Synthesis of Enantiomerically Pure Amino Acids Containing 2,5-Disubstituted THF Rings in the Molecular Backbone

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N- and *C*-protected derivatives of 2,5-disubstituted *trans*- and *cis*-THF amino acids **6** and **7** were prepared in enantiomerically pure form from L-alanine. Felkin–Anh-controlled reduction of the ketone **9** was achieved with a 85:15 diastereoselectivity. Epoxidation of **10** and subsequent intramolecular epoxide opening gave the *trans*- and *cis*-THF alcohols **11** and **12**, which were further transformed into the corresponding *N*- and *C*-protected 2,5-disubstituted *trans*- and *cis*-THF amino acids. Conformational studies show that the *cis*-THF diamide **34** is a β-turn mimetic in the solid state and in $CDCl_3$ solution.

Combining the cation-binding ability of ether subunits with the synthetic and conformational potential of amino acids has caused great interest in the synthesis of amino acids containing ether functionalities in the side chain and/or the molecular backbone. Examples of naturally occurring ether amino acids are neuraminic acid and muraminic acid.

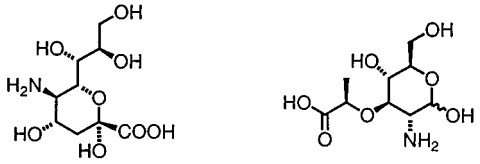

Figure 1. Naturally ocurring ether amino acids

Most contributions to the field of synthetic ether amino acids start from carbohydrates. Sugar amino acids were developed by Kessler et al.[1] (**1**, **2**), Lansbury et al.[2] (**3**), as well as by Dondoni et al.[3] (**4**). Wessel et al.[4a] and Ichikawa et al.[4b] have reported the synthesis of saccharide−peptide hybrids based on sugar amino acids. Sugar-derived THF amino acids of type **5**[1] have been synthesized by several groups.[5] THF peptides made out of **5** show remarkable secondary structures.[6]

Our approach to THF amino acids such as **6** and **7** chooses naturally occurring α-amino acids as a chiral pool source.[7] *N*-Tosylalanine chloride **8** was allowed to react with butenylmagnesium bromide to yield the ketone **9** in 64% yield.[8] Conversion of the Grignard reagent to an organocopper species prior to the reaction with the acid chloride improved the yield to 94%. The acid chloride was found to be a superior starting material than the lithium salt of *N*-tosylalanine, which gave yields in the 40% range only. L-Selectride reduction of **9** (Cram stereoselectivity 85:15) and separation of the major epimer by crystallisation lead to the desired alcohol **10** in 83% yield.[8] After epoxidation of the terminal double bond in **10**, followed by an intramolecular 5-*exo* opening of the resulting epoxy-func-

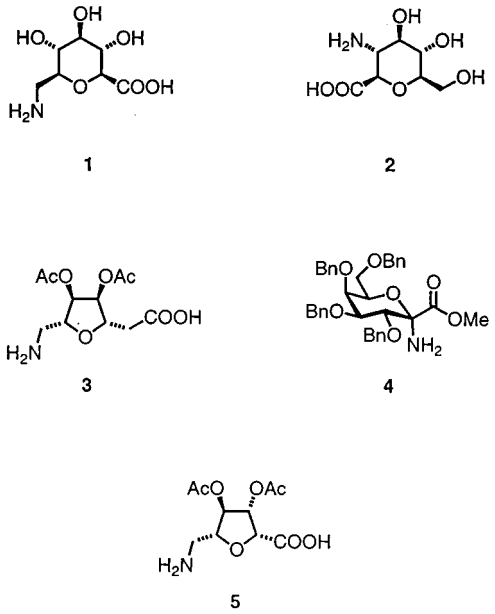

Figure 2. Sugar-derived synthetic THP and THF amino acids

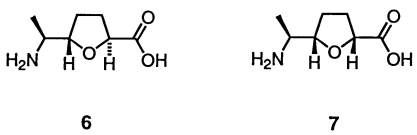

Figure 3. *trans*- and *cis*-THF amino acids **6** and **7**

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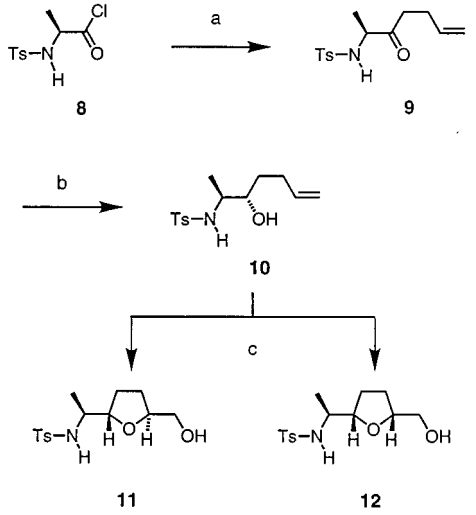
tion the *trans*-THF alcohol **11** and the *cis*-THF alcohol **12** could be obtained in 38% and 42% yield, respectively.

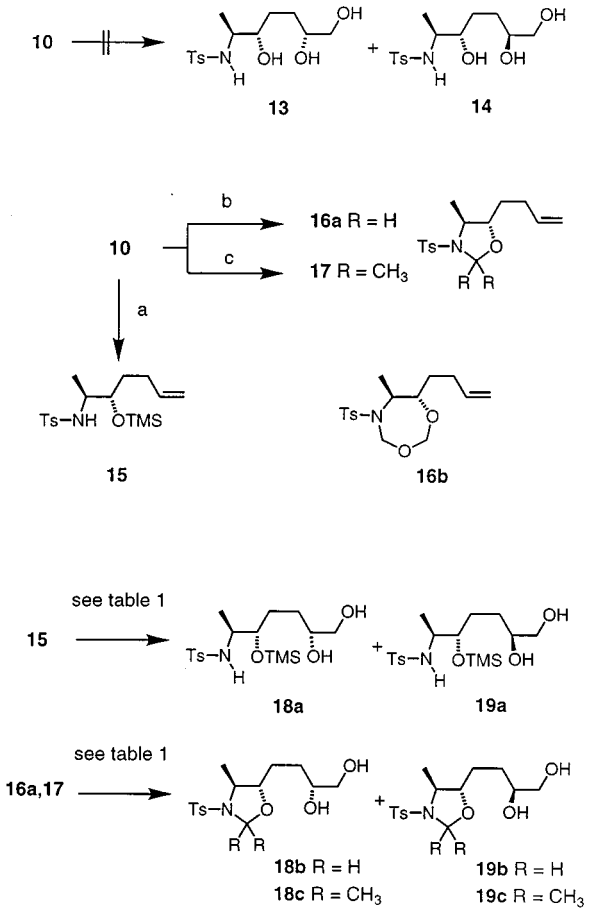


Scheme 1. Synthesis of *N*-Ts THF alcohols **11** and **12**: (a) $H_2C = CHCH_2CH_2MgBr$, Et_2O, −78°C to room temp., 12 h, 64% or CuCN · 2 LiCl, $H_2C{=}CHCH_2CH_2MgBr$, THF, −70°C 1 h, to 0°C, 5 min, 94% (b) L-selectride, THF, −100 to −60°C, 3 h, 83%. (c) i: MCPBA, CH_2Cl_2, room temp., 12 h; ii: *p*-TsOH, CH_2Cl_2, room temp., 3 h; 38% **11**, 40% **12**; L-selectride = lithium tri-*sec*-butylborohydride, MCPBA = *meta*-chloroperbenzoic acid, *p*-TsOH = *para*-toluenesulfonic acid

Attempts to achieve a stereoselective epoxidation of **10** [$VO(acac)_2$/*t*BuOOH[9] or Jacobsen conditions[10]] failed, mainly due to problems of low conversion. Therefore, Sharpless asymmetric dihydroxylation was examined as a stereoselective entry into the *cis* or *trans* series (Scheme 2). The sulfonamide alcohol **10** gave no turnover under standard AD conditions.[11] While the sulfonamide NH and the hydroxyl group may act as a concurrent coordination site for the catalyst, we decided to block these positions. According to this idea, the TMS ether **15** and the two oxazolidines **16a** and **17** were prepared. During the formation of **16a** the seven-membered ring compound **16b** was formed as a side product.

The results of the asymmetric dihydroxylations of the substrates **15**, **16a**, and **17** are summarized in Table 1. The TMS ether **15** showed a clear case of double stereodifferentiation: the AD-mix α gave a 42:58 ratio (mismatched case) of the diols **18a** and **19a** while the AD-mix β produced a 85:15 ratio (matched case). Almost no double stereodifferentiation was observed during the asymmetric dihydroxylations of compounds **16a** and **17**. The corresponding diols **18** and **19** were obtained in good yields and selectivities in the range between 2:1 and 4:1.

The mixture of the diols **18** and **19** was transformed into the corresponding epoxides by reaction with NaH/tosylimidazole (Scheme 3).[12] Treatment of the epoxides with acid resulted in the cleavage of the silyl ether in **15** and of the oxazolidines in **16a** and **17** followed by intramolecular epoxide opening and formation of the THF alcohols **11** and **12**. Both epimers **11** and **12** were separated by column chromatography. In the case of the formaldehyde-derived oxazolidines **18b/19b** the *cis* isomer provided the bicyclic compound **20**. The structural assignment of **20** was achieved by X-ray crystal-structural analysis.



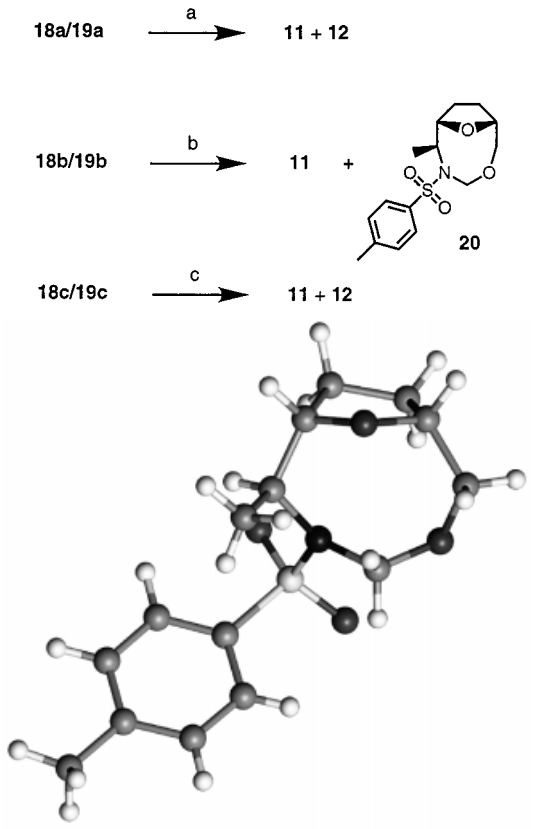
Scheme 2. Preparation of the alkenes **15**, **16a**, and **17** and asymmetric dihydroxylation into the diols **18** and **19**: (a) TMSCl, Et_3N, CH_2Cl_2, 94%; (b) paraformaldehyde, CSA, toluene, Dean−Stark trap, 65% **16a** and 32% **16b**; treatment of **16b** with CSA in CH_2Cl_2 afforded **16a** in 98% yield; (c) 2,2-dimethoxypropane, CSA, room temp., 2 h, 92%; CSA = camphersulfonic acid

Table 1. Asymmetric dihydroxylations of alkenes **15**, **16a**, and **17**

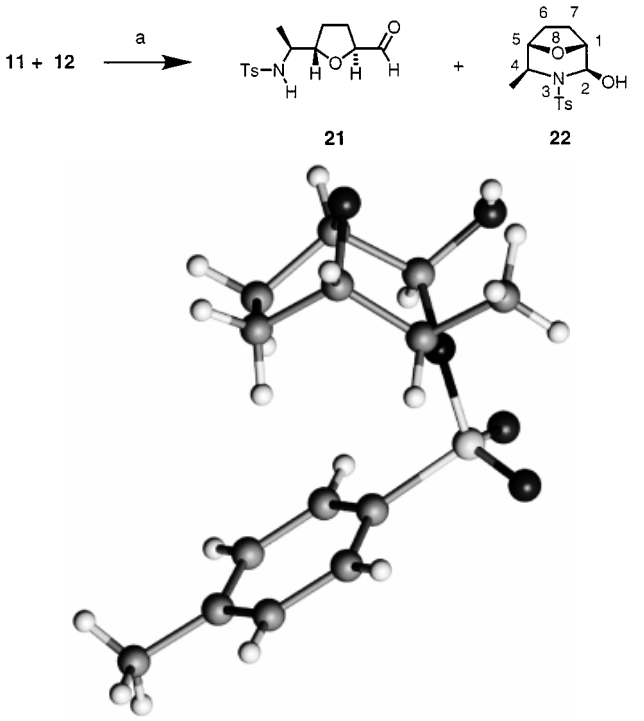
	AD-mix	Yield (%)	**18/19**
15	α	88	42:58
15	β	94	85:15
16a	α	88	73:27
16a	β	94	37:63
17	α	97	80:20
17	β	90	22:78

The oxidation of the *N*-tosyl-protected THF alcohols **11** and **12** into the corresponding aldehydes was examined next (Scheme 4). While the *trans*-alcohol **11** could be cleanly oxidized into the *trans*-aldehyde **21** using Dess−Martin conditions,[13] the *cis*-alcohol **12** was transformed via the corresponding aldehyde into the hemiaminal **22** as a single diastereomer. The structural assignment of **22** was possible by X-ray crystal-structural analysis.

