

Synthesis of a Conformationally Flexible β -Hairpin Mimetic

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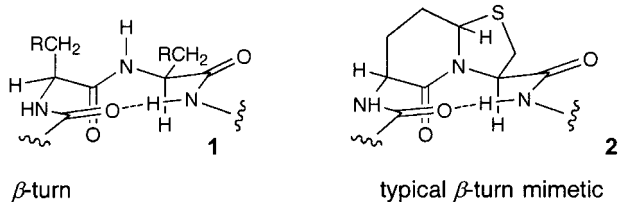
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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

Rational conformation design led us to a synthesis of the ω -amido-undecenamide **4**, which was shown by theoretical means (simulated annealing techniques) and by NMR and IR spectroscopy to have a high tendency to populate a conformation corresponding to a natural β -II'-type hairpin, despite possessing a conformationally fully flexible open-chain backbone.

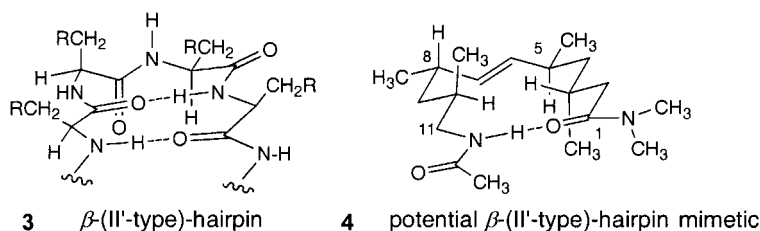
Introduction. – The folding of proteins into distinct three-dimensional structures is prerequisite to allow proteins to fulfil biological functions. Foldamers [1] are artificial protein-like compounds that likewise fold in a predictable manner into three-dimensional structures. Obviously, in the design of foldamers, one tries to mimic the structural motifs such as helices and sheets found in proteins. To attain this, artificial building blocks – frequently called peptido-mimetics [2] – are incorporated into peptidic structures [3]. These peptido-mimetics give the remaining peptide strand a certain folding pattern, *e.g.*, similar to that of a β -turn (*cf.* **1**).



Commonly, β -turn mimetics are rigid structures, such as **2** [4]. Conformationally flexible β -turn mimetics, though, may come closer to the situation found in nature. Residual flexibility within a designed secondary-structure-stabilizing element could account for a higher probability of binding towards a protein target, since a nonrigid turn mimic with appropriate side-chain decoration might adopt more easily a target-complementary conformation when compared to more-constrained analogues.

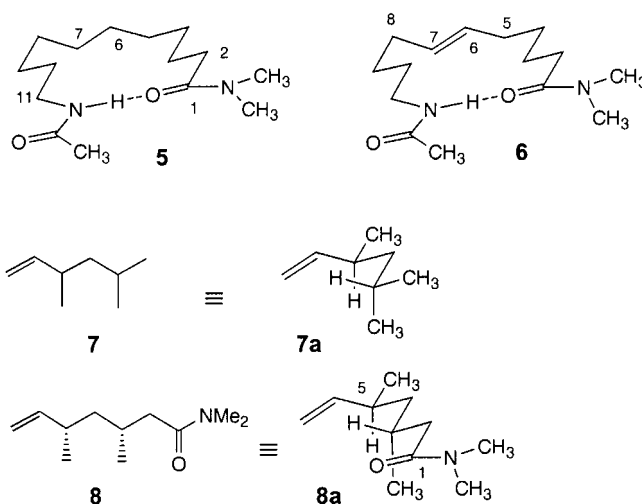
A realization of conformationally flexible β -turn mimetics would have to be based on the principles of conformation design [5], *i.e.*, our ability to generate flexible structures with a single preferred conformation. In the ideal case, a preferred conformation should prevail at every rotatable bond of the flexible mimetic. When following this line of thought, we realized that a somewhat larger structure, that of a β -

hairpin [6] **3** (with five amino acid residues), would offer more room for the creation of a fully flexible mimetic than the structurally more-confined simple β -turn **1** with three amino acid residues.



The target molecule eventually chosen by us was compound **4**. We detail¹⁾ here the design elements that led us to **4**, its synthesis, and the conformational analysis of **4**.

The Design. – The minimum requirement for a β -hairpin is that it should hold the bonds C(1)–C(2) and C(11)–N(12) properly arranged in space. The backbone of a β -hairpin could be approximated by an ω -amino-undecanoic acid **5**, which, of course, is devoid of any conformational preorganization. The β -hairpin **3** has the shape of a letter 'U'. Its bottom is formed by an amide group, *i.e.*, a π -system that confines four backbone atoms in one plane. This can be imitated by a C=C bond in position 6 and 7 of **5**, *cf.* such as in compound **6**. The use of a C=C bond as an isoster for an amide group is well established in the design of peptido-mimetics (see [8] and refs. cit. therein).



As the next task of design, we should introduce two bends into the backbone at C(5) and C(8) of **6**, *i.e.*, a *gauche* arrangement in the atom sequence C(3)–C(4)–C(5)–C(6) and likewise in C(7)–C(8)–C(9)–C(10). This *gauche* arrangement can be favored, albeit with only a small preference, by placing a Me

¹⁾ For a preliminary communication, see [7].

group at C(5). Indeed, the conformational analysis of **7** established that the conformation **7a**, in which the slimmer vinyl group rather than the larger Me group takes up a position perpendicular to the zig-zag chain, is favored [9].

The final task is to give the sides of the ‘U’ an extended conformation, *i.e.*, a *trans*-arrangement of the atom sequence C(2)–C(3)–C(4)–C(5). This can be attained by placing a Me group at C(3), with the proper relative configuration, as shown in the model structure **8**. The ‘syndiotactic’ relative configuration in **8** renders the C(2)-to-C(6) backbone segment biconformational, but, as conformational analysis of **8** showed [10][11], it is the nature of the terminal atoms, *i.e.*, the sp^2 C(6) and sp^3 C(2), that biases the local conformation in favor of conformation **8a** [12], in which the vinyl group is perpendicular to the C(1)-to-C(5)–Me chain. Once we recognize **8** as a flexible building block with a preferred conformation, it is easy to mentally ‘double up’ [12] compound **8** to the β -hairpin mimetic **4**. It remains to be shown, however, to what extent compound **4** populates the conformation shown above.

Müller *et al.* have described a computational technique [13] that allows assessment of the conformational performance of putative β -hairpin mimetics. The procedure mainly involves molecular-mechanics simulations employing a stochastic Monte Carlo approach carried out in torsion space. The emphasis of the underlying conformational analysis is on the generation of conformational ensembles comprising, *e.g.*, 2500 distinct entities that represent a relevant energy-distribution profile for a given target temperature, rather than producing a single structure at its global conformational minimum. According to a simulated annealing procedure, randomly generated conformers of a molecule under investigation are subjected to a tailored protocol that adjusts the ensemble temperature over 2000 Monte Carlo steps from the initial temperature of 10000 K to the target temperature of 300 K. Each distinct Monte Carlo step comprises n torsional changes around randomly chosen bonds within the molecule, n being the number of rotatable bonds.

For compound **4**, a surprisingly homogeneous conformational ensemble emerged from the outlined procedure, indicating a strong intrinsic tendency to adopt the rationally designed conformation. The analysis of the pseudo-dihedral angle δ spanned by C(2) $\cdots$ C(5) $\cdots$ C(8) $\cdots$ C(11), *i.e.*, the backbone positions corresponding to the C(α) atoms of a peptide hairpin structure, reveals a sharp peak exhibiting a narrow distribution profile at *ca.* 25° (*Fig. 1,a*). The ideal geometry for that pseudo-dihedral is found for hairpin structures at a *syn*-periplanar arrangement ($0^\circ \pm 50^\circ$) [14]. Additionally, a ‘cross-hairpin’ distance d between C(2) and C(11) (C(α)^{*i*} $\cdots$ C(α)^{*i+3*}) of *ca.* 5 Å underlines the dominance of the hairpin-type conformation within the generated ensemble (*Fig. 1,a*). Ideal values for that geometric parameter within hairpins are found at 4.1–4.8 Å [15]. The superposition of 100 representatives extracted from the conformational ensemble is shown in *Fig. 1,b*. For validation purposes, compound **5** was subjected to the identical computational procedure yielding a non-hairpin conformation as depicted in *Fig. 1,c*. Compound **5** clearly favors an overall-extended conformation with a C(2) $\cdots$ C(11) distance centered at *ca.* 10 Å, thus preventing any head-to-tail proximity, mandatory for the required H-bond.

The design concepts implemented in structure **4** have since been successfully applied as well to the generation of flexible, but conformationally pre-organized host molecules for the complexation of anions [16][17].

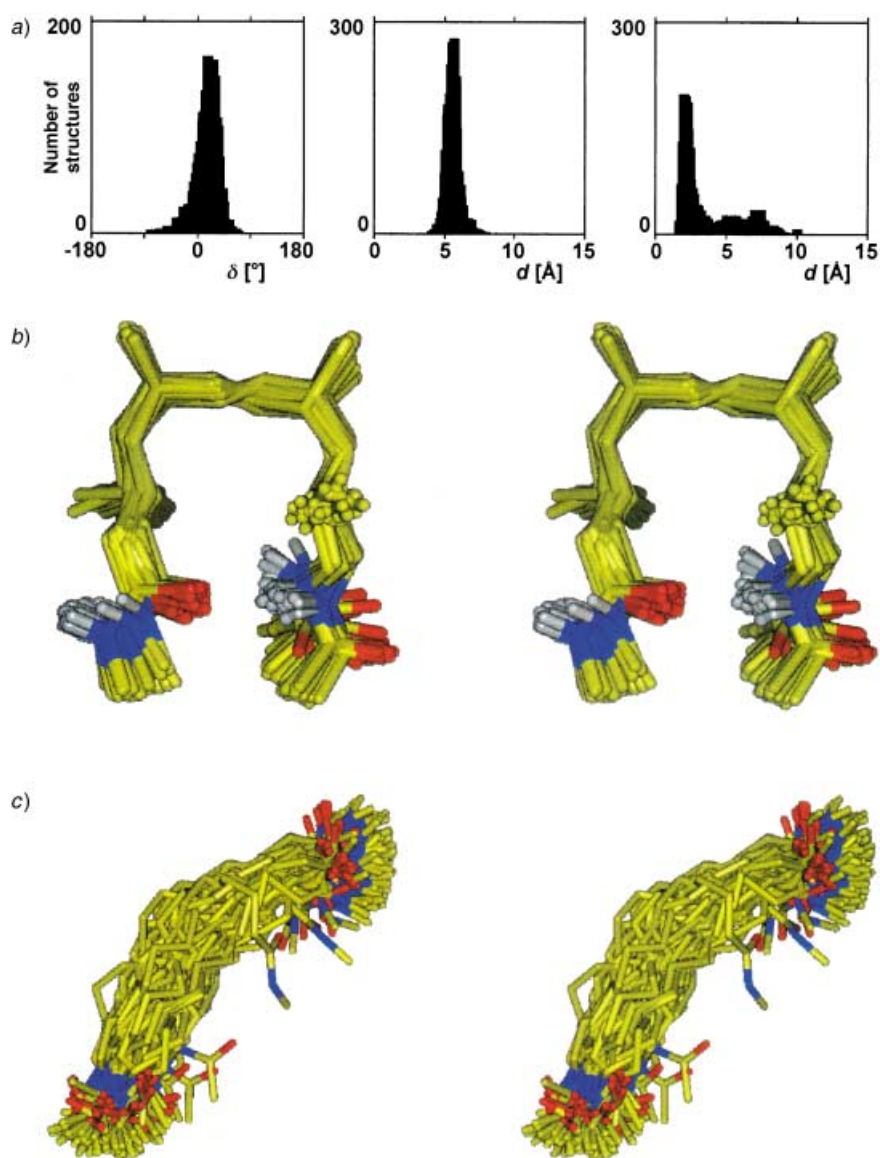
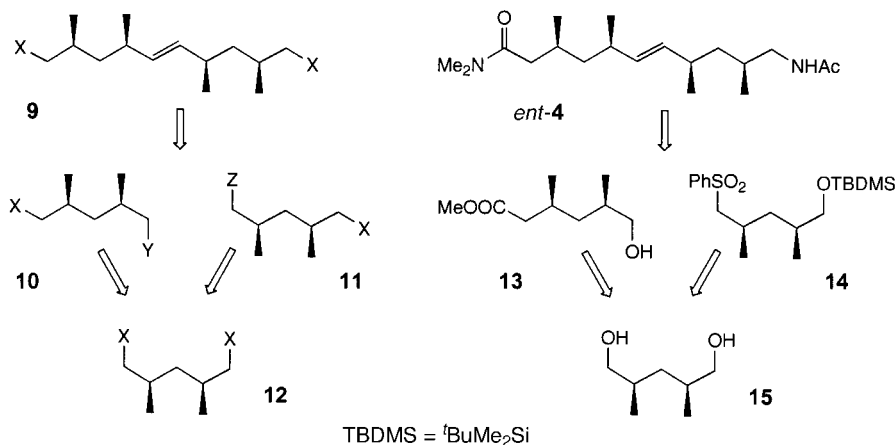


