (s), 1297 (m), 1253 (m), 1162 (s), 1112 (m), 1067 (m), 852 (w), 808 cm^{-1} (w); ^1H NMR δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.34 (sext, *J* = 7.6 Hz, 2H), 1.50 (s, 6H), 1.58-1.63 (s and m, 11 H), 2.45 (t, *J* = 6.6 Hz, 2H), 6.31 (dd, *J* = 6.1, 1.5 Hz, 1H), 6.85 (dd, *J* = 1.05, 0.5 Hz, 1H), 7.62 (dd, *J* = 6.1, 0.5 Hz, 1H); FAB MS (*m*-NBA matrix) *m/z* = 294 (38%) [M^+ + H], 238 (83), 194 (73), 180 (39), 151 (22). Anal. Calcd. for $C_{17}H_{27}NO_3$ (293.41): C 69.59, H 9.28. Found: C 69.44, H 9.21.

2-Methyl-6,7,8,9-tetrahydro-3*H*-1-benzazepine (22). Azepine **12f** (44 mg, 0.27 mmol) was refluxed in *t*-BuOMe (25 ml) for 19 h. Chromatography of the yellow solution yielded the azepines **18f** (11 mg, 25%) and **22** (8.0 mg, 18%): yellow film, R_F = 0.49 (system I); UV (*t*-BuOMe) λ_{max} = 244 nm (lg ε = 3.59), 268 (3.53), 322 (sh, 2.51); ^1H NMR δ 1.62-1.78 (m, 4H), 2.12 (s, 3H), 2.32-2.50 (m, 6H), 5.19 (dt, *J* = 8.8, 6.8 Hz, 1H), 5.96 (d, *J* = 8.9, 1H); ^{13}C NMR δ 22.75, 22.83, 26.05, 29.92, 31.36, 37.41, 113.85, 121.40, 130.90, 146.70, 148.40; IR (film) 3020 (w), 1630 (s), 1430 (s), 1290 (s), 1225 (s), 765 cm^{-1} (s); $C_{11}H_{15}N$ (161.25).

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