The hemiaminal formation of the *N*-tosyl-protected compound in the *cis* series can be explained by the relative



Scheme 3. Conversion of the diols **18** and **19** into the THF alcohols **11** and **12**: (a) i: NaH, tosylimidazole, THF; ii: 1 equiv. CSA, CH_2Cl_2, room temp., 2 h; (b) i: NaH, tosylimidazole, THF; ii: epoxide purification by column chromatography; iii: 0.1 equiv. CSA, CH_2Cl_2, room temp., 12 h; (c) i: NaH, tosylimidazole, THF; ii: $HOAc/H_2O$ 4:1, 40°C, 30 min; CSA = camphersulfonic acid

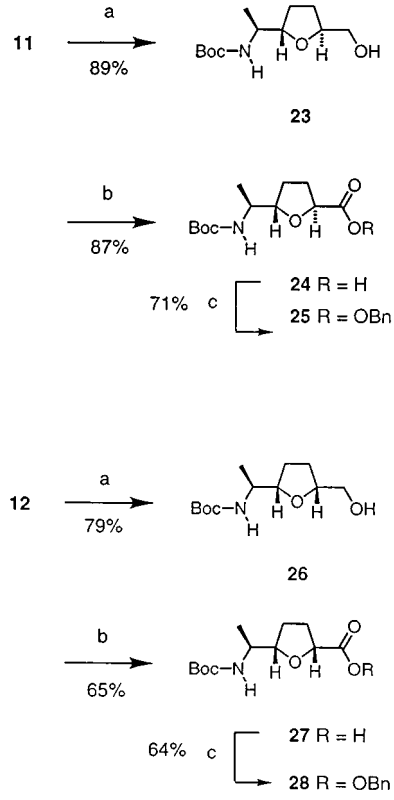


Scheme 4. Oxidation of a 1:1 mixture of the THF alcohols **11** and **12**: (a) Dess–Martin oxidation, 40% **21** and 40% **22**; Swern oxidation, 31% **21** and 66% **22**; X-ray structure of **22**

acidic NH of the sulfonamide. Therefore, a change of the *N*-protective group to *tert*-Butoxycarbonyl (Boc) with a less acidic NH was undertaken (Scheme 5). The deprotection of the *N*-tosyl group of **11** and **12** could be achieved with Na in liq. NH_3. The resulting amino-THF alcohols were Boc-protected to give the *trans*-*N*-Boc-THF alcohol **23** and the the *cis*-*N*-Boc-THF alcohol **26**, respectively. Oxidation of the alcohols **23** and **26** by a two-step procedure (Swern oxidation followed by $NaClO_2$ oxidation) yielded the *N*-Boc-protected THF amino acids **24** and **27**. Figure 4 shows the results of X-ray crystal structural analyses of compounds **24** and **27**. The corresponding benzyl esters **25** and **28**, which are useful building blocks for THF peptide synthesis in solution, were prepared by reaction of the carboxylic acids with benzyl bromide.

N-Fmoc-protected amino acids are standard building blocks for solid-phase peptide synthesis. For this reason, the *N*-Fmoc protected THF amino acids **30** (*trans*) and **32** (*cis*) were prepared by analogy to the *N*-Boc series (Scheme 6).

Inspection of molecular models indicated that the *cis*-THF amino acid **7** could function as a β-turn inducer in peptides. Turns are defined as sites in a peptide structure where the peptidic chain reverses its overall direction.[14] Following Venkatachalam,[15] β-turns are classified into dif-



Scheme 5. Conversion of the THF alcohols **11** and **12** into the Boc-protected THF amino acid derivatives: (a) i: Na, NH_3, −40°C, 10 min; ii: Boc_2O, NaOH, MeOH; (b) i: dimethyl sulfoxide, oxalyl chloride, Et_3N; ii: $NaClO_2$, NaH_2PO_4, *t*BuOH; (c) BnBr, Et_3N, acetone; Boc = *tert*-butoxycarbonyl

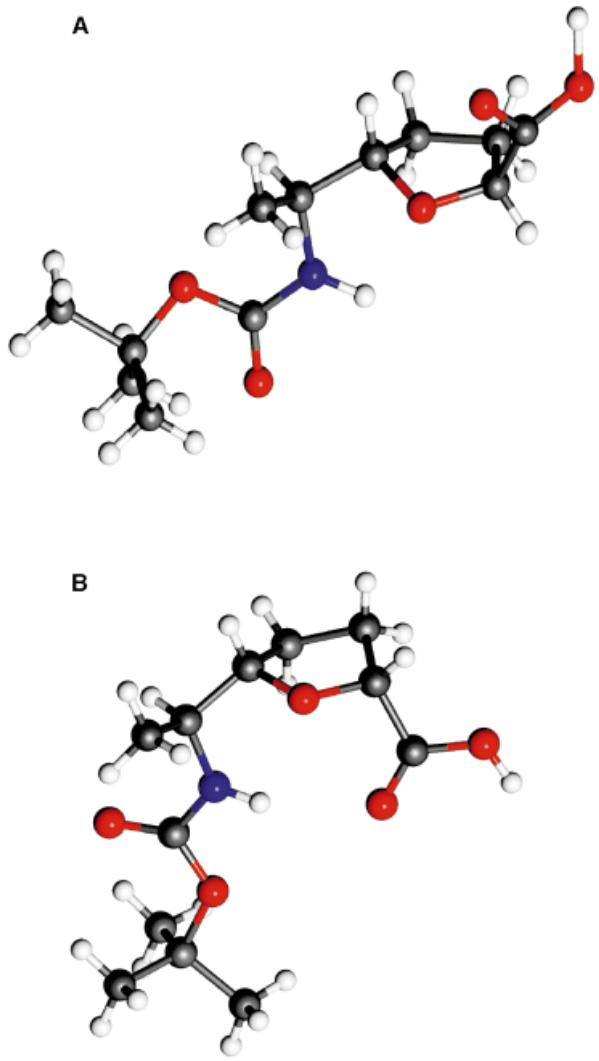
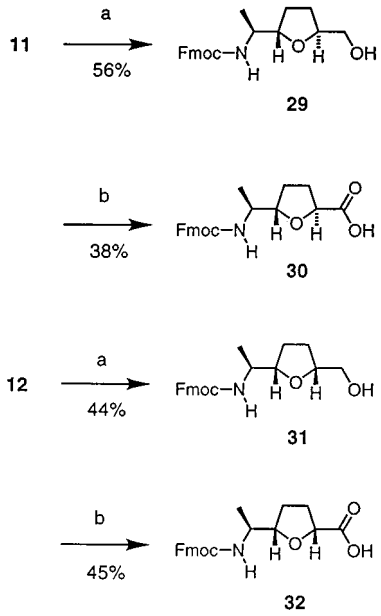
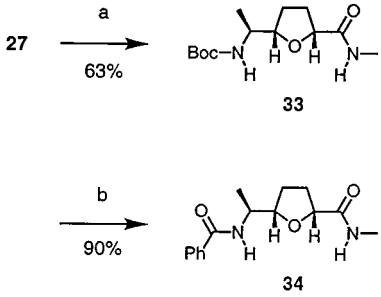


Figure 4. A: solid-state conformation of the *trans*-THF amino acid derivative **24** obtained by X-ray crystal-structural analysis; B: solid-state conformation of the *cis*-THF amino acid derivative **27** obtained by X-ray crystal-structural analysis



Scheme 6. Conversion of the THF alcohols **11** and **12** into the Fmoc-protected THF amino acid derivatives: (a) i: Na, NH_3, −40 °C, 10 min; ii: Fmoc-succinimide, $NaHCO_3$, $MeCN/H_2O$, 12 h room temp.; (b) i: dimethyl sulfoxide, oxalyl chloride, Et_3N; ii: $NaClO_2$, NaH_2PO_4, *t*BuOH;. Fmoc = 9-fluorenylmethoxycarbonyl



Scheme 7. Synthesis of the THF diamide **34**: (a) $MeNH_2 \cdot HCl$, EDC, HOBT, $EtNiPr_2$, THF, room temp., 18 h; (b) i: TFA, CH_2Cl_2, room temp., 4 h; ii: PhCOCl, $NaHCO_3$, THF/H_2O, room temp., 1 h; EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, HOBT = 1-hydroxy-1*H*-benzotriazole, TFA = trifluoroacetic acid

ferent conformational types depending on the torsion angle values for Φ_1, Ψ_1, Φ_2, and Ψ_2 (Figure 5a). According to Kabsch and Sander, the αC_i to αC_{i+3} distance must be shorter than 7 Å.[16] To explore the β-turn forming potential of **7** the dipeptide **34** was synthesized (Scheme 7).

An X-ray crystal-structural analysis of **34** was undertaken. The solid-state conformation of **34** showed indeed a β-turn type conformation with a 10-membered-ring hydrogen bond (Figure 5b). One highly ordered molecule of water was found in the solid state.

The solution structure of **34** was investigated by NMR studies. Interproton distances derived from quantified NOESY crosspeaks were used as input for MD Simulations. The calculations were done with "Insight Discover 97" (MSI, San Diego, CA) using the force field *cvff*. In $CDCl_3$ a preferred conformation was found that displayed the same 10-membered-ring hydrogen bond as in the solid state (Figure 5c). In contrast, the NOESY spectrum of a 2 mM [D_6]DMSO solution of **34** was consistent with a fast equilibrium of different conformers. In addition the temperature dependence of the NH shifts (−4.6 and −5.2 ppb/K respectively) revealed the absence of any intramolecular hydrogen bond in this solvent. Due to solubility reasons, no conformational studies could be accomplished in water. Further work, with elongated peptide chains containing polar amino acids should allow us to study the effect of THF amino acids on peptide secondary structures under physiological conditions.

In conclusion, a synthetic route towards enantiomerically pure *cis*- and *trans*-2,5-disubstituted THF amino acids has been elaborated. While the work presented here concentrates on L-alanine as the starting point, other THF amino acids with side chains other than methyl should be accessible along this route by using other α-amino acids as the chiral pool source. The THF amino acids are interesting candidates as peptidomimetics or for the assembly of artificial ion channels.

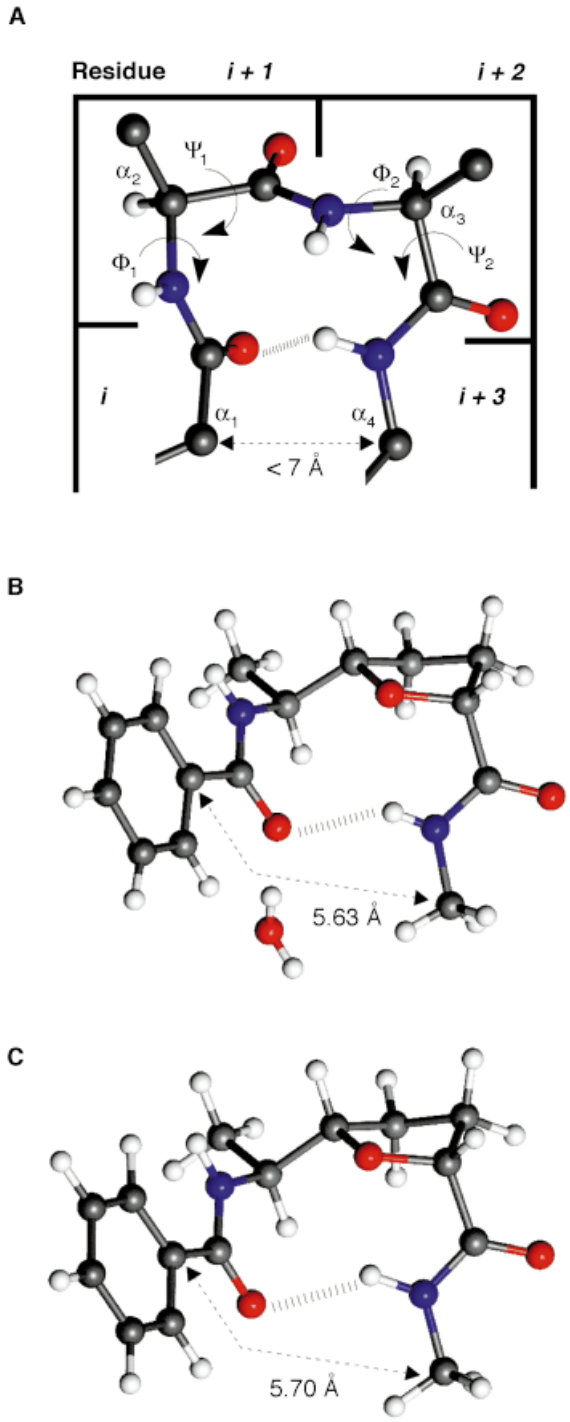


Figure 5. A: general β-turn structure; B: solid-state conformation of the *cis*-THF dipeptide **34** obtained by X-ray structural analysis; C: solution conformation ($CDCl_3$) of the *cis*-THF dipeptide **34** obtained by NMR studies and MD calculations

Experimental Section

General: All b.p.s and m.p.s are uncorrected values. − IR: Bruker IFS 88. − NMR: Bruker ARX-200, AC-300, DPX-300, AMX-500 and AMX-600. For ^1H NMR, $CDCl_3$ as solvent $\delta_H = 7.25$, [D_6]DMSO as solvent $\delta_H = 2.50$, [D_4]MeOH as solvent $\delta_H = 4.78$; for ^{13}C NMR, $CDCl_3$ as solvent $\delta_C = 77.0$, [D_6]DMSO as solvent $\delta_C = 39.5$, [D_4]MeOH as solvent $\delta_C = 49.0$. − Elemental analysis: CHN Rapid (Heraeus), CHNS-932 Analysator (Leco). − HRMS: Finnigan MAT 95. − All reactions were performed under an inert atmosphere of argon in oven- or flame-dried glassware. Dry solvents: THF, Et_2O, benzene, and toluene were distilled from sodium benzophenone. All commercially available reagents were used without purification unless otherwise noted. − All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck F-254 silica glass plates visualized with UV light and/or heat-gun treatment with 5% phosphomolybdic acid in ethanol or 1) 2% anisaldehyde in ethanol and 2) 20% H_2SO_4. − Column chromatography was performed with Merck silica gel 60 (70−200 mesh and 230−400 mesh). − PE: Light petroleum ether, b.p. 40−60°C. MTBE: *tert*-butyl methyl ether.

X-ray Structure Determination of 20, 22, 24, 27, and 34: Compounds **22** and **24** were measured on a four-circle diffractometer CAD4 (Enraf−Nonius, Delft), **27** was measured on a four-circle diffractometer STADI4 (Stoe, Darmstadt). The intensity data collection of **20** was performed on a IPDS one-circle diffractometer (Stoe, Darmstadt). The crystal-structure analyses were performed with the program packages SHELXS-86/SHELXL-93[17] and SHELXS-97.2/SHELXL-97.2;[18] for details see Table 2. Further crystallographic data, excluding structure-factor listings, have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-111903 (**20**), -103321 (**22**), -103320 (**24**), -111904 (**27**), and -103321 (**34**). Copies of the data can be obtained free of charge on application to CCCD, 12 Union Road, Cambridge CB21EZ, UK [Fax: (internat.) + 44-1223/336-033, E-mail: deposit@ccdc.cam.ac.uk].