Fig. 1. Results of the theoretical conformational analysis of **4** and **5**. a) Distribution profile of the pseudo-dihedral angle δ encompassing four consecutive backbone atoms occupying the native C(α) positions (left), the C(2) ... C(11) distance d profile (middle), and the C=O ... H-N H-bond distance d profile (right). b) Side-by-side stereo presentation of 100 superimposed conformers of **4** taken from the conformational ensemble (for clarity, only polar H-atoms are depicted). c) Side-by-side stereo presentation of 100 superimposed structures of **5**.

Synthesis of ent-4. – To verify these predictions, we initiated a synthesis of the potential β -turn mimetic **4**. Compound **4** has an element of symmetry, which becomes obvious when the groups at C(2) and C(11) are equivalent (see **9**). Compound **9**,

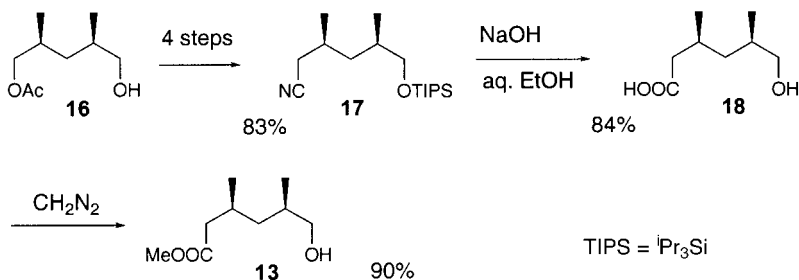
representing the backbone of **4**, possesses C_2 symmetry and, therefore, invites a convergent approach in which two homochirally related building blocks **10** and **11** are joined by an olefination reaction (*Scheme 1*). The building blocks **10** and **11** can be envisioned to be derived in an enantio-divergent manner from a common starting material **12**, itself a *meso*-compound.

Scheme 1



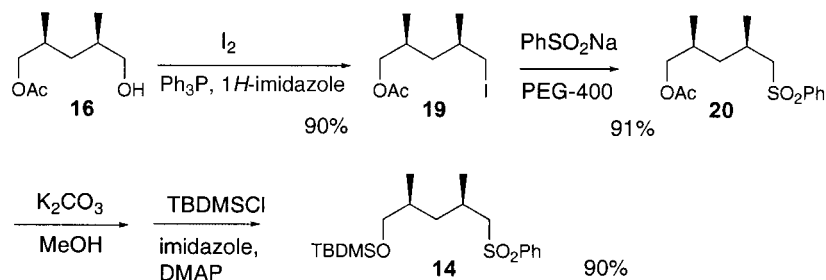
To put this approach into practice, we chose the *meso*-diol **15** [18] as the starting point. We embarked on a synthesis of *ent*-**4** because one of the intermediates, **17**, was already available from another study [11] as one enantiomer. The plan was to elaborate **17** into the alcohol **13** and into the sulfone **14** in preparation for a *Julia-Lythgoe* olefination (*Scheme 1*). Desymmetrization of **15** was effected by a lipase-catalysed acetylation to give **16** [19]. For one building block, **16** was converted over four steps to the nitrile **17** (83% overall) [11] (*Scheme 2*). Treatment with aq. NaOH solution removed the triisopropylsilyl (TIPS) group and saponified the nitrile. The resulting acid **18** (84%) was esterified with diazomethane to give 90% of **13**.

Scheme 2



For the other building block **14**, the acetate **16** was elaborated *via* the iodide **19** to the sulfone **20** followed by a protective-group change (*Scheme 3*).

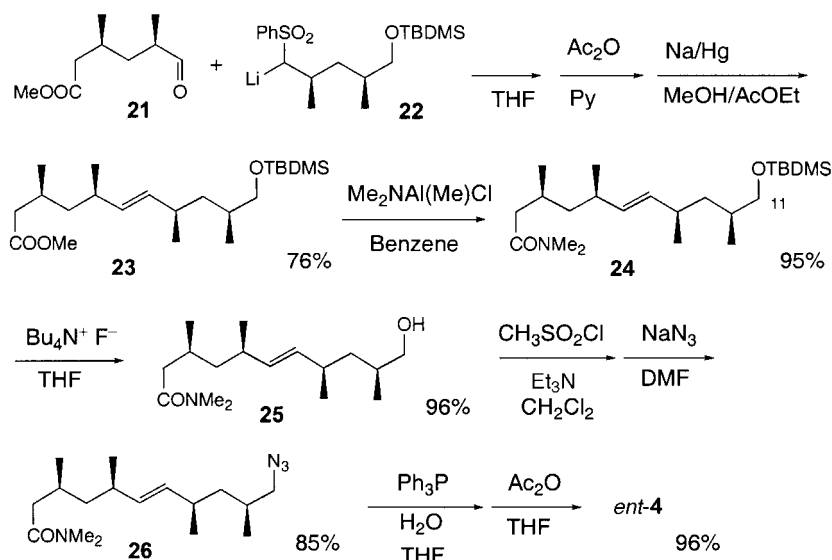
Scheme 3



TBDMS = $t\text{BuMe}_2\text{Si}$, DMAP = *N,N*-dimethylpyridin-4-amine

In preparation for the coupling step, alcohol **13** was oxidized to the aldehyde **21**, which was immediately treated with the lithiated sulfone **22** (from **14**) to give a diastereoisomer mixture of hydroxysulfonyl compounds (*Scheme 4*). This mixture was carried through the usual *Julia*-olefination steps (acetylation and Na/Hg reduction) furnishing 76% of the (*E*)-alkenoate **23**. At this point, we should comment that the enantiomer purity of **16** and, hence, of **13** and **14** was only *ca.* 80–87%. Nevertheless, the resulting coupled product should reach an ee of $\geq 98\%$ according to *Horeau's* principle [20].

Scheme 4



TBDMS = $t\text{BuMe}_2\text{Si}$

Now with the full skeleton assembled, the ester **23** was converted to the dimethylamide **24** by means of *Weinreb's* technique [21]. The protected alcohol

function at C(11) of **24** was liberated with Bu_4NF to give **25**. Mesylation followed by substitution with azide furnished the azido compound **26**. *Staudinger* reduction [22] and acetylation led then to the target compound *ent*-**4**.

Conformational Analysis. – The conformational properties of *ent*-**4** are determined by two factors that may reinforce one another: the possibility to form an intramolecular H-bond and a conformational preorganization within the arms C(2)-to-C(6) and C(7)-to-C(11). The tendency to form an intramolecular H-bond can be monitored by IR and NMR spectroscopy. *Fig. 2* shows the NH-stretching absorption in the IR for compounds *ent*-**4** and **5** in CCl_4 . Whereas compound *ent*-**4** exhibits only one absorption characteristic for H-bonded NH, the topologically equivalent but non-pre-organized compound **5** shows several absorptions in the NH-stretching region.

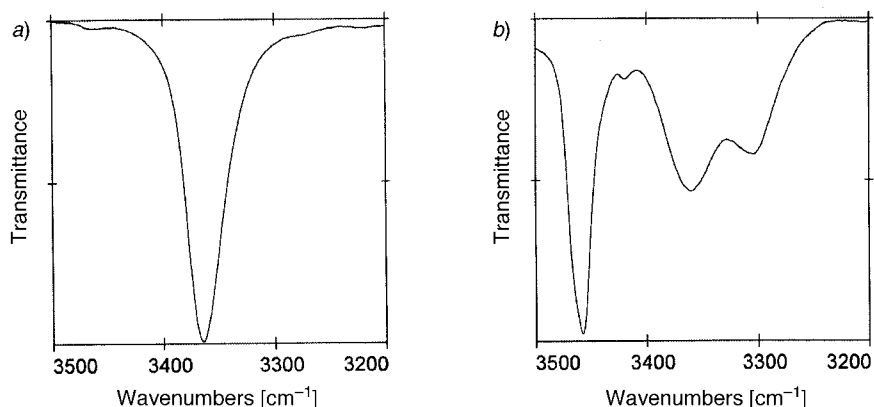


Fig. 2. NH Stretching region in the IR (CCl_4) of a) compound *ent*-**4** and b) compound **5**

To make sure that the NH H-bridge observed for *ent*-**4** is an intramolecular H-bridge, we monitored the chemical shift of NH in the ^1H -NMR spectrum in a dilution series. The results are reproduced in *Fig. 3*. Whereas the chemical shift of the NH proton of compound *ent*-**4** is concentration-independent over a concentration range of 10^3 , that of compound **5** shows a significant concentration dependence characteristic for the involvement of intermolecular H-bridges. Hence, we conclude that the H-bridge observed in compound *ent*-**4** is, indeed, intramolecular, in line with its design as a β -hairpin mimetic.

The conformational pre-organization within the side chains of *ent*-**4** can be monitored by the vicinal coupling constants between the protons at C(3) and C(5) and the diastereotopic protons H_a and H_b at C(4) (or the related spin system between the protons at C(8), C(9), and C(10); *cf. Table*) [23]. Compound **27** serves as a model structure. A strong alternation of the $^3J(\text{H,H})$ coupling constants (large/small) indicates a strong preference for a single local conformation. According to this criterion, the model structures **27** and **28** show just a moderate conformational preference of *ca.* 60–85%. The values measured for compounds **23** and **24** (a single proton value, *cf. Table*) indicate that this moderate conformational preference prevails as well in the extended molecular backbones.