(2*S*)-2-*N*-Tosylamino-6-hepten-3-one (9): Magnesium turnings (8.10 g, 333 mmol) were covered with Et_2O (30 mL). 2 mL of a solution of 4-bromo-1-butene (16.9 mL, 22.5 g, 167 mmol) in Et_2O (80 mL) was added. The reaction initiated exothermically after a short period of induction. The remainder of the bromide solution was added dropwise. The dropping funnel was rinsed with Et_2O (40 mL) and the reaction mixture was refluxed for 15 min. The cold Grignard solution was transferred via cannula into a 250 mL dropping funnel and added at −78°C within 75 min to a mechanically stirred solution of acid chloride **8** (20.8 g, 79.3 mmol) in Et_2O (800 mL). During the addition a yellowish solid precipitated. The reaction was allowed to warm to room temperature overnight and then quenched at 0°C by the addition of aqueous HCl (1 M, 200 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 300 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (2 × 200 mL) and with saturated NaCl solution (300 mL). After drying with $MgSO_4$ and removal of the solvent in vacuo, the crude product was purified by column chromatography (PE/MTBE 1:1, 600 g of silica) to yield 14.3 g of the ketone **9** (50.8 mmol, 64%) as colorless crystals. m.p. 94−98°C. − $R_f = 0.43$ (PE/MTBE 1:1). − $[\alpha]_D = +54.4$, $[\alpha]_{578} = +57.8$, $[\alpha]_{546} = +68.2$, $[\alpha]_{436} = +142.9$, $[\alpha]_{365} = +288.2$ ($c = 1.03$, $CHCl_3$, $T = 20$°C). − IR (KBr): $\tilde{\nu} = 3262$ cm^{-1} s (NH), 2979/2937/2920 m (CH), 1715 s (C=O), 1426 m, 1404 m, 1339 s, 1168 s, 1092 m, 995 w, 963 w, 908 w, 618 m, 594 m, 561 m, 548 m. − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (d, $J = 7.2$ Hz, 3 H, 1-H_3), 1.95−2.58 (m, 4 H, 4-H_2 and 5-H_2), 2.34 (s, 3 H, TsCH_3), 3.84 (q, $J = 7.2$ Hz, 1 H, 2-H), 4.78−4.89 (m, 2 H, 7-H_2), 5.47−5.67 (m, 2 H, N−H and 6-H), 7.21 (d, $J = 8.2$ Hz, 2 H, Ts), 7.64 (d, $J = 8.2$ Hz, 2 H, Ts). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.9 (C-1), 21.5 (TsCH_3), 27.2 (C-5), 38.0 (C-4), 57.1 (C-2), 115.6 (C-7), 136.1 (C-6), 127.1, 129.7, 136.8 and 143.6 (Ts), 207.2 (C=O). − $C_{14}H_{19}NO_3S$ (281.37): calcd. C 59.76, H 6.81, N 4.98; found C 59.46, H 7.02, N 4.91.

Preparation of Ketone 9 by Cuprate Addition: LiCl (13.9 g, 328 mmol) and CuCN (14.5 g, 162 mmol) were dried in vacuo at

Table 2. Crystal data for compounds **20**, **22**, **24**, **27**, and **34**

	20	**22**	**24**	**27**	**34**
Empiric formula	$C_{15}H_{21}NO_4S$	$C_{14}H_{19}NO_4S$	$C_{12}H_{21}NO_5$	$C_{12}H_{21}NO_5$	$C_{15}H_{22}N_2O_4$
Molecular mass	311.39	297.36	259.30	259.30	294.35
ρ [gcm^{-3}]	1.366	1.393	1.190	1.149	1.252
Z	4	4	2	2	4
Temperature [K]	1702)	193(2)	293(2)	298(2)	120(2)
Crystal system	rhombic (222)	rhombic (222)	monoclinic (2)	monoclinic (2)	rhombic (222)
Space group	$P2_12_12_1$ (no. 19)	$P2_12_12_1$ (no. 19)	$P2_1$ (no. 4)	$P2_1$ (no. 4)	$P2_12_12_1$ (no. 19)
Radiation [pm]	Mo-K_α (71.069)	Cu-K_α (154.178)	Cu-K_α (154.178)	Mo-K_α (71.069)	Mo-K_α (71.069)
Monochrom.	planar graph.	planar graph.	planar graph.	planar graph.	planar graph.
Crystal size [mm]	0.85×0.39×0.39	0.70×0.50×0.40	0.35×0.20×0.20	1.60×0.83×0.08	0.42×0.30×0.19
a [pm] =	807.99(13)	845.5(1)	762.3(1)	862.69(7)	935.3(1)
b [pm] =	1296.90(15)	1165.6(1)	991.3(1)	925.1(2)	1050.0(1)
c [pm] =	1445.10(18)	1438.3(1)	962.4(1)	978.9(1)	1590.0(2)
α [°] =					
β [°] =		95.90(1)	106.459(8)		
γ [°] =					
F_{000}	664			280	632
Volume [10^6 pm^3]	1514.3(4)				
Scan range [°]	2.82 < Θ < 27.35	2.00 < Θ < 32.50	2.00 < Θ < 30	2.17 < Θ < 27.46	2.53 < Θ < 28.06
Type	ω-scan	ω.2Θ-scan	ω.2Θ-scan	ω.2Θ-scan	Θ-scan
	h: −10/10,	*h*: −9/9,	*h*: −8/10,	*h*: −11/11,	*h*: −12/12,
	k: 0/16,	*k*: −13/13,	*k*: −11/0,	*k*: 0/12,	*k*: 0/13,
	l: 0/18	*l*: −16/16	*l*: −10/0	*l*: −12/12	*l*: 0/20
Data; restraints; parameters	3352; 0; 275	2331; 0; 191	1143; 0; 174	3672; 1; 212	3460; 0
Absorption correction		Θ-scans		empirical	
Atom form factors	*International Tables for Crystallography*, vol. C, **1995** (Tables 4.2.6.8 and 6.1.1.4), Kluwer Academic Press, Dordrecht, Boston, London				
Refinement	*Full-matrix least squares based on* F^2				
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0330	*R*1 = 0.0538	*R*1 = 0.0492	*R*1 = 0.0382	*R*1 = 0.0303
Final *R* indices (all data)	*wR*2 = 0.0838	*wR*2 = 0.1588	*wR*2 = 0.1324	*wR*2 = 0.1107	*wR*2 = 0.0772
GoF	1.015	1.133	1.092	1.051	1.044
Flack parameter	−0.02(6) ≈ 0			−2.2(15) ≈ 0	0.8(7)
Difference electron density (min/max) [10^{-6} pm^{-3}]	−0.241/0.157 e	−0.341/0.202 e	−0.235/0.202 e	−0.127/0.122 e	−0.133/0.176 e

250°C for 5 h, cooled down and flushed with argon. Magnesium turnings (5.0 g, 200 mmol) were covered with THF (50 mL). Some drops of $C_2H_4Br_2$ and after it 4-bromo-1-butene (10.0 mL, 13.3 g, 99 mmol) in THF (100 mL) were added dropwise keeping the reaction solution gently boiling. After completed addition, the mixture was refluxed for 1 h. The previously dried LiCl and CuCN were covered with THF (200 mL) and the Grignard solution was added at −40°C via cannula. The color of the pale-green salt suspension turned chocolate brown. Acid chloride **8** (12.3 g, 44.3 mmol) in THF (150 mL) was added dropwise at −70°C. After stirring for 1 h, the cooling bath was replaced by an ice bath and the reaction was allowed to warm to 0°C within 5 min and then quenched with saturated NH_4Cl solution (250 mL). Water was added to redissolve the white precipitate and stirring was continued for 30 min at 0°C. The layers were separated and the aqueous layer was extracted with MTBE (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. Recrystallisation (MTBE) afforded 11.7 g (41.5 mmol, 94%) of ketone **9**.

(2*S*,3*S*)-2-*N*-Tosylamino-6-hepten-3-ol (10): The ketone **9** (6.175 g, 21.96 mmol) was dissolved in THF (100 mL) and cooled to −100°C. A 1 M solution of L-selectride in THF (44.0 mL, 44.0 mmol) was precooled to −78°C and added dropwise within 30 min to the reaction mixture. The reaction mixture was warmed to −60°C over 3 h and quenched with 200 mL of dropwise added AcOH/H_2O 1:1. After stirring for 3 h at room temperature, the solvents were removed in vacuo. Remaining water and acid was removed azeotropically with toluene (2 × 100 mL). The crude product was dissolved in saturated $NaHCO_3$ (100 mL) and $CHCl_3$/*i*PrOH (4:1, 100 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$/*i*PrOH (4:1, 3 × 100 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were removed in vacuo. The nonpolar impurities were removed by filtration over 200 g of silica (PE/MTBE 1:1 to PE/MTBE 1:2). The minor epimer was removed by recrystallisation from 30 mL of PE/MTBE (1:2). Thus, 5.15 g (18.2 mmol, 83%) of the alcohol **10** was obtained as colorless crystals. m.p. 68°C. − R_f = 0.11 (PE/Et_2O, 1:1). − $[\alpha]_D$ = −13.0, $[\alpha]_{578}$ = −13.3, $[\alpha]_{546}$ = −15.4, $[\alpha]_{436}$ = −28.1, $[\alpha]_{365}$ = −46.0 (*c* = 1.00, $CHCl_3$, *T* = 20°C). − IR (KBr): $\tilde{\nu}$ = 3499 cm^{-1} s (OH), 3287 m (NH), 2974/2943 m (CH), 1450 w, 1332 m, 1319 m, 1162 s, 1146 s, 1090 s, 815 m, 678 s, 555 s. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.7 Hz, 3 H, 1-H_3), 1.41−1.48 (m, 2 H, 4-H_2), 1.93−2.18 (m, 2 H, 5-H_2), 2.32 (d, *J* = 5.1 Hz, 1 H, OH), 2.37 (s, 3 H, $TsCH_3$), 3.14−3.28 (m, 1 H, 2-H), 3.34−3.41 (m, 1 H, 3-H), 4.87−4.98 (m, 2 H, 7-H_2), 5.08 (d, *J* = 8.5 Hz, 1 H, NH), 5.63−5.74 (m, 1 H, 6-H), 7.24 (d, *J* = 8.1 Hz, 2 H, Ts), 7.72 (d, *J* = 8.3 Hz, 2 H, Ts). −^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (C-1), 21.5 ($TsCH_3$), 29.8 (C-5), 32.8 (C-4), 53.7 (C-2), 74.1 (C-3), 115.1 (C-7), 138.1 (C-6), 127.0, 129.7 and 143.4 (Ts). − $C_{14}H_{21}NO_3S$ (283.39): calcd. C 59.34, H 7.47, N 4.94; found C 59.22, H 7.35, N 4.84.

(2*S*,5*S*,1′*S*)-5-Hydroxymethyl-2-[1′-(*N*-tosylamino)ethyl]-tetrahydrofuran (11) and (2*S*,5*R*,1′*S*)-5-Hydroxymethyl-2-[1′-(*N*-tosylamino)ethyl]tetrahydrofuran (12): *m*-CPBA (60%, 13.9 g, 48.3 mmol) was dissolved in CH_2Cl_2 (300 mL). The organic layer of this mixture was added to a solution of the alcohol **10** (6.80 g, 24.2 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at room temperature. It was washed successively with

saturated Na_2SO_3 solution (300 mL), saturated $NaHCO_3$ solution (300 mL), saturated NaCl solution (300 mL) and dried with $MgSO_4$. The solution was concentrated to 150 mL, *para*-toluenesulfonic acid (207 mg, 1.2 mmol) was added, and the solution was stirred for 3 h at room temperature. It was washed with saturated $NaHCO_3$ solution (150 mL) and with saturated NaCl solution (150 mL). The aqueous layers were extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated in vacuo. The crude product was filtered over 500 g of silica gel (MTBE). Column chromatography (MTBE/DCM, 4:1, 500 g of silica) afforded 2.78 g (9.3 mmol, 38%) of the *trans*-alcohol **11** and 2.87 g (9.6 mmol, 40%) of the *cis*-alcohol **12** as colorless solids. − ***trans*-THF Alcohol 11:** m.p. 85−89°C (MTBE). − R_f = 0.27 (MTBE/CH_2Cl_2 4:1). − $[\alpha]_D$ = +6.0, $[\alpha]_{578}$ = +6.3, $[\alpha]_{546}$ = +6.7, $[\alpha]_{436}$ = +6.2 (*c* = 0.91, $CHCl_3$, *T* = 20°C). − IR (KBr): $\tilde{\nu}$ = 3506 and 3109 cm^{-1} (NH and OH), 2977/2912/2875 m (CH), 1493 m, 1468 m, 1441 w, 1318 m, 1146 s, 1090 s, 1052 s, 949 s, 815 m, 665 m, 546 s. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.7 Hz, 3 H, 2′-H_3), 1.56−1.98 (m, 4 H, 3-H_2 and 4-H_2), 2.30 (br. s, 1 H, OH), 2.41 (s, 3 H, $TsCH_3$), 3.23 (dp, *J* = 4.3 and 7.0 Hz, 1 H, 1′-H), 3.42 (dd, *J* = 6.2 and 11.3 Hz, 1 H, C*H*HOH), 3.56 (dd, *J* = 3.5 and 11.6 Hz, 1 H, CH*H*OH), 3.80 (ddd, *J* = 4.4, 6.0 and 7.8 Hz, 1 H, 2-H), 3.94 (ddt, *J* = 3.2, 8.0 and 6.1 Hz, 1 H, 5-H), 4.80 (d, *J* = 7.3 Hz, 1 H, N−H), 7.29 (d, *J* = 8.1 Hz, 2 H, Ts), 7.73−7.76 (m, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): 18.9 (C-2′), 21.5 ($TsCH_3$), 27.4 and 28.7 (C-4 and C-3), 52.7 (C-1′), 64.8 (*C*H_2OH), 80.1 (C-5), 81.9 (C-2), 127.1, 129.6, 138.1 and 143.2 (Ts). − $C_{14}H_{21}NO_4S$ (289.39): calcd. C 56.17, H 7.07, N 4.68; found C 56.15, H 6.84, N 4.65. − ***cis*-THF Alcohol 12:** m.p. 95−96°C (MTBE). − R_f = 0.35 (MTBE/CH_2Cl_2, 4:1). − $[\alpha]_D$ = +2.8, $[\alpha]_{278}$ = +3.2, $[\alpha]_{546}$ = +3.5, $[\alpha]_{436}$ = +4.4, $[\alpha]_{365}$ = +5.1 (*c* = 0.99, $CHCl_3$, *T* = 19°C). − IR (KBr): $\tilde{\nu}$ = 3494 cm^{-1} s, 3361 br. s and 3181 br. m (NH and OH), 2975/2955/2941/2905/2878 m (CH), 1596 m, 1494 w, 1474 s, 1456 s, 1404 m, 1380 m, 1367 m, 1328 s, 1209 m, 1188 m, 1159 s, 1148 s, 1111 s, 1087 s, 1053 s, 1040 s, 1018 m, 995 m, 980 m, 955 s, 887 m, 867 m, 822 s, 708 m, 666 s, 550 s, 474 m, 459 m. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.7 Hz, 3 H, 2′-H_3), 1.64−1.91 (m, 4 H, 3-H_2 and 4-H_2), 2.20 (br. s, 1 H, O−H), 2.41 (s, 3 H, $TsCH_3$), 3.19−3.36 (m, 1 H, 1′-H), 3.47 (dd, *J* = 4.9 and 11.6 Hz, 1 H, C*H*HOH), 3.70 (dd, *J* = 2.9 and 11.6 Hz, 1 H, CH*H*OH), 3.79 (dt, *J* = 4.0 and 6.7 Hz, 1 H, 2-H), 3.89−4.09 (m, 1 H, 5-H), 5.43 (d, *J* = 7.5 Hz, 1 H, N−H), 7.28 (d, *J* = 8.2 Hz, 2 H, Ts), 7.76 (d, *J* = 8.3 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (C-2′), 21.4 ($TsCH_3$), 26.8 and 28.5 (C-3 and C-4), 53.2 (C-1′), 64.7 (*C*H_2OH), 79.9 (C-5), 82.3 (C-2), 127.0, 129.5, 138.4 and 143.1 (Ts). − $C_{14}H_{21}NO_4S$ (289.39): calcd. C 56.17, H 7.07, N 4.68; found C 55.95, H 7.06, N 4.49.

(2*S*,3*S*)-2-*N*-Tosylamino-3-trimethylsilyloxy-6-heptene (15): To a solution of alcohol **10** (1.00 g, 3.53 mmol) in CH_2Cl_2 (25 mL) were added at 0°C TMSCl (0.9 mL, 7.57 mmol) and NEt_3 (2.0 mL, 14.1 mmol). Stirring was continued for 15 min. (0°C to room temperature). Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL), the combined organic layers were washed with saturated NaCl solution (20 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (cyclohexane/MTBE 4:1, 50 g of silica) afforded 1.19 g of the TMS ether **15** (3.36 mmol, 94%) as a colorless oil, R_f = 0.38 (cyclohexane/MTBE, 4:1). − $[\alpha]_D$ = +0.6, $[\alpha]_{578}$ = +0.7, $[\alpha]_{546}$ = +1.0, $[\alpha]_{436}$ = +2.5, $[\alpha]_{365}$ = +5.2 (*c* = 0.97, $CHCl_3$, *T* = 27°C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 9 H, TMS-H_3), 0.99 (d, *J* = 6.4 Hz, 3 H, 1-H_3), 1.25−1.45 (m, 2 H, 4-H_2), 1.93−2.18 (m, 2 H, 5-H_2), 2.39 (s, 3 H, $TsCH_3$), 3.29 (ddq, *J* = 8.7, 1.9 and 6.6 Hz, 1 H, 2-H), 3.44 (dt, *J* = 6.6 and 1.9 Hz, 1 H, 3-H), 4.65 (d, *J* = 8.7 Hz, 1 H, N−H), 4.81−4.92 (m, 2 H, 7-H_2), 5.60 (ddt, *J* = 18.1, 9.1 and 6.6 Hz, 1 H, 6-H), 7.26 (d, *J* = 8.7 Hz, 2 H, Ts), 7.73 (d, *J* = 8.3 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.4 (TMS), 19.2 (C-1), 21.5 ($TsCH_3$), 29.7 (C-5), 32.8 (C-4), 51.8 (C-2), 74.8 (C-3), 114.7 (C-7), 127.0, 129.6 (Ts), 138.0 and 138.6 (Ts and C-6), 143.3 (Ts). − $C_{17}H_{29}NO_3SiS$ (355.57): calcd.C 57.43, H 8.22, N 3.94, S 9.02; found C 57.34, H 8.22, N 3.81, S 9.03.

(4*S*,5*S*)-5-(3′-Butenyl)-4-methyl-*N*-tosyl-1,3-oxazolidine (16a) and (6*S*,7*S*)-7-(3′-Butenyl)-6-methyl-*N*-tosyl-1,3,5-dioxazolepine (16b): Alcohol **10** (14.1 g, 49.8 mmol), paraformaldehyde (4.49 g, 149.5 mmol) and camphorsulfonic acid (580 mg, 2.49 mmol) in toluene (300 mL) were heated on a Dean−Stark trap for 1 h. The reaction mixture was washed with saturated $NaHCO_3$ solution (100 mL) and saturated NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (PE/MTBE 3:1, 150 g of silica) yielded 4.41 g of the acetal **16a** and 10.4 g of 1:1 mixture of the acetals **16a** and **16b**. The latter fraction was dissolved in CH_2Cl_2 (100 mL), camphorsulfonic acid (cat.) was added and the reaction mixture was stirred overnight. The solution was washed with saturated $NaHCO_3$ solution (50 mL) and with saturated NaCl solution (50 mL) and dried with Na_2SO_4. Column chromatography (PE/MTBE, 3:1, 250 g of silica) afforded additional 9.71 g of five-membered acetal **16a** and 0.27 g (0.83 mmol, 2%) of seven-membered acetal **16b** as a colourless oil. Overall yield: 14.20 g of **16a** (47.8 mmol, 96%), colorless oil, R_f = 0.30 (PE/MTBE, 3:1). − $[\alpha]_D$ = +110.2, $[\alpha]_{578}$ = +115.1, $[\alpha]_{546}$ = +132.1, $[\alpha]_{436}$ = +237.6, $[\alpha]_{365}$ = +406.6 (*c* = 0.94, $CHCl_3$, *T* = 27°C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02−1.20 (m, 1 H), 1.20−1.45 (m, 1 H) and 1.75−2.02 (m, 2 H, 1′-H_2, 2′-H_2), 1.30 (d, *J* = 7.0 Hz, 3 H, 4-CH_3), 2.39 (s, 3 H, $TsCH_3$), 3.16 (p, *J* = 7.1 Hz, 1 H, 4-H), 3.42 (dt, *J* = 4.5 and 8.4 Hz, 1 H, 5-H), 4.60 (d, *J* = 7.6 Hz, 1 H, 2-H), 4.82−4.98 (m, 2 H, 4′-H_2), 5.13 (d, *J* = 7.7 Hz, 1 H, 2-H), 5.62 (ddt, *J* = 7.3, 10.3 and 18.0 Hz, 1 H, 3′-H), 7.29 (d, *J* = 9.3 Hz, 2 H, Ts), 7.70 (d, *J* = 9.2 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (4-CH_3), 21.4 ($TsCH_3$), 29.5 (C-2′), 31.1 (C-1′), 59.1 (C-4), 79.1 (C-5), 85.0 (C-2), 115.0 (C-4′), 127.8 and 129.6 (Ts), 134.4 (C-3′), 137.2 and 143.9 (Ts). − $C_{15}H_{21}NO_3S$ (295.40): calcd. C 60.99, H 7.17, N 4.74, S 10.85; found C 60.99, H 6.94, N 4.88, S 10.85.

(6*S*,7*S*)-7-(3′-Butenyl)-6-methyl-*N*-tosyl-1,3,5-dioxazolepine (16b): R_f = 0.18 (PE/MTBE, 3:1). − $[\alpha]_D$ = +113.8, $[\alpha]_{578}$ = +118.2, $[\alpha]_{546}$ = +134.9, $[\alpha]_{436}$ = +235.7, $[\alpha]_{365}$ = +387.4 (*c* = 1.18, $CHCl_3$, *T* = 27°C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.5 Hz, 3 H, 6-CH_3), 1.09−1.45 (m, 2 H, 1′-H_2), 1.85−2.23 (m, 2 H, 2′-H_2), 2.40 (s, 3 H, $TsCH_3$), 3.25 (dt, *J* = 2.2 and 9.3 Hz, 1 H, 7-H), 3.60 (dq, *J* = 7.2 and 10.3 Hz, 1 H, 6-H), 4.36 (d, *J* = 7.1 Hz, 1 H, 2-H), 4.52 (d, *J* = 12.9 Hz, 1 H, 4-H), 4.85−5.01 (m, 3 H, 2-H, 4′-H_2), 5.56−5.77 (m, 1 H, 3′-H), 5.64 (d, *J* = 12.9 Hz, 4-H), 7.25 (d, *J* = 8.1 Hz, 2 H, Ts), 7.82 (d, *J* = 8.3 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (6-CH_3), 21.5 ($TsCH_3$), 29.6 (C-2′), 32.7 (C-1′), 57.9 (C-6), 74.3 (C-7), 86.2 (C-4), 97.8 (C-2), 115.4 (C-4′), 128.2 and 129.1 (Ts), 136.9 (C-3′), 137.5 and 143.4 (Ts). − $C_{16}H_{23}NO_4S$ (325.42): calcd. C 59.05, H 7.12, N 4.30, S 9.85; found C 59.11, H 7.34, N 4.18, S 9.87.

(4*S*,5*S*)-5-(3′-Butenyl)-2,2,4-trimethyl-*N*-tosyl-1,3-oxazolidine (17): Alcohol **10** (6.00 g, 21.2 mmol), 2,2-dimethoxypropane (26 mL, 212 mmol), and camphorsulfonic acid (49 mg, 0.22 mmol) were stirred at room temperature for 2 h and subsequently warmed in vacuo (40°C, 337 mbar) to remove MeOH. The reaction mixture was washed with saturated $NaHCO_3$ solution (25 mL) and satu-

rated NaCl solution (25 mL). The combined aqueous layers were extracted with MTBE (25 mL). The combined organic layers were dried with Na_2SO_4. The solvent and residual DMP were removed in vacuo. Column chromatography (PE/Et_2O 10:1, then PE/MTBE 1:2) afforded 287 mg of the starting material (1.01 mmol, 5%) and 6.29 g of **17** (19.5 mmol, 92%) as a colorless solid, m.p. 62°C. − R_f = 0.26 (PE/MTBE, 10:1). − $[\alpha]_D$ = −32.4, $[\alpha]_{578}$ = −34.0, $[\alpha]_{546}$ = −38.3, $[\alpha]_{436}$ = −63.9, $[\alpha]_{365}$ = −97.2 (c = 1.05, $CHCl_3$, T = 27°C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, J = 6.8 Hz, 3 H, 4-CH_3), 1.58 (s, 3 H, 2-CH_3) and 1.62 (s, 3 H, 2-CH_3), 1.39−1.62 (m, 2 H, 1′-H_2), 1.85−2.29 (m, 2 H, 2′-H_2), 2.44 (s, 3 H, $TsCH_3$), 3.22 (p, J = 7.0 Hz, 1 H, 4-H), 3.72 (ddd, J = 5.0, 7.5 and 8.5 Hz, 1 H, 5-H), 4.89−5.09 (m, 2 H, 4′-H_2), 5.77 (ddt, J = 18.6, 11.4 and 7.3 Hz, 1 H, 3′-H), 7.28 (2d, J = 9.5 and 10.3 Hz, 2 H, Ts), 7.74 (d, J = 9.2 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0 (4-CH_3), 21.4 ($TsCH_3$), 26.8 (C-2′), 29.7 and 29.8 (2-CH_3), 32.0 (C-1′), 59.9 (C-4), 81.1 (C-5), 97.7 (C-2), 115.1 (C-4′), 138.6 (C-3′), 127.2, 129.4, 137.5 and 143.4 (Ts). − $C_{17}H_{25}NO_3S$ (323.45): calcd. C 63.13, H 7.79, N 4.33; found C 62.86, H 7.47, N 4.30.

General Procedure for the Asymmetric Dihydroxylations of Alkenes 15, 16a, and 17: AD-Mix (1.54 g/mmol) and $MsNH_2$ (1.4 equiv.) were added to a solution of the alkene in tBuOH/H_2O (1:1, 10 mL/mmol) at 0°C. The suspension was stirred overnight. $Na_2S_2O_3$ (1 g/mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 ×). The combined organic layers were washed with saturated NH_4Cl solution and with saturated NaCl solution and dried with Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography.

(2*R*,5*S*,6*S*)-6-*N*-Tosylamino-5-trimethylsilyloxyheptan-1,2-diol (18a): TMS ether **15** (1.50 g, 4.22 mmol), AD-mix-β (6.50 g), $MsNH_2$ (372 mg, 5.91 mmol). Column chromatography (PE/MTBE 1:1, then MTBE) yielded 1.69 g of a 5.7:1 mixture of the alcohols **18a/19a** [contains MTBE (9%), 3.97 mmol, 94%] as a colorless oil. 20 mg of the diol mixture was silylated using TMSCl/NEt_3 for *ds* determination by comparison of the integrals over N−H. − R_f = 0.39 ($CHCl_3$/MeOH, 10:1). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 9 H, TMS), 0.89 (d, J = 6.8 Hz, 3 H, 1-H_3), 1.25−1.55 (m, 3 H) and 1.52−1.74 (m, 1 H, 4-H_2 and 5-H_2), 2.39 (s, 3 H, $TsCH_3$), 3.25−3.75 (m, 7 H, 2-H, 3-H, 6-H, 7-H, 2 × OH), 5.42 (d, J = 8.7 Hz, NH, minor epimer), 5.55 (d, J = 8.7 Hz, NH, major epimer), 7.28 (d, J = 8.1 Hz, 2 H, Ts), 7.76 (d, J = 8.1 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.1 (TMS), 16.7 (C-1), 21.3 ($TsCH_3$), 28.3 and 29.8 (C-4, C-5), 58.2 (C-2), 66.4 (C-7), 72.1 (C-6), 75.1 (C-3), 126.8, 129.5, 138.1 and 143.0 (Ts). − HRMS (ESI): $C_{17}H_{31}NO_5SSi$: calcd. 412.1590 $[M + Na]^+$; found 412.1601 $[M + Na]^+$.