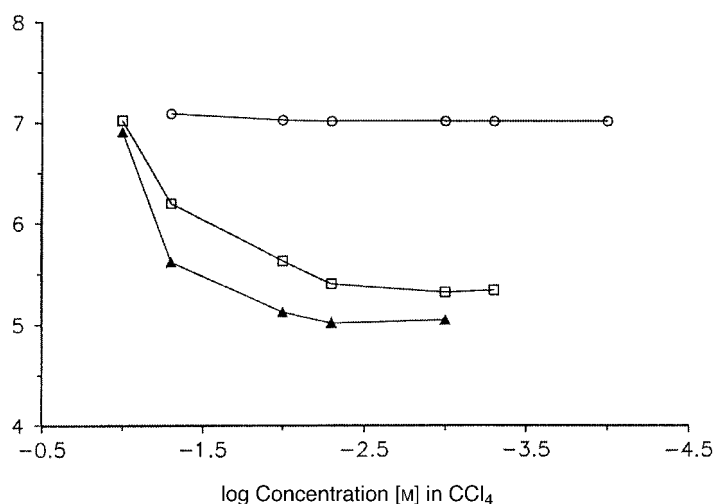


Fig. 3. Chemical shift of the NH proton signal in the ^1H -NMR spectrum of compound *ent-4* ($\circ$), compound **5** ($\square$), and N-methylacetamide ($\blacktriangle$)

Table. Conformation-Characteristic Coupling Constants $^3J(\text{H},\text{H})$ [Hz] (CDCl_3)

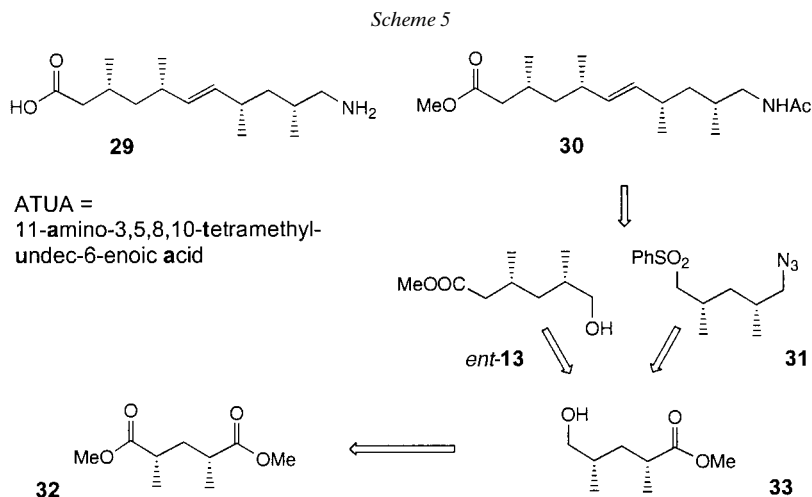
		$^3J(\text{H},\text{H})$ to H_a and H_b		Ref.
	27	4.3, 10.1	4.3, 10.9	[17]
	28	4.5, 9.8	5.0, 9.4	[12]
	23	5.1, 9.4 ^{a)} 5.1, 9.3 ^{a)}	5.4, 9.1 ^{a)} 4.5, 9.7 ^{a)}	
	24	5.5, 8.8 ^{b)}		
	<i>ent-4</i>	2.9, 10.5 ^{b)}		

^{a)} The couplings could not be assigned to the C(3)/C(5) or C(8)/C(10) spin systems, respectively. ^{b)} Only one proton signal was resolved. It is unknown whether it is part of the C(3)/C(5) or the C(8)/C(10) spin system.

There is, however, a notable change in going from **24** to *ent-4*: While only one proton signal of the two relevant spin systems of *ent-4* could be resolved (it is unknown whether it is that of the C(3)-to-C(5) or C(8)-to-C(10) spin system), the $^3J(\text{H},\text{H})$ values of 2.9 and 10.5 Hz indicate a much stronger conformational preference within the side chains of *ent-4* than in that of its precursors. This can be ascribed to the

beneficial effect of the H-bridge in stabilizing the overall conformation. Thus, these measurements substantiate the notion that compounds of type **4** could, indeed, serve as conformationally fully flexible β -hairpin mimetics.

Synthesis of 30. – To put this notion to test, we initiated a synthesis of the amino acid **29** (Scheme 5) with the aim to incorporate it into a peptide and to study the conformation of the latter. Our attention turned to RGD (Arg-Gly-Asp) peptides, as the biological activity of the latter can be controlled by incorporating this sequence into conformationally defined cyclopeptides [24]. These cyclopeptides have by necessity a turn segment as a conformation-controlling element. Therefore, for such an endeavor, we targeted structure **30**, which has the proper absolute configuration to mimic a natural β -II'-type hairpin.

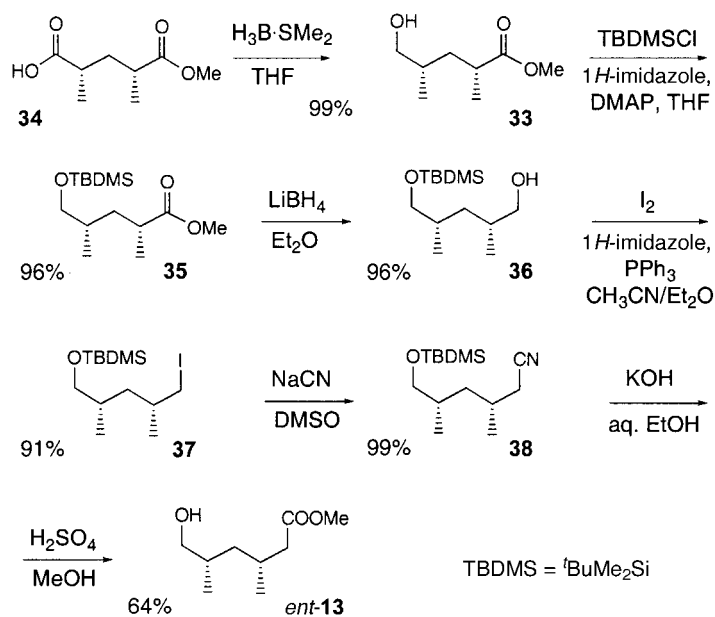


Again, we planned a convergent approach based on a *Julia* olefination. Building block *ent-13* corresponds to that used in our synthesis of *ent-4*. Otherwise, we wanted to introduce the N-function at C(11) early and opted for **31** as the second building block (Scheme 5). This led us to consider the well-known hydroxypentanoate **33** [25] as starting material. The latter is available from the *meso*-diester **32** via a α -chymotrypsin-catalyzed enantioselective hydrolysis [26] followed by reduction of the half ester **34** (Scheme 6). Compound **34** of ca. 85% ee (upgraded by crystallization of the (*R*)-phenylethylammonium salt) [27] was then converted to *ent-13* in a series of simple high-yielding steps via **35**, the mono-protected diol **36** [28], and **37** and **38**.

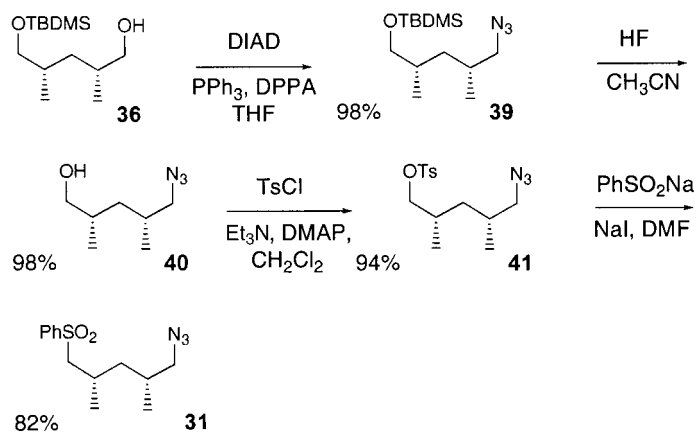
Compound **36** served as a relay to access the other building block **31** (Scheme 7). Conversion of **36** to the azido alcohol **40** via **39** followed literature precedent [28]. The subsequent introduction of the sulfone moiety via **41** was unproblematic.

The presence of the azido function in the building block **31** required careful conditions in the *Julia* olefination with *ent-21* (Scheme 8). A balance between reactivity and decomposition of **42** (from **31**) was struck by running the addition at -50° . After acetylation of the diastereoisomeric hydroxysulfonyl esters to the (acetyloxy)sulfonyl

Scheme 6



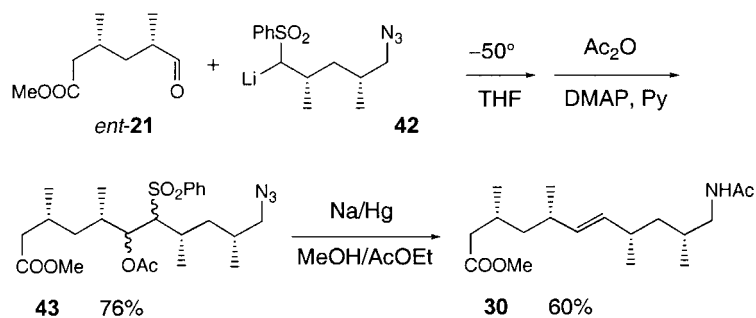
Scheme 7



TBDMS = $t\text{BuMe}_2\text{Si}$, DIAD = diisopropyl azodicarboxylate,
 DPPA = diphenoxyphosphoryl azide, DMAP = *N,N*-dimethylpyridin-4-amine

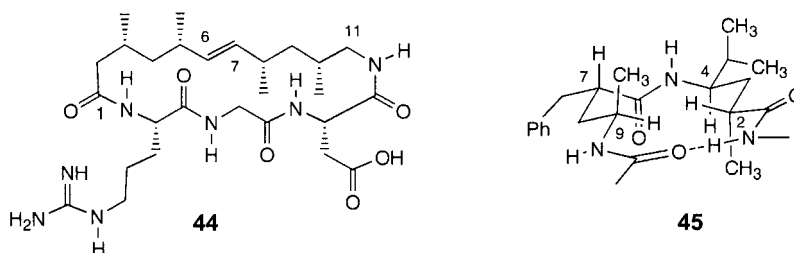
esters **43**, sodium amalgam reduction served as a multipurpose tool: it established the (*E*)-double bond, reduced the azido function, and led to acetylation of the formed primary amino group by the solvent AcOEt, all in one operation, yielding the target **30**.

Scheme 8



DMAP = *N,N*-dimethylpyridin-4-amine

Discussion. – The amino acid ATUA **29** derived from **30** has since been incorporated into a cyclic RGD peptide **44** [29]. A detailed conformational analysis of the latter showed that the ATUA unit was not a proper substitute for the FV (D-Phe-Val) moiety in the biologically highly active cyclo(-RGDFV-) (cyclo(-Arg-Gly-Asp-D-Phe-Val)). Rather, the H-bridge in the β -hairpin mimetic, *cf.* **4**, opened due to intra-annular strain. This led to quite different folding for the RGD part of the cyclopeptide **44** [29]. The conformation design implemented in compound **4** was found to hold, however, for the major part of the backbone, *i.e.*, the bonds from C(2) to C(11). The culprit were the bonds C(1)–C(2) and C(11)–N(12), about which rotation led to a different conformation than that projected and found in compound **4**. In fact, our conformation design had not addressed these two bonds. Rather we had assumed, that the H-bridge would take care of this. Unfortunately this assumption did not hold for the cyclopeptide **44**.