(2*RS*,5*S*,6*S*)-6-*N*-Tosylamino-5-trimethylsilyloxyheptan-1,2-diol (18a/19a): TMS ether **15** (1.50 g, 4.22 mmol), AD-mix-α (6.50 g), $MsNH_2$ (372 mg, 5.91 mmol). Column chromatography (PE/MTBE 1:1, then MTBE) yielded 1.56 g of a 1.4:1 mixture **19a/18a** [contains MTBE (9%), 3.69 mmol, 88%] as a colorless oil. 20 mg of the diol mixture was silylated using TMSCl/NEt_3 for *ds* determination by comparison of the integrals over N−H. − R_f = 0.39 ($CHCl_3$/MeOH, 10:1). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 9 H, TMS), 0.91 (d, J = 6.6 Hz, 3 H, 1-H_3), 1.21−1.57 (m, 3 H) and 1.57−1.74 (m, 1 H, 4-H_2 and 5-H_2), 2.40 (s, 3 H, $TsCH_3$), 2.46 (br. s 1 H, OH), 2.61 (br. s, 1 H, OH), 3.25−3.64 (m, 5 H, 2-H, 3-H, 6-H, 7-H), 5.00 (d, J = 8.7 Hz, 0.58 H, NH), 5.04 (d, J = 8.7 Hz, 0.42 H, NH), 7.27 (d, J = 7.9 Hz, 2 H, Ts), 7.73 (d, J = 8.1 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3 (TMS), 18.5 (C-1), 21.5 ($TsCH_3$), 28.8 and 29.4 (C-4, C-5), 51.9 (C-2), 66.1 (C-7), 71.9 (C-6), 75.2 (C-3), 127.0, 129.6, 138.4 and 143.3 (Ts). − HRMS (ESI): $C_{17}H_{31}NO_5SSi$: calcd. 412.1590 $[M + Na]^+$; found 412.1590 $[M + Na]^+$.

(4*S*,5*S*,3′*R*)-5-(3′,4′-Dihydroxybutyl)-4-methyl-*N*-tosyl-1,3-oxazolidine (18b): Acetal **16a** (227 mg, 0.768 mmol), AD-mix-β (1.18 g), $MsNH_2$ (68 mg, 1.08 mmol). Column chromatography (MTBE) yielded 239 mg of a 1.7:1 mixture of the alcohols **18b/19b** (0.73 mmol, 94%), as a colorless oil; *ds* ratio determined by comparison of the integrals over O−H (δ = 2.24/2.41). − R_f = 0.16 (AcOEt). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.3 Hz, 3 H, 4-CH_3), 0.96−1.64 (m, 4 H, 1′-H_2 and 2′-H_2), 2.01 (br. s, 1 H, OH), 2.24 (s, 0.63 H, OH), 2.41 (s, 3 H, $TsCH_3$), 3.13−3.34 (m, 2 H, 4-H and 4′-H), 3.36−3.61 (m, 3 H, 5-H, 3′-H and 4′-H), 4.59 (d, J = 7.0 Hz, 0.63 H, major epimer, 2-H), 4.60 (d, J = 7.0 Hz, 0.37 H, minor epimer, 2-H), 5.15 (d, J = 7.0 Hz, 1 H, 2-H), 7.31 (d, J = 8.1 Hz, 2 H, Ts), 7.70 (d, J = 8.3 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (4-CH_3), 21.5 ($TsCH_3$), 27.9 (C-2′), 29.3 (C-1′), 59.3 (C-4), 66.5 (C-4′), 71.5 (C-3′), 79.9 (C-5), 85.9 (C-2), 127.9, 128.8, 134.4 and 144.1 (Ts). − HRMS (ESI): $C_{15}H_{23}NO_5S$: calcd. 352.1195 $[M + Na]^+$; found 352.1193 $[M + Na]^+$.

(4*S*,5*S*,3′*S*)-5-(3′,4′-Dihydroxybutyl)-4-methyl-*N*-tosyl-1,3-oxazolidine (19b): Acetal **16a** (465 mg, 1.57 mmol), AD-mix-α (2.42 g), $MsNH_2$ (139 mg, 2.20 mmol). Column chromatography (MTBE) yielded 458 mg of a 2.7:1 mixture of the alcohols **19b/18b** (1.39 mmol, 88%) as a colorless oil, *ds* ratio determined by comparison of the integrals over O−H (δ = 2.14/2.50). − R_f = 0.16 (AcOEt). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, J = 6.3 Hz, 3 H, 4-CH_3), 0.94−1.64 (m, 4 H, 1′-H_2 and 2′-H_2), 2.09 (br. s, 1 H, OH), 2.14 (s, 0.27 H, OH), 2.41 (s, 3 H, $TsCH_3$), 2.50 (s, 0.73 H, OH), 3.12−3.34 (m, 2 H, 4-H and 4′-H), 3.42−3.64 (m, 3 H, 5-H, 3′-H and 4′-H), 4.59 (d, J = 7.0 Hz, 0.27 H, 2-H), 4.60 (d, J = 7.0 Hz, 0.73 H, 2-H), 5.15 (d, J = 7.0 Hz, 1 H, 2-H), 7.31 (d, J = 8.2 Hz, 2 H, Ts), 7.70 (d, J = 8.2 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (4-CH_3), 21.6 ($TsCH_3$), 27.9 (C-2′), 29.0 (C-1′), 59.1 (C-4), 66.5 (C-4′), 71.5 (C-3′), 79.9 (C-5), 85.6 (C-2), 127.9, 128.8, 134.4 and 144.2 (Ts). − HRMS (ESI): $C_{15}H_{23}NO_5S$: calcd. 352.1195 $[M + Na]^+$; found 352.1196 $[M + Na]^+$.

(4*S*,5*S*,3′*R*)-5-(3′,4′-Dihydroxybutyl)-2,2,4-trimethyl-*N*-tosyl-1,3-oxazolidine (18c): Acetonide **17** (500 mg, 1.55 mmol), AD-mix-β (2.38 g), $MsNH_2$ (136 mg, 2.16 mmol). Column chromatography (AcOEt) yielded 574 mg of a 3.5:1 mixture of the alcohols **18c/19c** [contains AcOEt (13%), 1.40 mmol, 90%] as a colorless oil; *ds* ratio determined by comparison of the integrals over O−H (δ = 2.63/2.93). − R_f = 0.25 (AcOEt). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.4 Hz, 3 H, 4-CH_3), 1.30−1.77 (m, 4 H, 1′-H_2 and 2′-H_2), 1.53 (s, 3 H, 2-CH_3) and 1.55 (s, 3 H, 2-CH_3), 2.32 (br. s, 1 H, OH), 2.38 (s, 3 H, $TsCH_3$), 2.63 (s, 0.76 H, OH), 2.93 (s, 0.24 H, OH), 3.25−3.42 (m, 2 H, 4-H and 4′-H), 3.49−3.75 (m, 3 H, 5-H, 3′-H and 4′-H), 7.25 (d, J = 8.7 Hz, 2 H, Ts), 7.67 (d, J = 8.3 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6 (4-CH_3), 21.3 ($TsCH_3$), 26.7 (C-2′), 28.9 and 29.4 (2-CH_3), 29.5 (C-1′), 59.9 (C-4), 66.4 (C-4′), 71.7 (C-3′), 81.6 (C-5), 97.2 (C-2), 127.1, 129.4, 138.2 and 143.2 (Ts). − HRMS (ESI): $C_{17}H_{27}NO_5S$: calcd. 380.1508 $[M + Na]^+$; found 380.1525 $[M + Na]^+$.

(4*S*,5*S*,3′*S*)-5-(3′,4′-Dihydroxybutyl)-2,2,4-trimethyl-*N*-tosyl-1,3-oxazolidine (19c): Acetonide **17** (500 mg, 1.55 mmol), AD-mix-α (2.38 g), $MsNH_2$ (136 mg, 2.16 mmol). Column chromatography (AcOEt) yielded 536 mg of a 4:1 mixture of the alcohols **19c/18c** (1.50 mmol, 97%) as a colorless oil; *ds* ratio determined by com-

parison of the integrals over O−H (δ = 2.60/2.85). − R_f = 0.25 (AcOEt). − $[\alpha]_D$ = +12.9, $[\alpha]_{578}$ = +13.8, $[\alpha]_{546}$ = +15.5, $[\alpha]_{436}$ = +24.6, $[\alpha]_{365}$ = +33.4 (*c* = 0.93, $CHCl_3$, *T* = 27°C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.3 Hz, 3 H, 4-CH_3), 1.40−1.74 (m, 4 H, 1′-H_2 and 2′-H_2), 1.54 (s, 3 H, 2-CH_3) and 1.57 (s, 3 H, 2-CH_3), 2.26 (br. s, 1 H, OH), 2.39 (s, 3 H, TsCH_3), 2.60 (s, 0.20 H, OH), 2.85 (s, 0.80 H, OH), 3.26−3.45 (m, 2 H, 4-H and 4′-H), 3.49−3.85 (m, 3 H, 5-H, 3′-H and 4′-H), 7.26 (d, *J* = 8.7 Hz, 2 H, Ts), 7.69 (d, *J* = 8.3 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (4-CH_3), 21.4 (TsCH_3), 26.7 (C-2′), 28.6 and 29.1 (2-CH_3), 29.5 (C-1′), 59.8 (C-4), 66.5 (C-4′), 71.6 (C-3′), 81.4 (C-5), 97.3 (C-2), 127.1, 129.5, 138.3 and 143.2 (Ts). − HRMS (ESI): $C_{17}H_{27}NO_5S$: calcd. 380.1508 $[M + Na]^+$; found 380.1519 $[M + Na]^+$.

Conversion of the Diols 18a/19a into the THF Alcohols 11/12: NaH was added to a solution of the mixture of the diols **18a/19a** in dry THF (5 mL/mmol) at 0°C and the suspension was stirred for 30 min. Tosylimidazole was added. The suspension became clear for a moment and then a colorless solid precipitated. The ice bath was removed and the reaction was stirred for a further 3 h. Water (1 mL/mmol) was added, the layers separated and the aqueous layer extracted with MTBE (3 ×). The combined organic layers were washed with saturated NH_4Cl solution, saturated NaCl solution and dried with Na_2SO_4. The solvent was removed in vacuo. The crude epoxide was dissolved in CH_2Cl_2 (0.07 mmol/mL). Camphorsulfonic acid (1 equiv.) was added and the reaction mixture was stirred for 2 h at room temp. The solution was washed with saturated $NaHCO_3$ solution, with saturated NaCl solution and dried with $MgSO_4$. The solvents were removed in vacuo. Purification and separation of the epimers were done by column chromatography (PE/MTBE 1:2, then 1:5, then MTBE).

Conversion of the Diols 18b/19b into THF Alcohol 11 and Acetal 20: The epoxide (preparation vide supra) was purified by column chromatography (PE/MTBE, 1:1) to remove residual tosylimidazole and then dissolved in CH_2Cl_2 (0.15 mmol/mL). CSA (0.1 equiv.) was added and the reaction was stirred overnight. The solution was washed with saturated $NaHCO_3$ solution and with saturated NaCl solution and dried with Na_2SO_4. The solvent was removed in vacuo. The acetal **20** and the *trans*-alcohol **11** were separated by column chromatography (PE/MTBE 1:2, then MTBE).

(1*R*,6*S*,7*S*)-6-Methyl-*N*-tosyl-3,10-dioxa-5-azabicyclo[5.2.1]decane (20): Colorless crystals, m.p. 122°C (MTBE). − R_f = 0.50 (MTBE/CH_2Cl_2 4:1). − $[\alpha]_D$ = +72.3, $[\alpha]_{578}$ = +75.9, $[\alpha]_{546}$ = +86.4, $[\alpha]_{436}$ = +150.0, $[\alpha]_{365}$ = +244.1 (*c* = 2.41, $CHCl_3$, *T* = 19°C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.1 Hz, 3 H, 1′-H_3), 1.83−2.23 (m, 4 H, 8-H_2 and 9-H_2), 2.37 (s, 3 H, TsCH_3), 3.58 (dd, *J* = 1.0 and 13.2 Hz, 1 H, 2-H), 3.69 (dd, *J* = 1.8, 13.2 Hz, 1 H, 2-H), 3.84 (dq, *J* = 1.0 and 7.1 Hz, 1 H, 6-H), 4.04−4.06 (m, 1 H, 7-H), 4.12−4.15 (m, 1 H, 1-H), 4.45 (d, *J* = 12.4 Hz, 1 H, 4-H), 5.39 (d, *J* = 12.4 Hz, 1 H, 4-H), 7.24 (d, *J* = 8.6 Hz, 2 H, Ts), 7.65 (d, *J* = 8.4 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): 16.6 (C-1′), 21.4 (TsCH_3), 27.1 and 28.5 (C-8 and C-9), 55.0 (C-6), 65.7 (C-2), 76.5 (C-4), 79.5 (C-7), 82.0 (C-1), 126.9, 129.5, 138.1 and 143.2 (Ts). − $C_{15}H_{21}NO_4S$ (311.40): calcd. C 57.86, H 6.80, N 4.50, S 10.30; found C 57.72, H 6.86, N 4.35, S 10.28.

Conversion of the Diols 18c/19c into the THF Alcohols 11/12: A solution of the epoxide (preparation vide supra) in AcOH/H_2O (4:1, 0.2 mmol/mL) was stirred for 30 min at 40°C. The solvents were removed in vacuo and the crude products were dried azeotropically with toluene (2 ×). The epimers were separated by column chromatography (PE/MTBE 1:2, then 1:5, then MTBE).

Oxidation of 1:1 Mixture of *N*-Tosyl THF Alcohols 11 and 12 to (2*S*,5*S*,1′*S*)-5-[1′-(Tosylamino)ethyl]tetrahydrofuran-2-carbaldehyde (21) and (1*R*,2*R*,4*S*,5*S*)-4-Methyl-*N*-tosyl-8-oxa-3-azabicyclo-[3.2.1.]octan-2-ol (22). − (A) Swern Oxidation: DMSO (3.76 mL, 4.14 g, 52.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of oxalyl chloride (2.37 mL, 3.36 g, 26.5 mmol) in CH_2Cl_2 (60 mL) at −60°C. After stirring for 5 min, a 1:1 mixture of alcohols **11** and **12** (3.96 g, 13.2 mmol) in CH_2Cl_2 (20 mL) was added. The solution was allowed to stir for 20 min at −60°C, then NEt_3 (17 mL, 13.4 g, 132 mmol) was added and stirring was continued for 5 min at −60°C. The mixture was warmed to 0°C and water (20 mL) was added dropwise. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated NH_4Cl solution (50 mL), saturated NaCl solution (50 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (MTBE, 200 g of silica) afforded aldehyde **21** (1.21 g, 4.07 mmol, 31%) as a colorless oil and hemiaminal **22** (2.6 g, 8.81 mmol, 66%) as colorless crystals. − **(B) Dess−Martin Oxidation:** To a solution of a 1:1 mixture of alcohols **11** and **12** (4.46 g, 14.9 mmol) in CH_2Cl_2, pyridine (13 mL, 13.3 g, 168 mmol) and periodinane (7.94 g, 18.6 mmol) were added at 0°C. The mixture was allowed to stir overnight. Saturated $NaHCO_3$ solution (100 mL) was added, the layers were separated and the organic layer was washed with saturated NH_4Cl solution (50 mL), saturated NaCl solution (50 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (MTBE, 40 g of silica) afforded aldehyde **21** (1.78 g, 5.97 mmol, 40%) and hemiaminal **22** (1.76 g, 5.92 mmol, 40%).

(2*S*,5*S*,1′*S*)-5-[1′-(Tosylamino)ethyl]tetrahydrofuran-2-carbaldehyde (21): R_f = 0.31 (MTBE). $[\alpha]_D$ = −13.5, $[\alpha]_{578}$ = −13.9, $[\alpha]_{546}$ = −16.5, $[\alpha]_{436}$ = −32.0, $[\alpha]_{365}$ = −58.0 (*c* = 1.29, $CHCl_3$, *T* = 18°C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.7 Hz, 3 H, 2′-H_3), 1.72−2.15 (m, 4 H, 3,4-H_2), 2.35 (s, 3 H, CH_3-Ts), 3.19−3.30 (m, 1 H, 1′-H), 3.87−3.92 (m, 1 H) and 4.13−4.18 (m, 1 H, 2,5-H), 4.85 (d, *J* = 8.1 Hz, 1 H, N−H), 7.23 (d, *J* = 8.1 Hz, 2 H, Ts), 7.69 (d, J = 8.3 Hz, 2 H, Ts), 9.49 (d, *J* = 1.5 Hz, 1 H, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (C-2′), 21.5 (Ts-CH_3), 27.0 and 27.4 (C-3 and C-4), 52.3 (C-1′), 83.1 and 83.2 (C-2,5), 126.9, 129.6, 137.9 and 143.4 (Ts), 201.9 (C=O). − HRMS (EI): $C_{14}H_{19}NSO_4$ calcd. 297.1035; found 297.1033.

(1*R*,2*R*,4*S*,5*S*)-4-Methyl-*N*-tosyl-8-oxa-3-azabicyclo[3.2.1]octan-2-ol (22): m.p. 164°C (MTBE/PE). − R_f = 0.58 (PE/MTBE, 2:1). $[\alpha]_D$ = −7.7, $[\alpha]_{578}$ = −8.0, $[\alpha]_{546}$ = −9.7, $[\alpha]_{436}$ = −20.1, $[\alpha]_{365}$ = −44.2 (*c* = 0.64, $CHCl_3$, *T* = 18°C). − IR (KBr): $\tilde{\nu}$ = 3522 cm^{-1} s (OH), 2993 sh, 2978 m, 2963 m, 2879 w (CH), 1452 m, 1407 m, 1378 m, 1335 s, 1326 s, 1179 m, 1160 s (C−O), 1124 m, 1060 s, 995 s, 981 s, 963 m, 670 s, 562 m, 544 s. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.8 Hz, 3 H, 4-CH_3), 1.30−1.43 (m, 2 H) and 1.67−1.82 (m, 2 H, 6-H_2, 7-H_2), 2.36 (s, 3 H, Ts), 3.14 (d, *J* = 6.9 Hz, 1 H, OH), 3.48 (q, *J* = 6.9 Hz, 1 H, 4-H), 4.06 (d, *J* = 6.5 Hz, 1 H, 5-H), 4.23 (d, *J* = 6.4 Hz, 1 H, 1-H), 4.83 (dd, *J* = 1.2 and 6.8 Hz, 1 H, 2-H), 7.21 (d, *J* = 8.1 Hz, 2 H, Ts), 7.68 (d, *J* = 8.3 Hz, 2 H, Ts). − ^{13}C NMR (75 MHz, $CDCl_3$): 20.0 (C-1′), 21.5 (TsCH_3), 26.9 (C-6), 27.3 (C-7), 55.0 (C-4), 77.2, 78.7 and 79.2 (C-1, C-2 and C-5), 127.0, 129.6, 137.8 and 143.5 (Ts). − $C_{14}H_{19}NO_4S$ (297.37): calcd. C 56.55 H 6.44, N 4.71; found C 56.43, H 6.47, N 4.60.

(2*S*,5*S*,1′*S*)-2-{1′-[(*tert*-Butoxycarbonyl)amino]ethyl}-5-(hydroxymethyl)tetrahydrofuran (23): To a solution of the *trans*-alcohol **11** (3.20 g, 10.1 mmol) in THF (15 mL) and liquid NH_3 (150 mL) was added sodium (552 mg, 24.2 mmol) in small portions at −40°C

until the arising blue color persisted for more than 10 s. After stirring for 10 min, the reaction was quenched by adding dropwise glacial acetic acid (2 mL). The NH_3 was allowed to evaporate. The crude product was dried in vacuo for 1 h and dissolved in methanol (250 mL). Boc_2O (2.21 g, 10.1 mmol) was added in one portion. 12 mL of 1 M aqueous NaOH (12 mmol) were added dropwise. Stirring was continued for 10 min at room temperature, when Boc_2O (1.10 g, 5.10 mmol) and 6 mL of 1 M aqueous NaOH were added. After stirring for additional 10 min, the latter addition procedure was repeated. Then, the solvents were removed in vacuo and the crude product was partitioned between CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ solution (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (PE/MTBE 1:3, 100 g of silica) afforded 334 mg of starting material **11** (1.1 mmol, 11%) and 2.21 g (9.0 mmol, 89%) of the *N*-Boc-protected alcohol **23** as a colorless oil. − R_f = 0.35 (PE/MTBE 1:3). − $[\alpha]_D = -12.9$, $[\alpha]_{578} = -13.1$, $[\alpha]_{546} = -15.7$, $[\alpha]_{436} = -31.2$, $[\alpha]_{365} = -54.8$ (c = 1.34, $CHCl_3$, T = 25°C). − IR (neat): $\tilde{\nu}$ = 3445 and 3348 cm^{-1} m (NH and OH), 2975/2934 m (CH), 1693 br. s, 1525 m, 1454 m, 1391 m, 1367 m, 1247 m, 1171 s, 1097 m, 1044 m. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.8 Hz, 3 H, 2′-H_3), 1.43 [s, 9 H, $C(CH_3)_3$], 1.66−1.74 (m, 3 H, 3-H and 4-H axial and O−H), 1.74−1.93 (m, 2 H, 3-H and 4-H equatorial), 3.47 (dd, J = 11.5 and 6.4 Hz, 1 H, C*H*HOH), 3.62−3.70 (m, 1 H, 1′-H), 3.63 (dd, J = 11.5 and 3.2 Hz, 1 H, CH*H*OH), 3.86 (ddd, J = 8.4, 5.3 and 3.0 Hz, 1 H, 2-H), 4.11 (ddt, J = 3.2, 7.8 and 6.2 Hz, 1 H, 5-H), 4.66 (br. s, 1 H, N−H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2 (C-2′), 27.6 and 28.9 (C-3 and C-4), 28.4 [C(CH_3)$_3$], 47.0 (C-1′), 65.0 (CH_2OH), 79.1 [C(CH_3)$_3$], 80.0 (C-5), 82.0 (C-2), 155.9 (C=O, Boc). − NMR spectra were assigned using homo- and heteronuclear correlation spectroscopy (^{1}H-^{1}H and ^{13}C-^{1}H COSY) and two-dimensional NOE spectroscopy (^{1}H-^{1}H NOESY). − $C_{12}H_{23}NO_4$ (245.32): calcd. C 58.75, H 9.45, N 5.71; found C 58.61, H 9.36, N 5.80.

(2*S*,5*S*,1′*S*)-5-{1′-([*tert*-Butyloxycarbonyl)amino]ethyl}tetrahydrofuran-2-carboxylic Acid (24): A solution of DMSO (2.51 mL, 2.76 g, 35.3 mmol) in CH_2Cl_2 (20 mL) was added to a solution of oxalyl chloride (1.5 mL, 2.24 g, 17.6 mmol) in CH_2Cl_2 (60 mL) at −60 to −55°C. The reaction mixture was stirred for 5 min at −60°C. Then, a solution of the alcohol **23** (2.71 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After stirring for further 15 min, NEt_3 (11.2 mL, 8.15 g, 80.5 mmol) was added and the reaction mixture was stirred for an additional 5 min. The reaction mixture was allowed to warm to 2°C during 10 min. Then, water (10 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (PE/MTBE 3:1, 50 g of silica) afforded 2.59 g of the corresponding *trans*-aldehyde, (10.6 mmol, 97%) as a colorless oil. **(2*S*,5*S*,1′*S*)-5-{1′-[(*tert*-Butoxycarbonyl)amino]ethyl}tetrahydrofuran-2-carbaldehyde:** R_f = 0.41 (PE/MTBE, 1:3). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, J = 6.9 Hz, 3 H, 2′-H_3), 1.43 [s, 9 H, $C(CH_3)_3$], 1.71−1.78 (m, 1 H, 4-H axial), 1.91−2.01 (m, 2 H, 4-H equatorial, 3-H axial), 2.26−2.36 (m, 1 H, 3-H equatorial), 3.66−3.86 (m, 1 H, 1′-H), 3.98 (ddd, J = 3.1, 5.8 and 8.6 Hz, 1 H, 5-H), 4.34 (ddd, J = 1.8, 6.6 and 8.1 Hz, 1 H, 2-H), 4.62 (br. s, 1 H, N−H), 9.63 (d, J = 1.8 Hz, 1 H, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (C-2′), 27.1 and 27.9 (C-3 and C-4), 28.4 [C(CH_3)$_3$)], 48.7 (C-1′), 80.8 [C(CH_3)$_3$], 83.0 (C-5), 83.5 (C-2), 155.8 (C=O, Boc), 202.2 (C=O). − The aldehyde was converted directly to the corresponding acid. Therefore, a solution of $NaH_2PO_4 \cdot 2\,H_2O$ (7.61 g, 48.8 mmol) and $NaClO_2$ (5.52 g, 61.0 mmol) in water (80 mL) was added to a solution of the *trans*-aldehyde (1.49 g, 6.10 mmol) and amylene (32.4 mL, 305 mmol) in *t*BuOH (100 mL) at room temperature. The mixture was stirred overnight at room temperature. *t*BuOH was removed in vacuo and MTBE (100 mL) was added. The reaction mixture was acidified with 2 M aqueous HCl (25 mL, 50 mmol) at 0°C. The layers were separated and the aqueous layer was extracted with MTBE (5 × 50 mL). The organic layers were combined and the solvent was removed in vacuo. For purification, the crude product was dissolved in a solution of K_2CO_3 (8.43 g, 61 mmol) in water (200 mL). The carboxylic salt solution was washed with MTBE (2 × 50 mL), covered with MTBE (50 mL) and acidified under vigorous stirring at 0°C with 2 M aqueous HCl (61 mL, 122 mmol). The layers were separated and the aqueous layer was extracted with MTBE (5 × 500 mL). The combined organic layers were washed with saturated NaCl solution (50 mL) and dried with Na_2SO_4. After evaporation of the solvent in vacuo, 1.40 g (5.40 mmol, 89%) of the carboxylic acid **24** was obtained as a colorless solid. An analytical sample was recrystallized from MTBE/PE to give colorless crystals, m.p. 67°C. − R_f = 0.29 ($CHCl_3$/MeOH/AcOH, 100:10:1). − $[\alpha]_D = -2.9$, $[\alpha]_{278} = -3.2$, $[\alpha]_{546} = -3.7$, $[\alpha]_{436} = -6.5$, $[\alpha]_{365} = -10.2$ (c = 1.84, EtOH, T = 19°C). − IR (KBr): $\tilde{\nu}$ = 3853−2739 cm^{-1} mb (OH), 3298 s (NH), 3002/2931/2938/2892 s (CH), 2606 m, 2533 m, 1728 s, 1636 s, 1481 m, 1461 m, 1417 s, 1369 s, 1327 m, 1249 m, 1228 s, 1159 s, 1115 s, 1090 s, 1056 m, 1011 m, 998 m, 956 m, 915 m. − ^{1}H NMR (600 MHz, [D_4]methanol): δ = 1.13 (d, J = 6.8 Hz, 3 H, 2′-CH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 1.70 (dddd, J = 7.5, 7.6, 8.7, 12.5 Hz, 1 H, 4-H axial), 1.98 (dddd, J = 5.9, 7.6, 8.1, 12.7 Hz, 1 H, 3-H axial), 1.98 (dddd, J = 5.5, 6.7, 8.1, 12.3, Hz, 1 H, 4-H equatorial), 2.30 (dddd, J = 5.5, 8.1, 8.7, 12.3 Hz, 1 H, 3-H equatorial), 3.62 (dq, J = 4.8 and 6.8 Hz, 1 H, 1′-H), 4.05 (ddd, J = 4.8, 6.7, 7.5 Hz, 1 H, 5-H), 4.49 (dd, J = 5.9 and 8.1 Hz, 1 H, 2-H). − N−H not visible because of H/D exchange. − ^{13}C NMR (125 MHz, [D_4]methanol): 17.5 (C-2′), 28.1 [C-4, C(CH_3)$_3$], 30.6 (C-3), 49.8 (C-1′), 77.4 (C-2), 79.0 [C(CH_3)$_3$], 83.6 (C-5), 157.5 (C=O, Boc), 176.4 (COOH). − NMR spectra were assigned using homo- and heteronuclear correlation spectroscopy (^{1}H-^{1}H and ^{13}C-^{1}H COSY) and two-dimensional NOE spectroscopy (^{1}H-^{1}H NOESY), the coupling constants were determined by WIN-DAISY simulation. − $C_{12}H_{21}NO_5$ (259.30): calcd. C 55.58, H 8.16, N 5.40; found C 55.30, H 8.25, N 5.48.