In this context, the turn mimetic **45** described recently by Brenner and Seebach [30] comes into focus. The γ -dipeptide **45** does not have the same topology as a β -II-hairpin **3** or as **4**; it has two atoms less in the turn. Otherwise the side arms in **45** are conformationally pre-organized [31] in a similar manner as in the hairpin mimetic **4** described above. Whereas, in **4**, a lack of conformational pre-organization about the bonds C(1)–C(2) and C(11)–N(12) turned out to be the *Achilles* heel of the overall design, it is these two bonds that are missing in **45**. This, however, does not necessarily imply a high(er) conformational preference: it is high ($J=11.2$ and 2.7 Hz) in the segment C(2)-to-C(4), but low ($J=8.4$ and 6.0 Hz) in the segment C(7)-to-C(9).

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Experimental Part

General. All temps. quoted are uncorrected. ^1H - and ^{13}C -NMR: Bruker ARX-200, AC-300, WH-400, AM-400, and AMX-500; δ in ppm, J in Hz. Flash chromatography (FC): silica gel SI 60 (40–63 μm), E. Merck KGaA, Darmstadt. pH 7 Buffer: $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$ (56.2 g) and $\text{Na}_2\text{HPO}_4 \cdot 4 \text{H}_2\text{O}$ (213.6 g) filled up to 1 l with H_2O .

1. (3*S*,5*R*)-6-Hydroxy-3,5-dimethylhexanoic Acid (**18**). NaOH (0.6 g, 15 mmol) was added to a soln. of (3*S*,5*R*)-3,5-dimethyl-6-[(triisopropylsilyl)oxy]hexanenitrile (**17**) [11] (0.298 g, 1.00 mmol) in EtOH/ H_2O 2:1 (6 ml). After stirring for 2 d at 80°, the soln. was extracted with tBuOMe (220 ml). The aq. layer was acidified with conc. HCl soln. and extracted with tBuOMe (3 $\times$ 20 ml). The combined org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to FC (tBuOMe /pentane 1:3): **18** (0.135 g, 84%). Colorless oil. $[\alpha]_{\text{D}}^{20} = +4.8$ ($c = 1.0$, MeOH), 80% ee²). ^1H -NMR (400 MHz, CDCl_3): 0.93 ($d, J = 6.7$, Me–C(5)); 0.98 ($d, J = 6.6$, Me–C(3)); 1.02–1.08 (m , H_a –C(4)); 1.41 ($td, J = 6.7, 13.7$, H_b –C(4)); 1.65–1.73 (m , H–C(5)); 2.00–2.09 (m , H–C(3)); 2.14 ($dd, J = 7.4, 15.2$, H_a –C(2)); 2.32 ($dd, J = 6.3, 15.2$, H_b –C(2)); 3.56–3.58 (m , 2 H–C(6)); 5.26–5.59 (br., OH, COOH). ^{13}C -NMR (100 MHz, CDCl_3): 17.4 (Me–C(5)); 20.5 (Me–C(3)); 27.6 (C(3)); 33.0 (C(5)); 40.4; 41.2; 67.7 (C(6)); 178.4 (C(1)). Anal. calc. for $\text{C}_8\text{H}_{16}\text{O}_3$ (160.2): C 59.98, H 10.07; found: C 59.84, H 10.37.

2. Methyl (3*S*,5*R*)-6-Hydroxy-3,5-dimethylhexanoate (**13**). A soln. of diazomethane in Et₂O (ca. 1M) was added dropwise at 0° to a soln. of **18** (0.050 g, 0.31 mmol) in Et₂O (20 ml) until the yellow color persisted. Excess diazomethane was destroyed by adding 2 drops of AcOH/Et₂O 1:1. The mixture was washed with sat. aq. NaHCO_3 soln. (5 ml), the aq. layer extracted with tBuOMe (10 ml), the combined org. extract dried (Na_2SO_4) and evaporated, and the residue submitted to FC (tBuOMe /pentane 1:1) **13** (48 mg, 90%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -1.0$ ($c = 0.8$, CH_2Cl_2), 88% ee²). For ^1H - and ^{13}C -NMR: see Exper. 17. Anal. calc. for $\text{C}_9\text{H}_{18}\text{O}_3$ (174.2): C 62.04, H 10.41; found: C 61.85, H 10.65.

3. (2*S*,4*R*)-5-Iodo-2,4-dimethylpentan-1-ol Acetate (**19**). Ph_3P (0.30 g, 1.1 mmol), 1*H*-imidazole (0.20 g, 2.2 mmol), and I_2 (0.36 g, 1.1 mmol) were added sequentially to a soln. of (2*R*,4*S*)-5-(acetyloxy)-2,4-dimethylpentan-1-ol (0.17 g, 1.0 mmol) in THF (5 ml). After stirring for 12 h tBuOMe (20 ml) was added, the resulting precipitate filtered, and the filtrate evaporated. The residue was taken up in CH_2Cl_2 (10 ml), and 5.5M *tert*-butyl hydroperoxide in 2,2,4-trimethylpentane (0.02 ml, 0.1 mmol) was added. After stirring for 5 min, sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ soln. (10 ml) was added, the aq. layer extracted with tBuOMe (3 $\times$ 10 ml), the combined org. layer dried (Na_2SO_4), and evaporated, and the residue submitted to FC (tBuOMe /pentane 1:9): **19** (0.25 g, 90%). Colorless liquid. $[\alpha]_{\text{D}}^{20} = -2.1$ ($c = 1.4$, CH_2Cl_2), 93% ee²). ^1H -NMR (300 MHz, CDCl_3): 0.90 ($d, J = 6.7$, Me–C(4)); 0.94 ($d, J = 6.3$, Me–C(2)); 0.96–1.06 (m , H_a –C(3)); 1.34–1.52 (m , H_b –C(3), H–C(4)); 1.72–1.85 (m , H–C(2)); 2.01 (s , Ac); 3.09 ($dd, J = 5.4, 9.7$, H_a –C(5)); 3.18 ($dd, J = 4.2, 9.7$, H_b –C(5)); 3.82 ($dd, J = 6.5, 10.8$, H_a –C(1)); 3.88 ($dd, J = 5.9, 10.8$, H_b –C(1)). ^{13}C -NMR (75 MHz, CDCl_3): 17.2 (Me–C(2)); 17.3 (C(5)); 20.8 (MeCO); 21.2 (Me–C(4)); 29.9 (C(4)); 31.5 (C(2)); 40.3 (C(3)); 68.9 (C(1)); 170.9 (MeCO). Anal. calc. for $\text{C}_9\text{H}_{17}\text{IO}_2$ (284.1): C 38.04, H 6.03; found: C 38.22, H 6.09.

4. (2*R*,4*S*)-5-(Acetyloxy)-2,4-dimethylpentyl Phenyl Sulfone (**20**). Sodium benzenesulfinate (10.05 g, 61.2 mmol) and **19** (5.36 g, 18.8 mmol) were heated in poly(ethylene glycol)-400 (61 ml) for 2.5 h to 130°. After cooling, H_2O (500 ml) was added, the mixture extracted with tBuOMe (4 $\times$ 100 ml), the combined org. layer dried (Na_2SO_4) and evaporated, and the residue submitted to FC (tBuOMe /pentane 1:1): **20** (5.11 g, 91%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -1.7$ ($c = 0.7$, CH_2Cl_2), 93% ee²). ^1H -NMR (300 MHz, CDCl_3): 0.80 ($d, J = 6.7$, Me–C(4)); 1.02–1.13 (m , Me–C(2), H_a –C(3)); 1.41–1.50 (m , H_b –C(3)); 1.68–1.79 (m , H–C(2)); 2.00 (s , Ac); 2.08–2.16 (m , H–C(4)); 2.87 ($dd, J = 7.9, 14.2$, H_a –C(1)); 3.03 ($dd, J = 4.1, 14.2$, H_b –C(1)); 3.77 ($dd, J = 6.4, 10.9$, H_a –C(5)); 3.84 ($dd, J = 5.9, 10.9$, H_b –C(5)); 7.53–7.58 (m , 2 arom. H); 7.60–7.66 (m , 1 arom. H); 7.87–7.91 (m , 2 arom. H). ^{13}C -NMR (75 MHz, CDCl_3): 17.1 (Me–C(4)); 20.7 (Me–C(2)); 20.8 (MeCO); 26.2 (C(2)); 29.8 (C(4)); 40.9 (C(3)); 62.2 (C(1)); 68.8 (C(5)); 127.8 (2 arom. C); 129.3 (2 arom. C); 133.6 (Ph); 140.0 (Ph); 171.0 (MeCO). Anal. calc. for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{S}$ (298.4): C 60.38, H 7.43; found: C 60.16, H 7.21.

2) The ee value given is that of the precursor (2*R*,4*S*)-5-(acetyloxy)-2,4-dimethylpentan-1-ol determined by NMR analysis of the (S)- α -methoxy- α -(trifluoromethyl)benzeneacetate.

5. (2*R*,4*S*)-5-[[*tert*-Butyl]dimethylsilyloxy]-2,4-dimethylpentyl Phenyl Sulfone (**14**). K_2CO_3 (5.34 g, 38.4 mmol) was added to a soln. of **20** (5.08 g, 17.0 mmol) in MeOH (200 ml) and H_2O (100 ml). After stirring for 12 h, the mixture was evaporated and the residue partitioned between 'BuOMe (50 ml) and H_2O (50 ml). The aq. layer was extracted with 'BuOMe (3×50 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC ('BuOMe/petroleum ether 1:3): alcohol (3.96 g, 91%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -12.9$ ($c = 0.7$, CH_2Cl_2), 93% ee³). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.77 (*d*, $J = 6.5$, Me–C(4)); 1.05 (*d*, $J = 6.7$, Me–C(2)); 1.45–1.58 (*m*, 2 H–C(3)); 2.07–2.18 (*m*, H–C(2), H–C(4)); 2.86 (*dd*, $J = 7.7$, 14.2, H_a –C(1)); 3.06 (*dd*, $J = 4.4$, 14.2, H_b –C(1)); 3.36–3.42 (*m*, 2 H–C(5)); 7.50–7.56 (*m*, 2 arom. H); 7.59–7.65 (*m*, 1 arom. H); 7.85–7.89 (*m*, 2 arom. H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 16.9 (Me–C(4)); 20.9 (Me–C(2)); 26.2 (C(2)); 32.8 (C(4)); 40.5 (C(3)); 62.2 (C(1)); 67.2 (C(5)); 127.7 (2 arom. C); 129.2 (2 arom. C); 133.5 (Ph); 139.9 (Ph). Anal. calc. for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{S}$ (256.4): C 60.91, H 7.86; found: C 60.98, H 8.05.

(*tert*-Butyl)chlorodimethylsilane (50% in hexane; 13.38 g, 44.4 mmol) was added to a soln. of the obtained alcohol (3.78 g, 14.8 mmol), 1*H*-imidazole (3.02 g, 44.4 mmol), and DMAP (1.30 g, 8.2 mmol) in THF (75 ml). After stirring for 12 h, the mixture was partitioned between 'BuOMe (10 ml) and H_2O (50 ml). The aq. layer was extracted with petroleum ether (3×10 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:9): **14** (5.45 g, 99%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -6.7$ ($c = 0.9$, CH_2Cl_2), 93% ee³). $^1\text{H-NMR}$ (300 MHz, CDCl_3): –0.02 (*s*, Me_2Si); 0.76 (*d*, $J = 6.6$, Me–C(4)); 0.84 (*s*, 'BuSi); 0.93–1.04 (*m*, H_a –C(3)); 1.13 (*d*, $J = 6.6$, Me–C(2)); 1.35–1.54 (*m*, H_b –C(3), H–C(2)); 2.06–2.17 (*m*, H–C(4)); 2.84 (*dd*, $J = 8.8$, 14.2, H_a –C(1)); 3.08 (*dd*, $J = 3.4$, 14.2, H_b –C(1)); 3.25–3.35 (*m*, 2 H–C(5)); 7.51–7.57 (*m*, 2 arom. H); 7.60–7.66 (*m*, 1 arom. H); 7.88–7.92 (*m*, 2 arom. H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): –5.5 (2 C, Me_2Si); 16.9 (Me–C(4)); 18.2 (Me_3CSi); 20.9 (Me–C(2)); 25.9 (3 C, Me_3CSi); 26.4 (C(2)); 33.0 (C(4)); 41.0 (C(3)); 62.3 (C(1)); 67.8 (C(5)); 127.8 (2 arom. C); 129.2 (2 arom. C); 133.4 (Ph); 140.2 (Ph). Anal. calc. for $\text{C}_{19}\text{H}_{34}\text{O}_3\text{SSi}$ (370.6): C 61.57, H 9.25; found: C 61.63, H 9.26.

6. Methyl (3*S*,5*R*,6*E*,8*R*,10*S*)-11-[[*tert*-Butyl]dimethylsilyloxy]-3,5,8,10-tetramethylundec-6-enoate (**23**). Methyl (3*S*,5*R*)-3,5-dimethyl-6-hydroxyhexanoate (**13**; 0.52 g, 3.0 mmol) was added to a mixture of pyridinium chlorochromate (0.97 g, 4.5 mmol) and silica gel (1 g) in CH_2Cl_2 (10 ml). After stirring for 3 h, the mixture was filtered over silica gel and the filtrate evaporated. The aldehyde **21** formed (for spectral data, see *Exper.* 22) was taken up in THF (10 ml).

At -78° 1.95*M* BuLi (3.7 ml, 7.3 mmol) was added to a soln. of sulfone **14** (2.78 g, 7.5 mmol) in THF (40 ml). After stirring for 20 min, the soln. of **21** was added dropwise. The mixture was stirred for 3 h and allowed to reach -50° . Sat. aq. NH_4Cl soln. (20 ml) was added, the aq. layer extracted with 'BuOMe (3×20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:4): hydroxysulfonyl compounds (1.56 g, 97%). Colorless oil. Anal. calc. for $\text{C}_{28}\text{H}_{50}\text{O}_6\text{SSi}$ (542.9): C 61.95, H 9.28; found: C 62.03, H 8.99.

The hydroxysulfonyl compounds obtained were taken up in pyridine (5 ml), and Ac_2O (1.84 g, 18.0 mmol) and DMAP (92 mg, 0.75 mmol) were added. After stirring for 1 d, sat. aq. NH_4Cl soln. (20 ml) was added, the aq. layer extracted with 'BuOMe (3×30 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:2): (acetyloxy)sulfonyl compounds (1.51 g, 90%). Colorless oil. Anal. calc. for $\text{C}_{30}\text{H}_{52}\text{O}_7\text{SSi}$ (584.88): C 61.61, H 8.96; found: C 61.48, H 8.97.

Disodium hydrogenphosphate (1.76 g, 4.9 mmol) and 6% sodium amalgam (3.5 g) were added at -30° to a soln. of the (acetyloxy)sulfonyl compounds (0.48 g, 0.8 mmol) in MeOH/ AcOEt 2:1 (12 ml). After stirring for 3 h at -30° , the mixture was allowed to reach -10° . The soln. was decanted and the remaining amalgam washed with 'BuOMe (3×10 ml). The combined org. layers were washed with H_2O (2×20 ml), dried (Na_2SO_4), and evaporated. FC ('BuOMe/pentane 1:10) of the residue furnished **23** (0.26 g, 88%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -14.3$ ($c = 1.0$, CH_2Cl_2), >98% ee³). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 0.01 (*s*, Me_2Si); 0.82 (*d*, $J = 6.6$, Me–C(10)); 0.84–0.90 (*m*, 'BuSi, Me–C(3)); 0.93 (*d*, $J = 6.6$, Me–C(5) or Me–C(8)); 0.94 (*d*, $J = 6.8$, Me–C(5) or Me–C(8)); 0.96 (*ddd*, $J = 5.1$, 9.4, 13.6, H_a –C(9) or H_a –C(4)); 1.08 (*ddd*, $J = 5.4$, 9.1, 13.6, H_a –C(9) or H_a –C(4)); 1.23 (*ddd*, $J = 5.1$, 9.3, 13.6, H_b –C(4)); 1.32 (*ddd*, $J = 4.5$, 9.7, 13.6, H_b –C(9)); 1.55–1.64 (*m*, H–C(10)); 1.93–1.98 (*m*, H–C(3), H–C(4)); 2.09 (*dd*, $J = 7.9$, 14.6, H_a –C(2)); 2.11–2.17 (*m*, H–C(5), H–C(8)); 2.25 (*dd*, $J = 6.2$, 14.6, H_b –C(2)); 3.32 (*dd*, $J = 6.5$, 9.9, H_a –C(11)); 3.39 (*dd*, $J = 6.0$, 9.9, H_b –C(11)); 3.64 (*s*, CO_2Me); 5.11–5.19 (*m*, H–C(6), H–C(7)). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): –5.4 (2 C, Me_2Si); 16.4 (C(10)); 18.3 (Me_3CSi); 19.4 (C(3)); 21.7 (C(5)); 22.1 (C(8)); 25.9 (3 C, Me_3CSi); 28.1 (C(3)); 33.5 (C(10)); 34.2 (C(5) or C(8)); 34.3 (C(5) or (8)); 40.8 (C(9)); 42.1 (C(4)); 44.2 (C(2)); 51.2 (MeO); 68.8 (C(11)); 134.0 (C(6)

³) The ee value given is that estimated on the basis of Horeau's principle [20].

or C(7)); 134.8 (C(6) or C(7)); 173.5 (C(1)). Anal. calc. for $C_{22}H_{44}O_3Si$ (384.7): C 68.69, H 11.53; found: C 68.42, H 11.64.

7. (3*S*,5*R*,6*E*,8*R*,10*S*)-11-[[*tert*-Butyl]dimethylsilyl]oxy]-*N,N*,3,5,8,10-hexamethylundec-6-enamide (**24**). First a soln. of chloro(dimethylamino)methylaluminum was prepared: A soln. of 2*M* Me_3Al (10 ml) in toluene was added slowly at 5° into a suspension of $(Me_2NH_2)Cl$ (1.63 g, 20.0 mmol) in toluene (20 ml). The mixture was stirred for *ca.* 2.5 h until the evolution of methane had ceased. The soln. was stored in a refrigerator.

A soln. of 0.65*M* chloro(dimethylamino)methylaluminum in toluene (0.9 ml, 0.6 mmol) was added into a soln. of **23** (75 mg, 0.19 mmol) in benzene (2 ml). After heating for 12 h under reflux, the mixture was cooled and acidified with 5% aq. HCl soln. The aq. layer was extracted with AcOEt (3×20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC (BuOMe/pentane 1:2): **24** (72 mg, 95%). Colorless oil. $[\alpha]_D^{20} = -14.0$ ($c = 0.4$, CH_2Cl_2), > 98% ee³. ¹H-NMR (300 MHz, $CDCl_3$): 0.01 (*s*, Me_3Si); 0.81 (*d*, $J = 6.6$, $Me-C(10)$); 0.84–1.00 (*m*, BuSi, $Me-C(3)$, $Me-C(5)$, $Me-C(8)$ or $Me-C(4)$, $H_a-C(9)$ or $H_a-C(4)$); 1.11 (*ddd*, $J = 5.5, 8.8, 14.0$, $H_a-C(9)$ or $H_a-C(4)$); 1.21–1.35 (*m*, $H_b-C(4)$ or $H_b-C(9)$); 1.51–1.67 (*m*, $H-C(10)$); 1.90–2.05 (*m*, $H-C(3)$); 2.05–2.19 (*m*, $H-C(5)$, $H-C(8)$, $H_a-C(2)$); 2.25 (*dd*, $J = 5.9, 14.4$, $H_b-C(2)$); 2.92, 2.97 (2 *s*, $CONMe_2$); 3.31 (*dd*, $J = 6.6, 9.7$, $H_a-C(11)$); 3.40 (*dd*, $J = 6.0, 9.7$, $H_b-C(11)$); 5.19–5.23 (*m*, $H-C(6)$, $H-C(7)$). ¹³C-NMR (75 MHz, $CDCl_3$): –5.3 (2 *C*, Me_2Si); 16.5 (C(10)); 18.3 (Me_3Si); 19.7 (C(3)); 21.8 (C(5)); 22.0 (C(8)); 25.9 (3 *C*, Me_3Si); 28.1 (C(3)); 33.5 (C(10)); 34.1 (C(5) or C(8)); 34.3 (C(5) or C(8)); 35.3 (MeN); 37.5 (MeN); 40.9 (C(9)); 41.3 (C(4)); 44.6 (C(2)); 68.8 (C(11)); 134.2 (C(6) or C(7)); 134.6 (C(6) or C(7)); 172.6 (C(1)). Anal. calc. for $C_{23}H_{47}NO_2Si$ (397.7): C 69.46, H 11.91, N 3.52; found: C 69.32, H 11.90, N 3.59.