Benzyl (2*S*,5*S*,1′*S*)-5-{1′-[(*tert*-Butoxycarbonyl)amino]ethyl}tetrahydrofuran-2-carboxylate (25): NEt_3 (9.7 mL, 7.07 g, 69.4 mmol) was added to a solution of *trans*-acid **24** (4.00 g, 15.4 mmol) in acetone (150 mL) at 0°C. After stirring for 1 h, benzyl bromide (8.3 mL, 11.9 g, 69.4 mmol) was added dropwise and stirring was continued overnight. The solvent was removed in vacuo and the residue was redissolved in MTBE (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL) and saturated NaCl solution (20 mL) and dried with Na_2SO_4. Column chromatography (PE/MTBE 3:1, 400 g of silica) afforded 4.18 g of the benzyl ester **25** (12.0 mmol, 71%) as a colorless solid, m.p. 72−73°C (MTBE/PE). − R_f = 0.38 (PE/MTBE, 3:1). $[\alpha]_D = -2.2$, $[\alpha]_{578} = -2.2$, $[\alpha]_{546} = -3.0$, $[\alpha]_{436} = -4.4$, $[\alpha]_{365} = -8.2$ (c = 0.27, $CHCl_3$, T = 19°C). − IR (KBr): $\tilde{\nu}$ = 3469 cm^{-1} br. w and 3378 m (NH), 3068 br. w, 3035, 3008 (CHPh), 2983 m (CH), 1758 s, 1686 s, 1520 s, 1454 m, 1390 m, 1371 m, 1366 m, 1251 m, 1186 s, 1171 s, 1107 s, 1070 s, 1029 m, 613 m. − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.20

(d, J = 6.8 Hz, 3 H, 2′-CH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 1.71 (dddd, J = 7.4, 7.5, 8.9, 12.5 Hz, 1 H, 4-H axial), 1.95 (dddd, J = 5.5, 6.8, 8.4, 12.5 Hz, 1 H, 4-H equatorial), 1.98 (dddd, J = 5.5, 7.4, 8.4, 12.7 Hz, 1 H, 3-H equatorial), 2.24 (dddd, J = 5.5, 8.1, 8.9, 12.7 Hz, 1 H, 3-H axial), 3.71 (dq, J = 3.2 and 6.8 Hz, 1 H, 1′-H), 4.11 (ddd, J = 3.2, 6.8, 7.5 Hz, 1 H, 5-H), 4.55 (dd, J = 5.5 and 8.1 Hz, 1 H, 2-H), 5.13 (d, J = 12.3 Hz, 1 H, PhC*H*H), 4.63−4.64 (m, 1 H, N−H), 5.15 (d, J = 12.3 Hz, 1 H, PhCH*H*), 7.30−7.38 (m, 5 H, Ph). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.1 (C-2′), 27.7 (C-4), 28.3 [C(*C*H_3)$_3$], 30.0 (C-3), 48.8 (C-1′), 66.4 (CH_2−Ph), 77.1 (C-2), 79.1 [*C*$(CH_3)_3$], 83.1 (C-5), 128.1, 128.3, 128.5, 135.6 (Ph), 155.8 (C=O, Boc), 173.3 (COOBn). − NMR spectra were assigned using homo- and heteronuclear correlation spectroscopy (^{1}H-^{1}H and ^{13}C-^{1}H COSY) and two-dimensional NOE spectroscopy (^{1}H−^{1}H NOESY); coupling constants were determined by WIN-DAISY simulation. − $C_{19}H_{27}NO_5$ (349.42): calcd. C 65.31 H 7.79, N 4.01; found C 65.25, H 7.79, N 4.11.

(2*S*,5*R*,1′*S*)-2-{1′-[(*tert*-Butoxycarbonyl)amino]ethyl}-5-(hydroxymethyl)tetrahydrofuran (26): To a solution of the *cis* alcohol **12** (3.0 g, 10.0 mmol) in THF (15 mL) and liquid NH_3 (150 mL) was added sodium (470 mg, 20.0 mmol) in small portions and the solution was stirred for 30 min at −40°C. Additional sodium (120 mg, 5.01 mmol) was added, until the arising blue color persisted for more than 10 s. After stirring for 10 min, the reaction was quenched by adding dropwise glacial acetic acid (3 mL). The NH_3 was allowed to evaporate. The crude product was dried in vacuo for 1 h and dissolved in methanol (150 mL). Boc_2O (2.18 g, 10.0 mmol) was added in one portion. 12 mL of 1 M aqueous NaOH was added dropwise. Stirring was continued for 10 min at room temperature, when once again Boc_2O (2.18 g, 10.0 mmol) and 12 mL of 1 M aqueous NaOH were added. After stirring for additional 30 min, the solvents were removed in vacuo and the crude product was partitioned between CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ solution (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (PE/MTBE 1:3, 150 g of silica) afforded 630 mg of starting material **12** (2.1 mmol, 21%) and 1.94 g of the *N*-Boc protected *cis*-alcohol **26** (7.91 mmol, 79%) as a colorless oil. − R_f = 0.37 (PE/MTBE, 1:3). − $[\alpha]_D$ = −3.1, $[\alpha]_{578}$ = −3.9, $[\alpha]_{546}$ = −3.2, $[\alpha]_{436}$ = −4.3 (c = 1.34, $CHCl_3$, T = 21°C). − IR (neat): $\tilde{\nu}$ = 3335 cm^{-1} s (NH and OH), 2975 s (CH_3), 2933 s (CH_2), 2875 s (NH), 1693 s (C=O), 1530 s (CO−NHR), 1454 s (COR), 1391 m [$C(CH_3)_3$], 1335 m, 1249 s (OH), 1171 s (C−O), 1104 m, 1047 m. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (d, J = 6.7 Hz, 3 H, 2′-H_3), 1.42 [s, 9 H, $C(CH_3)_3$], 1.67−1.73 (m, 1 H, 3-H axial), 1.82−2.01 (m, 3 H, 4-H_2 and 3-H equatorial), 2.15 (s, 1 H, OH), 3.45 (dd, J = 10.6 and 7.0 Hz, 1 H, C*H*HOH), 3.59 (dq, J = 6.7 and 2.7 Hz, 1 H, 1′-H), 3.65−3.73 (m, 2 H, CH*H*OH and 2-H), 3.99−4.03 (m, 1 H, 5-H), 4.62 (d, J = 8.4 Hz, 1 H, N−H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (C-2′), 26.3 (C-3), 28.3 [C(*C*H_3)$_3$], 28.8 (C-4), 50.3 (C-1′), 64.0 (*C*H_2OH), 79.4 [*C*$(CH_3)_3$], 80.3 (C-5), 83.4 (C-2), 156.6 (C=O, Boc). − $C_{12}H_{23}NO_4$ (245.32): calcd. C 58.75, H 9.45, N 5.71; found C 58.61, H 9.36, N 5.80.

(2*R*,5*S*,1′*S*)-5-{1′-[(*tert*-Butoxycarbonyl)amino]ethyl}tetrahydrofuran-2-carboxylic Acid (27): A solution of DMSO (1.1 mL, 1.2 g, 15.3 mmol) in CH_2Cl_2 (10 mL) was added to a solution of oxalyl chloride (0.9 mL, 1.3 g, 10 mmol) in CH_2Cl_2 (40 mL) at −60 to −55°C. The reaction mixture was stirred for 20 min at −60°C. Then a solution of the alcohol **26** (0.50 g, 2.04 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for further 20 min, NEt_3 (4.3 mL, 3.1 g, 31 mmol) was added and the reaction mixture was stirred for additional 5 min. The reaction mixture was allowed to warm to room temperature during 30 min. A saturated $NaHCO_3$ solution (40 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and MTBE (5 × 10 mL). The combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo. The crude product was directly converted into the carboxylic acid. Therefore, amylene (10.8 mL, 7.20 g, 102 mmol), $NaH_2PO_4 \cdot 2\,H_2O$ (2.54 g, 16.3 mmol) and $NaClO_2$ (1.84 g, 20.4 mmol) were added to a solution of the aldehyde (1.49 g, 6.10 mmol) in *t*BuOH (40 mL) at room temperature. The mixture was stirred overnight at room temperature. *t*BuOH was removed in vacuo and water (100 mL) was added. The mixture was extracted with MTBE (5 × 30 mL), acidified with 2 M HCl to pH = 3 and extracted with MTBE (2 × 20 mL). The combined organic layers were washed with ice water and dried with $MgSO_4$. Column chromatography ($CHCl_3$/MeOH 10:1, 25 g of silica) afforded 343 mg (1.342 mmol, 65%) of the carboxylic acid **27** as a colorless solid. An analytical sample was recrystallized from MTBE/PE to give colorless crystals, m.p. 125°C (MTBE/PE). − R_f = 0.13 ($CHCl_3$/MeOH, 15:1). − $[\alpha]_D$ = +44.3, $[\alpha]_{578}$ = +46.3, $[\alpha]_{546}$ = +53.0, $[\alpha]_{436}$ = +93.6, $[\alpha]_{365}$ = +155.4 (c = 1.24, EtOH, T = 25°C). − IR (KBr): $\tilde{\nu}$ = 3433 cm^{-1} s (OH), 3070 w (NH), 2975 s, 2932 m, 2877 w, 1698 s (C=O), 1614 w, 1526 m, 1366 s, 1246 m, 1171 s (C−O), 1056 s, 1027 s, 1008 s, 866 w, 822 s, 759 s. − ^{1}H NMR (600 MHz, [D_4]methanol): δ = 1.18 (d, J = 6.8 Hz, 3 H, 2′-CH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 1.66 (dddd, J = 8.1, 9.1, 10.4, 12.3 Hz, 1 H, 4-H axial), 1.93 (dddd, J = 3.3, 6.2, 7.8, 12.5 Hz, 1 H, 4-H equatorial), 2.09 (dddd, J = 12.7, 3.3, 4.0, 8.1 Hz, 1 H, 3-H equatorial), 2.30 (dddd, J = 7.8, 9.0, 10.4, 12.7 Hz, 1 H, 3-H axial), 3.65 (dq, J = 3.2 and 6.8 Hz, 1 H, 1′-H), 3.98 (ddd, J = 3.3, 6.2, 9.1 Hz, 1 H, 5-H), 4.42 (dd, J = 4.0, 9.0 Hz, 1 H, 2-H). − N−H not visible because of H/D exchange. − ^{13}C-NMR (75 MHz, [D_4]methanol): δ = 19.5 (C-2′), 25.5 (C-4), 28.6 [C(*C*H_3)$_3$], 32.0 (C-3), 49.4 (C-1′), 79.0, 80.4 [C-2, *C*$(CH_3)_3$], 85.8 (C-5), 158.9 (C=O, Boc), 177.9 (COOH). − NMR spectra were assigned using homo- and heteronuclear correlation spectroscopy (^{1}H-^{1}H and ^{13}C-^{1}H COSY) and two-dimensional NOE spectroscopy (^{1}H-^{1}H NOESY); coupling constants were determined by WIN-DAISY simulation. − HRMS (CI): $C_{12}H_{21}NO_5$ (259.30): calcd. 260.1498 $[M + H]^+$; found 260.2377 $[M + H]^+$.

Benzyl (2*R*,5*S*,1′*S*)-5-{1′-[(*tert*-Butoxycarbonyl)amino]ethyl}tetrahydrofuran-2-carboxylate (28): NEt_3 (2.29 mL, 1.67 g, 16.5 mmol, 5 equiv.) was added to a solution of the *cis*-acid **27** (858 mg, 3.31 mmol) in acetone (30 mL) at 0°C. After stirring for 1 h, benzyl bromide (1.97 mL, 2.83 g, 16.5 mmol, 5 equiv.) was added and stirring was continued overnight. The solvent was removed in vacuo and the residue was redissolved in MTBE (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL) and dried with Na_2SO_4. Column chromatography (PE/MTBE 3:1, 100 g of silica) afforded 740 mg of the benzyl ester **28** (2.12 mmol, 64%) as a colorless solid, m.p. 82°C (MTBE/PE). − R_f = 0.25 (PE/MTBE, 2:1). $[\alpha]_D$ = −1.5, $[\alpha]_{578}$ = −1.6, $[\alpha]_{546}$ = −1.9, $[\alpha]_{436}$ = −3.6, $[\alpha]_{365}$ = −5.8 (c = 0.75, $CHCl_3$, T = 18°C). − IR (KBr): $\tilde{\nu}$ = 3279 cm^{-1} s (NH), 2975 s (CH), 2931 m (CH_2), 1736 m (C=O), 1518 m, 1454 m (C−O), 1390 w, 1365 m [$C(CH_3)_3$], 1295 w, 1245 w, 1170 m (C−O), 865 w. − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (d, J = 6.8 Hz, 3 H, 2′-CH_3), 1.38 [s, 9 H, $C(CH_3)_3$], 1.75 (m, 1 H, 4-H axial), 1.87 (m, 1 H, 4-H equatorial), 2.08 (m, 1 H, 3-H equatorial), 2.24 (m, 1 H, 3-H axial), 3.75 (m, 1 H, 1′-H), 4.03 (dd, J = 7.4 and 7.5 Hz, 1 H, 5-H), 4.50 (dd, J = 3.5 and 9.1 Hz, 1 H, 2-H), 5.16 (d, J = 12.2 Hz, 1 H, C*H*H−Ph),

5.22 (d, J = 12.3 Hz, 1 H, CHH−Ph), 5.95 (d, J = 7.0 Hz, 1 H, N−H), 7.30 (m, 5 H, Ph). − ^{13}C NMR (125 MHz, $CDCl_3$): 18.7 (C-2′), 27.1 (C-4), 28.5 [C(CH_3)$_3$], 30.9 (C-3), 48.1 (C-1′), 66.8 (CH_2−Ph), 76.6 (C-2), 78.8 [C(CH_3)$_3$], 84.4 (C-5), 128.3, 128.4, 128.6, 135.5 (Ph), 156.2 (C=O, Boc), 173.8 (COOBn). − NMR spectra were assigned using homo- and heteronuclear correlation spectroscopy (^{1}H-^{1}H and ^{13}C-^{1}H COSY) and two-dimensional NOE spectroscopy (^{1}H-^{1}H NOESY). − $C_{19}H_{27}NO_5$ (349.42): calcd. C 65.31 H 7.79, N 4.01; found C 65.34, H 7.69, N 3.82.