8. (3*S*,5*R*,6*E*,8*R*,10*S*)-11-Hydroxy-*N,N*,3,5,8,10-hexamethylundec-6-enamide (**25**). $Bu_4NF \cdot 3 H_2O$ (0.47 g, 1.5 mmol) was added to a soln. of **24** (100 mg, 0.25 mmol) in THF (5 ml). Molecular sieves (4 Å) were added, and the mixture was stirred for 1 d. MeOH (5 ml) was added, and stirring was continued for 10 min. Sat. aq. NH_4Cl soln. (10 ml) was added, the aq. layer extracted with BuOMe (3×20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC (BuOMe): **25** (68 mg, 96%). Colorless oil. $[\alpha]_D^{20} = -52.3$ ($c = 0.3$, CH_2Cl_2), > 98% ee³. ¹H-NMR (300 MHz, $CDCl_3$): 0.81 (*d*, $J = 6.2$, $Me-C(10)$); 0.84 (*d*, $J = 6.6$, $Me-C(3)$); 0.91 (*d*, $J = 6.7$, $Me-C(5)$ or $Me-C(8)$); 0.91 (*d*, $J = 6.7$, $Me-C(5)$ or $Me-C(8)$); 1.02–1.26 (*m*, $CH_2(4)$, $CH_2(9)$); 1.59–1.70 (*m*, $H-C(10)$); 2.00–2.16 (*m*, $CH_2(2)$, $H-C(3)$, $H-C(5)$, $H-C(8)$); 2.87, 2.94 (2 *s*, $CONMe_2$); 3.34 (*dd*, $J = 6.6, 11.8$, $H_a-C(11)$); 3.38–3.42 (*m*, $H_b-C(11)$); 3.60 (*br.*, OH); 4.92–5.07 (*m*, $H-C(6)$, $H-C(7)$). ¹³C-NMR (75 MHz, $CDCl_3$): 16.6 (C(10)); 19.1 (C(3)); 22.2 (C(5)); 22.4 (C(8)); 27.9 (C(3)); 34.1 (C(10)); 35.0 (C(5) or C(8)); 35.1 (C(5) or C(8)); 35.4 (MeN); 37.3 (MeN); 41.0 (2 *C*, C(4), C(9)); 44.8 (C(2)); 68.7 (C(11)); 134.4 (C(6) or C(7)); 135.4 (C(6) or C(7)); 172.7 (C(1)). Anal. calc. for $C_{17}H_{33}NO_2$ (283.5): C 72.04, H 11.73, N 4.94; found: C 71.91, H 11.59, N 5.16.

9. (3*S*,5*R*,6*E*,8*R*,10*S*)-11-Azido-*N,N*,3,5,8,10-hexamethylundec-6-enamide (**26**). Methanesulfonyl chloride (30 mg, 0.26 mmol) and Et_3N (51 mg, 0.5 mmol) were added sequentially at –40° to a soln. of **25** (36 mg, 0.13 mmol) in CH_2Cl_2 (2 ml). The mixture was allowed to reach –20° over 1 h with stirring. Sat. aq. NH_4Cl soln. (15 ml) was added, the aq. layer extracted with BuOMe (3×10 ml), and the combined org. phase dried (Na_2SO_4) and evaporated. The crude mesylate was taken up in DMF (3 ml), NaN_3 (0.1 g, 1.5 mmol) was added, and the soln. was stirred for 2 d at 50°. H_2O (100 ml) was added, the aq. layer extracted with BuOMe (3×20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC (BuOMe/petroleum ether 1:1): **26** (35 mg, 85%). Colorless oil. $[\alpha]_D^{20} = -15.0$ ($c = 0.4$, CH_2Cl_2), > 98% ee³. ¹H-NMR (300 MHz, $CDCl_3$): 0.89 (*d*, $J = 6.5, 3$ H); 0.91 (*d*, $J = 7.1, 3$ H); 0.93 (*d*, $J = 6.7, 3$ H); 0.94 (*d*, $J = 6.7, 3$ H); 0.99–1.13 (*m*, $H_a-C(4)$, $H_a-C(9)$); 1.23–1.35 (*m*, $H_b-C(4)$, $H_b-C(9)$); 1.65–1.79 (*m*, $H-C(10)$); 1.92–2.05 (*m*, $H-C(3)$); 2.06–2.24 (*m*, $H-C(5)$, $H-C(8)$); 2.12 (*dd*, $J = 7.7, 14.6$, $H_a-C(2)$); 2.23 (*dd*, $J = 6.2, 14.6$, $H_b-C(2)$); 2.92, 2.98 (2 *s*, $CONMe_2$); 3.07 (*dd*, $J = 6.8, 11.9$, $H_a-C(11)$); 3.15 (*dd*, $J = 6.1, 11.9$, $H_b-C(11)$); 5.13–5.26 (*m*, $H-C(6)$, $H-C(7)$). ¹³C-NMR (75 MHz, $CDCl_3$): 17.3 (C(10)); 19.6 (C(3)); 21.9 (C(5)); 22.0 (C(8)); 28.1 (C(3)); 31.4 (C(10)); 34.4 (2 *C*, C(5), C(8)); 35.3 (MeN); 37.5 (MeN); 41.2 (C(9)); 41.7 (C(4)); 44.6 (C(2)); 58.3 (C(11)); 134.0 (C(6) or C(7)); 134.9 (C(6) or C(7)); 172.5 (C(1)). Anal. calc. for $C_{17}H_{32}N_4O$ (308.5): C 66.19, H 10.46; found: C 65.98, H 10.65.

10. (3*S*,5*R*,6*E*,8*R*,10*S*)-11-(Acetylamino)-*N,N*,3,5,8,10-hexamethylundec-6-enamide (*ent*-**4**). Ph_3P (102 mg, 0.39 mmol) and H_2O (125 μ l) were added to a soln. of **26** (80 mg, 0.26 mmol) in THF (2 ml). After stirring for 30 h, Ac_2O (119 mg, 1.17 mmol) and K_2CO_3 (104 mg, 0.75 mmol) were added, and stirring was continued for 2 d. The mixture was adsorbed on alumina which was placed on top of a FC column. Triphenylphosphine oxide was eluted with BuOMe. Subsequent elution with $CHCl_3/MeOH$ 97:3 furnished *ent*-**4** (80 mg, 96%). Colorless oil. $[\alpha]_D^{20} = -26.0$ ($c = 1.0$, CH_2Cl_2), > 98% ee³. ¹H-NMR (500 MHz, $CDCl_3$): 0.82 (*d*, $J = 6.5$, $Me-C(10)$); 0.84 (*d*, $J = 6.6$, $Me-C(3)$); 0.80–0.96 (*m*, $H_a-C(4)$ or $H_a-C(9)$); 0.94 (*d*, $J = 6.6$, $Me-C(5)$ or $Me-C(8)$); 0.94

($d, J = 6.6$, Me–C(5) or Me–C(8)); 1.03 ($ddd, J = 2.9$, 10.5, 13.7, H_a –C(4) or H_a –C(9)); 1.08–1.15 (m , H_b –C(4) or H_b –C(9)); 1.60–1.68 (m , H–C(10)); 1.99 (s , Ac); 2.02–2.09 (m , H–C(3)); 2.10–2.19 (m , H–C(5), H–C(8)); 2.10 ($dd, J = 4.2$, 15.4, H_a –C(2)); 2.18 ($dd, J = 9.9$, 15.4, H_b –C(2)); 2.92, 3.00 (2 s , CONMe₂); 3.14 ($dd, J = 6.9$, 10.0, H_a –C(11)); 3.16 ($dd, J = 7.1$, 10.0, H_b –C(11)); 4.94–5.03 (m , H–C(6), H–C(7)); 7.45 (br., NH). ¹³C-NMR (125 MHz, CDCl₃): 16.9 (C(10)); 18.5 (C(3)); 22.3 (C(5)); 22.4 (C(8)); 22.9 (MeCO); 27.9 (C(3)); 31.2 (C(10)); 35.2 (C(5) or C(8)); 35.3 (C(5) or C(8)); 35.6 (MeN); 37.4 (MeN); 41.1 (C(9)); 42.2 (C(4)); 44.8 (C(2)); 46.4 (C(11)); 134.6 (C(6) or C(7)); 135.3 (C(6) or C(7)); 170.7 (Ac); 172.5 (C(1)). EI-HR-MS: 324.2777 (C₁₉H₃₆N₂O₂⁺; calc. 324.2777). Anal. calc. for C₁₉H₃₆N₂O₂ (324.5): C 70.33, H 11.18, N 8.63; found: C 69.98, H 11.15, N 8.89.

11. 11-(Acetylamino)-N,N-dimethylundecanamide (**5**). Ac₂O (0.61 g, 6.0 mmol) was added to a suspension of 11-amino-undecanoic acid in pyridine (50 ml). After stirring for 2 d at r.t., the solvent was evaporated and the residue recrystallized from H₂O: 11-(acetylamino)undecanoic acid. White solid (1.21 g, 100%). M.p. 83° ([32]: 83–84°). ¹H-NMR (300 MHz, CDCl₃): 1.17–1.30 (m , 12 H); 1.44–1.49 (m , 2 H); 1.59–1.63 (m , 2 H); 1.97 (s , MeCO); 2.32 ($t, J = 7.4$, 2 H); 3.13–3.24 (m , 2 H); 6.00 (br., NH). ¹³C-NMR (75 MHz, CDCl₃): 23.3; 24.7; 26.8; 28.9; 29.0; 29.1; 29.2; 29.3; 29.5; 34.0; 39.8; 170.4; 178.4. Anal. calc. for C₁₃H₂₅NO₃ (243.4): C 64.17, H 10.35, N 5.76; found: C 64.42, H 10.38, N 5.79.

A soln. of dicyclohexylcarbodiimide (DCC; 0.58 g, 2.8 mmol) and of Et₃N (0.3 g, 3 mmol) in CH₂Cl₂ (5 ml) was added dropwise to a mixture of (Me₂NH₂)Cl (0.21 g, 2.6 mmol) and 11-(acetylamino)undecanoic acid (0.57 g, 2.4 mmol) and CH₂Cl₂ (50 ml). After stirring for 12 h, the mixture was filtered over 'Kieselgur', and the filtrate was evaporated. The residue was recrystallized from H₂O and dried *in vacuo*: **5** (0.58 g, 90%). Colorless solid; M.p. 59°. ¹H-NMR (300 MHz, CDCl₃): 1.19–1.34 (m , 12 H); 1.38–1.50 (m , 2 H); 1.52–1.64 (m , 2 H); 1.94 (s , Ac); 2.27 ($t, J = 7.4$, 2 H); 2.91, 2.98 (2 s , 2 MeN); 3.13–3.22 (m , 2 H); 5.72 (br., NH). ¹³C-NMR (75 MHz, CDCl₃): 23.1; 24.9; 26.7; 29.0; 29.1; 29.2; 29.2; 29.4; 33.2; 35.1 (MeN); 37.1 (MeN); 39.5; 169.8; 173.0. EI-HR-MS: 270.2314 (C₁₅H₃₀N₂O₂⁺; calc. 270.2307). Anal. calc. for C₁₅H₃₀N₂O₂ (270.4): C 66.63, H 11.18, N 10.36; found: C 66.78, H 10.84, N 10.09.

12. Methyl (2*R*,4*S*)-5-Hydroxy-2,4-dimethylpentanoate (**33**). Borane·dimethylsulfide complex (4.6 ml, 48.5 mmol) was added at 0° to a soln. of the acid **34** (6.50 g, 37.0 mmol) in Et₂O (60 ml). After stirring for 1 h at r.t., glycerol/H₂O 1:3 (45 ml) was added at 0°. The aq. layer was extracted with Et₂O (4 × 25 ml), the combined org. phase dried (Na₂SO₄) and evaporated, and the residue submitted to FC ('BuOMe/pentane 3:7): **33** (5.91 g, 99%). Colorless oil. [α]_D²⁰ = –35.4 ($c = 5.66$, CHCl₃). ¹H-NMR (300 MHz, CDCl₃): 0.94 ($d, J = 6.7$, 3 H); 1.18 ($d, J = 7.0$, 3 H); 1.47–1.58 (m , 1 H); 1.75 ($ddd, J = 14.6$, 9.6, 5.4, 1 H); 2.42–2.57 (m , 3 H); 3.32 ($dd, J = 10.8$, 6.1, 1 H); 3.37–3.43 (m , 1 H); 3.60 (s , 3 H). ¹³C-NMR (75 MHz, CDCl₃): 16.6; 18.2; 34.0; 37.4; 37.5; 51.5; 67.8; 177.4. Anal. calc. for C₈H₁₆O₃ (160.2): C 59.97, H 10.07; found: C 60.29, H 9.84.

13. Methyl (2*R*,4*S*)-5-[(*tert*-Butyl)dimethylsilyloxy]-2,4-dimethylpentanoate (**35**). DMAP (130 mg, 1.06 mmol), 1*H*-imidazole (1.51 g, 22.0 mmol), and (*tert*-butyl)chlorodimethylsilane (50% in toluene; 6.62 g, 22.0 mmol) were added at 0° sequentially to a soln. of **33** (2.50 g, 15.6 mmol) in THF (50 ml). After stirring for 12 h at r.t., H₂O (30 ml) was added. The aq. layer was extracted with Et₂O (4 × 20 ml), the combined org. phase washed with brine (20 ml), dried (Na₂SO₄), and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:9): **35** (4.12 g, 96%). Colorless oil. [α]_D²⁰ = –14.7 ($c = 7.21$, CHCl₃). ¹H-NMR (300 MHz, CDCl₃): –0.10 (s , 6 H); 0.86 (s , 9 H); 0.87 ($d, J = 6.6$, 3 H); 1.13 ($d, J = 6.9$, 3 H); 1.06–1.18 (m , 1 H); 1.49–1.64 (m , 1 H); 1.75 ($ddd, J = 13.7$, 9.1, 5.2, 1 H); 2.50–2.59 (m , 1 H); 3.32 ($dd, J = 9.7$, 6.2, 1 H); 3.40 ($dd, J = 9.7$, 5.6, 1 H); 3.63 (s , 3 H). ¹³C-NMR (75 MHz, CDCl₃): –5.4 (2C); 16.7; 17.9; 18.3; 25.9 (3C); 33.7; 37.2; 37.8; 51.3; 68.2; 177.2. The NMR data correspond to those given in [33].

14. (2*R*,4*S*)-5-[(*tert*-Butyl)dimethylsilyloxy]-2,4-dimethylpentan-1-ol (**36**). LiBH₄ (206 mg, 9.5 mmol) was added at 0° to a soln. of **35** (1.70 g, 6.3 mmol) in Et₂O (15 ml). After stirring for 12 h at r.t., H₂O (15 ml) was added. The aq. layer was extracted with 'BuOMe (4 × 10 ml), the combined org. phase dried (Na₂SO₄) and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:5): **36** (1.46 g, 91%). Colorless oil. [α]_D²⁰ = +2.0 ($c = 5.26$, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): 0.01 (s , 6 H); 0.86 (s , 9 H); 0.87 ($d, J = 6.5$, 3 H); 0.91 ($d, J = 6.7$, 3 H); 0.82–0.89 (m , 1 H); 1.37–1.44 (m , 1 H); 1.63–1.73 (m , 2 H); 2.10 (br. s , 1 H); 3.34 ($dd, J = 9.7$, 6.4, 1 H); 3.36 ($dd, J = 10.5$, 6.6, 1 H); 3.42 ($dd, J = 9.8$, 5.8, 1 H); 3.46 ($dd, J = 10.6$, 5.2, 1 H). ¹³C-NMR (75 MHz, CDCl₃): –5.3 (2C); 17.7; 17.8; 18.2; 28.9 (3C); 33.2; 33.3; 37.3; 68.2; 68.3. Anal. calc. for C₁₃H₃₀O₂Si (246.5): C 63.35, H 12.27; found: C 63.22, H 11.96.

15. (2*R*,4*S*)-5-[(*tert*-Butyl)dimethylsilyloxy]-1-iodo-2,4-dimethylpentane (**37**). I₂ (1.75 g, 6.9 mmol), PPh₃ (1.81 g, 6.9 mmol), and 1*H*-imidazole (983 mg, 13.8 mmol) were added sequentially at 0° to a soln. of **36** (1.30 g, 5.3 mmol) in Et₂O/MeCN 3:1 (30 ml). After stirring for 12 h at r.t., H₂O (20 ml) was added, the aq. layer was extracted with Et₂O (3 × 20 ml), the combined org. phase washed with 20% aq. Na₂S₂O₃ soln. (20 ml), dried

(Na_2SO_4), and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:2): **37** (1.71 g, 91%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -4.2$ ($c = 6.96$, CHCl_3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.08 (s, 6 H); 0.85 (d, $J = 5.7$, 3 H); 0.86 (s, 9 H); 0.94 (d, $J = 6.4$, 3 H); 0.89–0.99 (m, 1 H); 1.32–1.39 (m, 1 H); 1.44–1.53 (m, 1 H); 1.57–1.69 (m, 1 H); 3.07 (dd, $J = 9.7$, 6.1, 1 H); 3.20 (dd, $J = 9.6$, 3.4, 1 H); 3.32 (dd, $J = 9.8$, 6.3, 1 H); 3.40 (dd, $J = 9.8$, 5.5, 1 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): –5.3 (2 C); 17.2; 17.9; 18.3; 21.5; 26.0 (3 C); 32.0; 33.2; 40.4; 68.2. Anal. calc. for $\text{C}_{13}\text{H}_{29}\text{IOSi}$ (356.4): C 43.81, H 8.20; found: C 43.71, H 8.16.

16. (3*R*,5*S*)-6-[[*tert*-Butyl]dimethylsilyloxy]-3,5-dimethylhexanenitrile (**38**). NaCN (1.02 g, 20.9 mmol) was added to a soln. of **37** (3.92 g, 11.0 mmol) in DMSO (60 ml). After stirring for 4 h at r.t., H_2O (50 ml) was added. The aq. layer was extracted with Et_2O (5×20 ml), the combined org. phase washed with H_2O (30 ml) and brine (30 ml), dried (Na_2SO_4), and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:2): **38** (2.78 g, 99%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -14.1$ ($c = 5.44$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 0.19 (s, 6 H); 0.85 (s, 9 H); 0.86 (d, $J = 6.6$, 3 H); 1.06 (d, $J = 6.6$, 3 H); 1.01–1.10 (m, 1 H); 1.44 (ddd, $J = 13.7$, 7.4, 6.3, 1 H); 1.56–1.65 (m, 1 H); 1.86–2.02 (m, 1 H); 2.14 (dd, $J = 16.7$, 7.1, 1 H); 2.30 (dd, $J = 16.6$, 5.1, 1 H); 3.35 (dd, $J = 9.8$, 5.9, 1 H); 3.39 (dd, $J = 9.8$, 5.8, 1 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): –5.1 (2 C); 17.1; 18.2; 20.1; 24.3; 25.8 (3 C); 28.0; 33.1; 39.9; 67.8; 118.6. Anal. calc. for $\text{C}_{14}\text{H}_{29}\text{NOSi}$ (255.5): C 65.83, H 11.44, N 5.48; found: C 65.90, H 11.60, N 5.49.

17. Methyl (3*R*,5*S*)-6-Hydroxy-3,5-dimethylhexanoate (*ent*-**13**). KOH (4.88 g, 81.2 mmol) was added to a soln. of **38** (1.47 g, 5.8 mmol) in $\text{EtOH}/\text{H}_2\text{O}$ 2:1 (35 ml). After heating to 80° for 1 d, H_2O (20 ml) was added. The aq. layer was extracted with 'BuOMe (2×10 ml) and then acidified with 5M aq. HCl and extracted with Et_2O (6×15 ml). The combined Et_2O extract was dried (Na_2SO_4) and evaporated and the residue dissolved in MeOH (30 ml). Conc. H_2SO_4 soln. (100 μl) was added, and the mixture was heated to reflux for 1 d. The mixture was evaporated again and diluted with H_2O (40 ml). The resulting soln. was extracted with Et_2O (4×20 ml), the combined extract washed with sat. aq. NaHCO_3 soln. (10 ml) and evaporated, and the residue taken up in MeOH (30 ml). K_2CO_3 (1 g) was added, and the mixture was stirred for 3 h and evaporated. H_2O (40 ml) was added, the mixture extracted with Et_2O (4×20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:2): *ent*-**13** (645 mg, 64%). Colorless oil. $[\alpha]_{\text{D}}^{20} = +0.6$ ($c = 7.11$, CHCl_3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.94 (d, $J = 6.6$, 3 H); 0.96 (d, $J = 6.0$, 3 H); 0.95–1.06 (m, 1 H); 1.34–1.43 (m, 1 H); 1.64–1.73 (m, 1 H); 1.95 (br. s, 1 H); 2.00–2.16 (m, 2 H); 2.31 (dd, $J = 14.6$, 5.9, 1 H); 3.49 (d, $J = 5.4$, 2 H); 3.67 (s, 3 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 17.4; 20.5; 27.7; 33.1; 40.5; 41.3; 51.4; 67.7; 173.9. ESI-HR-MS: 197.1156 ($[\text{C}_9\text{H}_{18}\text{O}_3 + \text{Na}]^+$; calc. 197.1154).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.84–1.00 (m, Me–C(3), Me–C(5), H_a –C(4)); 1.28–1.37 (m, H_b –C(4)); 1.58–1.68 (m, H–C(3)); 1.94–2.09 (m, H–C(5), H_a –C(2)); 2.20–2.29 (m, H_b –C(2)); 2.55 (br., OH); 3.37–3.46 (m, H–C(6)); 3.61 (s, MeO). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 17.3 (C(5)); 20.4 (C(3)); 27.6 (C(3)); 33.0 (C(5)); 40.5; 41.2; 51.3 (MeO); 67.6 (C(6)); 173.9 (C(1)).

18. (2*R*,4*S*)-1-Azido-5-[[*tert*-butyl]dimethylsilyloxy]-2,4-dimethylpentane (**39**). A soln. of **36** (123 mg, 0.50 mmol) and diphenoxyphosphoryl azide (DPPA; 261 mg, 0.95 mmol) in THF (1 ml) was added at 0° to a soln. of Ph_3P (249 mg, 0.95 mmol) and of diisopropyl azodicarboxylate (DIAD) (192 mg, 0.95 mmol) in THF (5 ml). The mixture was stirred for 1 d at r.t. Silica gel (ca. 2 g) was added, the mixture evaporated, and the residue placed on top of a chromatography column. FC ('BuOMe/pentane 1:5) furnished **39** (133 mg, 98%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -1.4$ ($c = 7.90$, CHCl_3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.03 (s, 6 H); 0.85 (d, $J = 6.7$, 3 H); 0.86 (s, 9 H); 0.94 (d, $J = 6.6$, 3 H); 0.89–1.00 (m, 1 H); 1.35–1.44 (m, 1 H); 1.59–1.65 (m, 1 H); 1.76–1.82 (m, 1 H); 3.01 (dd, $J = 12.0$, 7.2, 1 H); 3.20 (dd, $J = 11.9$, 5.2, 1 H); 3.32 (dd, $J = 9.7$, 6.2, 1 H); 3.40 (dd, $J = 9.8$, 5.5, 1 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): –5.6 (2 C); 17.5; 18.3; 18.6; 25.7 (3 C); 31.2; 33.1; 38.3; 57.9; 68.0. Anal. calc. for $\text{C}_{13}\text{H}_{29}\text{N}_3\text{OSi}$ (271.5): C 57.52, H 10.77; found: C 57.32, H 10.60.

19. (2*S*,4*R*)-5-Azido-2,4-dimethylpentan-1-ol (**40**). A 5% soln. of HF in MeCN (10 ml) was added to a soln. of **39** (4.17 g, 15.4 mmol) in MeCN (60 ml). After stirring for 2 h at r.t., sat. aq. NaHCO_3 soln. (40 ml) was added. The aq. layer was extracted with 'BuOMe (4×20 ml), the combined org. phase washed with brine (20 ml), dried (Na_2SO_4), and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:9): **40** (2.37 g, 98%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -10.4$ ($c = 4.69$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): 0.90 (d, $J = 6.7$, 3 H); 0.95 (d, $J = 6.6$, 3 H); 0.86–1.02 (m, 1 H); 1.34–1.48 (m, 1 H); 1.58–1.83 (m, 2 H); 2.37 (br. s, 1 H); 3.07 (dd, $J = 12.0$, 6.8, 1 H); 3.21 (dd, $J = 12.0$, 5.4, 1 H); 3.35 (dd, $J = 10.5$, 6.3, 1 H); 3.46 (dd, $J = 10.4$, 5.0, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 16.7; 17.7; 30.2; 32.2; 37.2; 56.9; 66.9. Anal. calc. for $\text{C}_7\text{H}_{15}\text{N}_3\text{O}$ (157.2): C 53.48, H 9.62; found: C 53.52, H 9.53.

20. (2*S*,4*R*)-5-Azido-2,4-dimethylpentan-1-ol 4-Methylbenzenesulfonate (**41**). Et_3N (3.2 ml, 21.8 mmol), DMAP (740 mg, 6.1 mmol), and TsCl (4.02 g, 21.1 mmol) were added sequentially at 0° to a soln. of **40** (1.90 g, 12.1 mmol) in CH_2Cl_2 (70 ml). After stirring for 3 h at r.t., H_2O (50 ml) was added. The aq. layer was extracted

with tBuOMe (4×20 ml), the combined org. phase washed with brine (20 ml), dried (Na_2SO_4), and evaporated, and the residue submitted to FC (tBuOMe/pentane 1:4): **41** (3.55 g, 94%). Colorless oil. $[\alpha]_{\text{D}}^{20} = +3.2$ ($c = 5.48$, CHCl_3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.92 ($d, J = 6.7$, 6 H); 0.91–1.14 (m , 1 H); 1.29–1.43 (m , 1 H); 1.69 ($oct.$, $J = 6.6$, 1 H); 1.87 ($oct.$, $J = 5.9$, 1 H); 2.45 (s , 3 H); 3.05 ($dd, J = 12.0$, 6.7, 1 H); 3.16 ($dd, J = 11.8$, 5.4, 1 H); 3.80 ($dd, J = 9.5$, 6.1, 1 H); 3.90 ($dd, J = 9.3$, 4.1, 1 H); 6.69 ($d, J = 7.2$, 2 H); 7.36 ($d, J = 8.1$, 2 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 17.2; 18.1; 21.5; 30.3; 30.8; 37.5; 57.4; 74.5; 127.8 (2 C); 128.7; 129.8 (2 C); 144.8. Anal. calc. for $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$ (311.4): C 54.00, H 6.80, N 13.49; found: C 54.15, H 6.55, N 13.20.

21. (2*S*,4*R*)-5-Azido-2,4-dimethylpentyl Phenyl Sulfone (**31**). NaI (3.69 g, 24.6 mmol) and sodium benzenesulfinate (7.07 g, 43.1 mmol) were added to a soln. of **41** (3.83 g, 12.3 mmol) in DMF (60 ml). After heating for 12 h to 75° , H_2O (60 ml) was added. The aq. layer was extracted with tBuOMe (4×20 ml), the combined org. phase washed with H_2O (2×10 ml), dried (Na_2SO_4), and evaporated, and the residue submitted to FC (tBuOMe/pentane 1:2): **31** (2.84 g, 82%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -1.0$ ($c = 5.12$, CHCl_3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.79 ($d, J = 6.6$, 3 H); 1.03 ($d, J = 6.7$, 3 H); 0.97–1.10 (m , 1 H); 1.36–1.42 (m , 1 H); 1.52–1.63 (m , 1 H); 2.00–2.19 (m , 1 H); 2.83 ($dd, J = 14.1$, 7.9, 1 H); 2.98 ($dd, J = 14.2$, 4.2, 1 H); 3.01 ($dd, J = 12.0$, 6.5, 1 H); 3.10 ($dd, J = 12.1$, 5.8, 1 H); 7.48–7.53 (m , 2 H); 7.57–7.62 (m , 1 H); 7.83–7.86 (m , 2 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 17.9; 20.7; 26.2; 30.9; 41.5; 57.3; 62.2; 127.8 (2 C); 129.3 (2 C); 133.6; 140.0. Anal. calc. for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ (281.4): C 55.49, H 6.81, N 14.93; found: C 55.45, H 6.89, N 14.75.

22. Methyl (3*R*,5*S*,6*RS*,7*RS*,8*S*,10*R*)-11-Azido-6-hydroxy-3,5,8,10-tetramethyl-7-(phenylsulfonyl)undecanoate. A mixture of silica gel (3 g) and pyridinium chlorochromate (1.14 g, 5.3 mmol) was added to a soln. of *ent*-**13** (614 mg, 3.52 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred for 2 h at r.t. and filtered. The silica gel was washed with Et_2O (20 ml). The combined solns. were evaporated: *ent*-**21** (588 mg, 97%). $[\alpha]_{\text{D}}^{20} = +8.0$ ($c = 3.78$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): 0.99 ($d, J = 6.9$, 3 H); 1.12 ($d, J = 7.0$, 3 H); 1.23–1.29 (m , 1 H); 1.70–1.79 (m , 1 H); 2.10–2.21 (m , 2 H); 2.30–2.39 (m , 2 H); 3.67 (s , 3 H); 9.60 ($d, J = 2.4$, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 14.0; 20.0; 27.9; 37.5; 41.2; 44.0; 51.5; 173.1; 204.9.

A soln. of 1.47*M* BuLi in hexane (1.1 ml, 1.7 mmol) was added at -78° to a soln. of **31** (512 mg, 1.82 mmol) in THF (9 ml). After stirring for 20 min, a soln. of *ent*-**21** (156 mg, 0.91 mmol) in THF (3 ml) was added dropwise. After stirring for 2 h at -78° , the temp. was allowed to reach -50° . Sat. aq. NH_4Cl soln. (15 ml) was added, the aq. layer extracted with tBuOMe (3×10 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC (tBuOMe/pentane 1:5): mixture of the hydroxysulfonyl compounds (361 mg, 88%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -18.3$ ($c = 12.7$, CHCl_3). Anal. calc. for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_5\text{S}$ (453.6): C 58.25, H 7.78, N 9.26; found: C 58.54, H 7.69, N 9.32.

23. Methyl (3*R*,5*S*,6*RS*,7*RS*,8*S*,10*R*)-6-(Acetyloxy)-11-azido-3,5,8,10-tetramethyl-7-(phenylsulfonyl)undecanoate (**43**). Ac_2O (2.10 ml, 22.3 mmol) and DMAP (114 mg, 0.94 mmol) were added to a soln. of the hydroxysulfonyl compounds described in *Exper.* 22. (1.60 g, 3.6 mmol) in pyridine (20 ml). The mixture was stirred for 3 d at r.t. Sat. aq. NH_4Cl soln. (30 ml) was added, the aq. layer extracted with tBuOMe (5×15 ml), the combined org. phase dried (Na_2SO_4), and evaporated, and the residue submitted to FC (tBuOMe/pentane 1:4): diastereoisomer mixture **43** (1.50 g, 87%). Colorless oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3 ; 1:1 diastereoisomer mixture): 0.53 ($d, J = 6.8$, 3 H); 0.72 ($d, J = 6.8$, 3 H); 0.87–0.93 (m , 15 H); 0.98 ($d, J = 6.6$, 3 H); 1.10–1.32 (m , 12 H); 2.01 (s , 3 H); 2.04 (s , 3 H); 2.10–2.30 (m , 12 H); 2.90–2.94 (m , 1 H); 3.20–3.25 (m , 1 H); 3.58 (s , 3 H); 3.60 (s , 3 H); 4.87–4.90 (m , 1 H); 5.11 ($dd, J = 6.4$, 4.2, 1 H); 7.50–7.55 (m , 6 H); 7.85–7.90 (m , 4 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 ; 1:1 diastereoisomer mixture): 15.1; 15.7; 17.6; 17.7; 18.5; 18.9; 19.6; 21.1; 21.6; 21.7; 28.2; 28.5; 29.6; 31.0 (2 C); 31.7; 34.4; 34.8; 39.4; 40.1; 40.3; 40.6 (2 C); 40.7; 51.8 (2 C); 57.4; 57.6; 67.5; 69.2; 72.7; 73.2; 128.2 (2 C); 128.8 (2 C); 129.1 (2 C); 129.5 (2 C); 133.8; 134.0; 140.8; 141.9; 170.2; 170.7; 173.5; 173.8. Anal. calc. for $\text{C}_{24}\text{H}_{37}\text{N}_3\text{O}_6\text{S}$ (459.6): C 58.16, H 7.52, N 8.48; found: C 57.98, H 7.32, N 8.47.

24. Methyl (3*R*,5*S*,6*E*,8*S*,10*R*)-11-(Acetylamino)-3,5,8,10-tetramethylundec-6-enoate (**30**). Disodium hydrogenphosphate (352 mg, 2.48 mmol) and 6% sodium amalgam (1.5 g) was added at -20° to a soln. of the isomer mixture **43** (163 mg, 0.34 mmol) in MeOH/AcOEt 2:1 (6 ml). After stirring for 12 h at r.t., the soln. was decanted. H_2O (10 ml) was added to the soln., the aq. layer extracted with tBuOMe (3×10 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue submitted to FC (5% MeOH/ CHCl_3): **30** (62 mg, 60%). Colorless viscous oil. $[\alpha]_{\text{D}}^{20} = +32.7$ ($c = 1.14$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 0.84 ($d, J = 6.4$, 3 H); 0.88 ($d, J = 6.6$, 3 H); 0.93 ($d, J = 6.6$, 3 H); 1.00–1.20 (m , 5 H); 1.79–1.83 (m , 2 H); 1.91–1.98 (m , 2 H); 1.98 (s , 3 H); 2.08–2.15 (m , 2 H); 2.09 ($dd, J = 15.4$, 6.4, 1 H); 2.22 ($dd, J = 15.4$, 4.9, 1 H); 2.98 ($dd, J = 13.3$, 5.0, 1 H); 3.05–3.14 (m , 1 H); 3.64 (s , 3 H); 5.00–5.05 (m , 2 H); 6.41 (*br. s*, 1 H). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 16.8; 18.6; 22.1; 22.2; 23.0; 28.0; 31.3; 34.9; 35.0; 42.0; 42.2; 44.3; 46.3; 51.4; 134.5; 135.0; 170.3; 174.2. EI-HR-MS: 311.2457 ($\text{C}_{18}\text{H}_{33}\text{NO}_3^+$; calc. 311.2460).

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