(2*S*,5*S*,1′*S*)-2-{1′-[(Fluorenylmethoxycarbonyl)amino]ethyl}-5-(hydroxymethyl)tetrahydrofuran (29): To a solution of the *trans*-alcohol **11** (1.7 g, 5.6 mmol) in THF (10 mL) and liquid NH_3 (100 mL) was added sodium (259 mg, 11 mmol) in small portions at −40°C until a persistent blue-colored solution was obtained. After stirring for 10 min, the reaction was quenched by dropwise addition of glacial acetic acid (2 mL). The NH_3 was allowed to evaporate. The crude product was dried in vacuo for 1 h and dissolved in acetonitrile (5 mL) and saturated $NaHCO_3$ solution (5 mL). Fmoc-succinimide (3.8 g, 11 mmol) was added in one portion. After stirring overnight, the acetonitrile was removed and the aqueous layer was extracted with MTBE (5 × 20 mL). The combined organic layers were washed with 0.1 M HCl (100 mL), saturated NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (PE/MTBE, 5:1 to 1:1) afforded 1.14 g (3.11 mmol, 56%) of **29** as colorless crystals. m.p. 110°C. − R_f = 0.15 (MTBE/PE, 2:1). − $[\alpha]_D$ = −58.2, $[\alpha]_{578}$ = −58.2, $[\alpha]_{546}$ = −58.8, $[\alpha]_{436}$ = −64.1, $[\alpha]_{365}$ = −72.5, (c = 0.47, $CHCl_3$, T = 19°C). − IR (KBr): $\tilde{\nu}$ = 3439 cm^{-1} (NH and OH), 3019/2977/2878 (CH), 1715 (C=O). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.8 Hz, 3 H, 2′-CH_3), 1.50−1.63 (m, 2 H, 3-H_2), 1.83−1.87 (m, 2 H, 4-H_2), 2.15 (m, 1 H, OH), 3.36−3.42 (m, 1 H, CHHOH), 3.53−3.56 (m, 1 H, CHHOH), 3.68 (m, 1 H, 1′-H), 3.79 (m, 1 H, 2-H), 3.98−4.00 (m, 1 H, 5-H), 4.11−4.16 (m, 1 H, Fmoc), 4.34−4.36 (d, J = 6.8 Hz, 2 H, Fmoc), 4.92 (m, 1 H, N−H), 7.17−7.69 (m, 8 H, Fmoc). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 19.2 (C−2′), 27.6, 28.9 (C-3 und C-4), 47.4 (CH−CH_2O, Fmoc), 49.5 (C-1′), 64.9 (CH$_2$OH), 66.4 (CH_2O, Fmoc), 80.2 (C-5), 81.8 (C-2), 120.0, 125.0, 127.0, 127.7, 141.3, 144.0, 156.3 (Fmoc). − $C_{22}H_{25}NO_4$ (367.18): calcd. C 71.91, H 6.86, N 3.81; found C 71.96, H 6.95, N 3.85.

(2*S*,5*S*,1′*S*)-2-{1′-[(-Fluorenylmethoxycarbonyl)amino]ethyl}tetrahydrofuran-2-carboxylic Acid (30): A solution of DMSO (0.89 mL, 980 mg, 12 mmol) in CH_2Cl_2 (15 mL) was added to a solution of oxalyl chloride (0.54 mL, 790 mg, 6.2 mmol) in CH_2Cl_2 (40 mL) at −60 to −55°C. The reaction mixture was stirred for 5 min at −60°C and a solution of the alcohol **29** (1.14 g, 3.10 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 15 min, NEt_3 (4.31 mL, 3.13 g, 31.0 mmol) was added and the reaction mixture was stirred for additional 5 min. The reaction mixture was allowed to warm to 2°C during 10 min and saturated $NaHCO_3$ solution (20 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried with Na_2SO_4. The aldehyde was converted directly to the corresponding acid. A solution of NaH_2PO_4·2 H_2O (3.40 g, 24.8 mmol) and $NaClO_2$ (2.81 g, 31.0 mmol) in water (14 mL) was added to a solution of the *trans*-aldehyde (1.14 g, 3.10 mmol) in *t*BuOH (14 mL) and amylene (16.5 mL, 10.9 g, 155 mmol) at room temperature. After stirring overnight, the reaction mixture was acidified with saturated oxalic acid solution to pH = 2. The layers were separated and the aqueous layer was extracted with MTBE (5 × 20 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and the organic solvents were evaporated. For purification, the crude product was dissolved in MTBE, and extracted with saturated $NaHCO_3$ solution (100 mL). The aqueous layer was covered with MTBE and acidified with HCl (conc.) to pH = 2. The layers were separated. The organic layer was washed with saturated aqueous NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Thus, 0.45 g (1.18 mmol, 38%) of the acid **30** was obtained as a colorless oil. − R_f = 0.33 ($CHCl_3$/MeOH/AcOH, 200:10:1). − $[\alpha]_D$ = −14.6, $[\alpha]_{578}$ = −15.1, $[\alpha]_{546}$ = −17.4, $[\alpha]_{436}$ = −30.9, $[\alpha]_{365}$ = −49.4 (c = 1.02, $CHCl_3$, T = 19°C). − IR (neat): $\tilde{\nu}$ = 3438 cm^{-1} (NH and OH), 3018/2981/2951/2878 (CH), 1716 (C=O). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, J = 8.6 Hz, 3 H, 2′-CH_3), 1.57−1.65 (m, 1 H, 4-H), 1.89−2.01 (m, 2 H, 4-H and 3-H), 2.15−2.37 (m, 1 H, 3-H), 3.35−3.80 (m, 1 H, 1′-H), 3.90−4.08 (m, 1 H, 5-H), 4.10−4.19 (m, 1 H, Fmoc), 4.35−4.49 (m, 3 H, 2-H, Fmoc), 4.81 (d, J = 8.3 Hz, 1 H, N−H), 7.18−7.70 (m, 8 H, Fmoc). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 19.1 (C-2′), 28.1, 30.1 (C-3 and C-4), 47.3 (CH−CH_2O), 49.4 (C-1′), 66.4 (CH_2O, Fmoc), 77.2 (C-2), 83.3 (C-5), 120.0, 124.9, 127.0, 127.7, 141.4, 143.8, 156.9 (Fmoc), 176.7 (C=O). − $C_{22}H_{23}NO_5$ (381.16): calcd. C 69.28, H 6.08, N 3.67; found C 69.18, H 6.06, N 3.64.

(2*S*,5*R*,1′*S*)-2-{1′-[(Fluorenylmethoxycarbonyl)amino]ethyl}-5-(hydroxymethyl)tetrahydrofuran (31): To a solution of the *cis*-alcohol **12** (1.7 g, 5.6 mmol) in THF (10 mL) and liquid NH_3 (100 mL) was added sodium (259 mg, 11 mmol) in small portions at −40°C until a persistent blue-colored solution was obtained. After stirring for 10 min, the reaction was quenched by dropwise addition of glacial acetic acid (2 mL). The NH_3 was allowed to evaporate. The crude product was dried in vacuo for 1 h and dissolved in acetonitrile (5 mL) and saturated $NaHCO_3$ (5 mL). Fmoc-succinimide (3.8 g, 11 mmol) was added in one portion. After stirring overnight the acetonitrile was removed and the aqueous layer was extracted with MTBE (5 × 20 mL). The combined organic layers were washed with 0.1 M HCl (100 mL), saturated NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Column chromatography (PE/MTBE, 5:1 to 2:1) afforded 1.52 g (4.14 mmol, 44%) of **31** as colorless solid. − R_f = 0.23 (MTBE/PE, 2:1). − $[\alpha]_D$ = +4.0, $[\alpha]_{578}$ = +4.3, $[\alpha]_{546}$ = +5.0, $[\alpha]_{436}$ = +10.7, $[\alpha]_{365}$ = +22.4 (c = 1.00, $CHCl_3$, T = 19°C). − IR: $\tilde{\nu}$ = 3437 cm^{-1} (NH and OH), 3011/2977/2951/2878 (CH), 1709 (C=O). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, J = 6.4 Hz, 3 H, 2′-CH_3), 1.57−1.65 (m, 2 H, 3-H_2), 1.72−1.79 (m, 2 H, 4-H_2), 1.83−1.91 (m, 1 H, OH), 3.35−3.40 (dd, J = 4.5 and 12.1 Hz, CHHOH), 3.62−3.66 (m, 1 H, CHHOH), 3.69−3.75 (m, 2 H, 2-H and 1′-H), 3.93−3.94 (m, 1 H, 5-H), 4.11−4.15 (m, 1 H, Fmoc), 4.25−4.39 (m, 2 H, Fmoc), 5.16 (d, J = 8.3 Hz, 1 H, N−H), 7.18 −7.68 (m, 8 H, Fmoc). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 18.6 (C-2′), 27.0, 28.9 (C-3 and C-4), 47.3 (CH−CH_2O), 50.7 (C-1′), 64.2 (CH$_2$O, Fmoc), 66.6 (CH_2OH), 80.2 (C-5), 83.1 (C-2), 119.9, 125.1, 127.0, 127.6, 141.3, 144.0, 156.9 (Fmoc). − $C_{22}H_{25}NO_4$ (367.18): calcd. C 71.82, H 6.96, N 3.78; found C 71.96, H 6.95, N 3.85.

(2*S*,5*R*,1′*S*)-2-{1′-[(Fluorenylmethoxycarbonyl)amino]ethyl}tetrahydrofuran-2-carboxylic Acid (32): A solution of DMSO (1.19 mL, 1.31 g, 16.5 mmol) in CH_2Cl_2 (20 mL) was added to a solution of oxalyl chloride (0.71 mL, 1.02 g, 6.2 mmol) in CH_2Cl_2 (50 mL) at −60 to −55°C. The reaction mixture was stirred for 5 min at −60°C and a solution of the alcohol **31** (1.52 g, 4.16 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 15 min, NEt_3 (5.74 mL, 4.19 g, 41.4 mmol) was added and the reaction mixture was stirred for additional 5 min. The reaction mixture was allowed to warm to 2°C during 10 min and saturated $NaHCO_3$ solution (20 mL) was added. The layers were separated and the

aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL) and dried with Na_2SO_4. The aldehyde was converted directly to the corresponding acid. A solution of $NaH_2PO_4 \cdot 2\ H_2O$ (4.55 g, 33.3 mmol) and $NaClO_2$ (3.77 g, 41.7 mmol) in water (19 mL) was added to a solution of the *cis*-aldehyde (1.52 g, 4.16 mmol) in *t*BuOH (19 mL) and amylene (22.1 mL, 14.6 g, 209 mmol) at room temperature. After stirring overnight at room temperature, the reaction mixture was acidified with saturated oxalic acid solution to pH = 2. The layers were separated and the aqueous layer was extracted with MTBE (5 × 20 mL). The combinined organic phases were washed with saturated NaCl (100 mL) and the organic solvents were evaporated. For purification, the crude product was dissolved in MTBE, and extracted with saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous layer was covered with MTBE and acidified with HCl (conc.) to pH = 2 and the layers were separated. The organic layer was washed with saturated NaCl solution (100 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. Thus, 0.71 g (1.86 mmol, 45%) of the acid **32** was obtained as a white solid. m.p. 142°C. − R_f = 0.30 ($CHCl_3$/MeOH/AcOH, 200:10:1). − $[\alpha]_D$ = +22.3, $[\alpha]_{578}$ = +23.5, $[\alpha]_{546}$ = +26.7, $[\alpha]_{436}$ = +45.7, $[\alpha]_{365}$ = +73.8 (*c* = 1.02, $CHCl_3$, *T* = 19°C). − IR: $\tilde{\nu}$ = 3300 cm^{-1} (NH and OH), 3100/2990/2900/2800 (CH), 1750 (C=O). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.8 Hz, 3 H, 2′-CH_3), 1.56 (m, 1 H, 4-H), 1.93−2.07 (m, 1 H, 4-H), 2.19−2.40 (m, 2 H, 3-H_2), 3.71−3.73 (m, 1 H, 1′-H), 3.83−3.88 (m, 1 H, 5-H), 4.22 (t, *J* = 7.0 Hz, 1 H, Fmoc), 4.47−4.55 (m, 3 H, 2-H, Fmoc), 5.30−5.33 (d, *J* = 8.5 Hz, 1 H, N−H), 7.26−7.77 (m, 8 H, Fmoc), 8.7 (br. s, 1 H, COOH). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 17.7 (C-2′), 28.4, 31.1 (C-3 and C-4), 47.2 (*C*H−CH_2O, Fmoc), 51.5 (C-1′), 67.1 (CH_2O, Fmoc), 77.2 (C-2), 86.3 (C-5), 120.0, 125.1, 127.1, 127.7, 141.3, 143.8, 156.9 (Fmoc), 175.8 (C=O). − HRMS(EI): $C_{22}H_{23}NO_5$: calcd. 381.1576 [M^+], found 381.1559 [M^+].

(2*R*,5*S*,1′*S*)-5-{1′-[(*tert*-Butoxycarbonyl)amino]ethyl}tetrahydrofuran-2-carboxylic Acid Methyl Amide (33): A solution of acid **27** (1.00 g, 3.86 mmol), methyl amine hydrochloride (390 mg, 5.78 mmol) and HOBt × H_2O (945 mg, 6.17 mmol) in THF (20 mL) was treated at 0°C with $EtN(iPr)_2$ (0.67 mL, 0.50 g, 3.87 mmol) and with EDC (814 mg, 4.25 mmol). After 50 min $EtN(iPr)_2$ (0.67 mL, 0.50 g, 3.87 mmol) was added again. The solution was allowed to stir for 18 h at room temperature before the solvent was removed in vacuo. The residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL), 5% aqueous citric acid (2 × 10 mL), saturated NaCl solution (20 mL) and dried with Na_2SO_4. Concentration in vacuo and recrystallization from MTBE afforded **33** (665 mg, 2.44 mmol, 63%) as a white solid, m.p. 156°C. − R_f = 0.33 (MTBE). − $[\alpha]_D$ = +61.6; $[\alpha]_{578}$ = +64.3; $[\alpha]_{546}$ = +73.0; $[\alpha]_{436}$ = +123.6; $[\alpha]_{365}$ = +192.6 (*c* = 0.99, $CHCl_3$, *T* = 20°C). − IR (KBr): $\tilde{\nu}$ = br. 3330 cm^{-1} m (NH), 3300 s (NH), 3010 w, 2970 m/2940 w/2875 w (CH), 1695 s (C=O), 1650 s, 1545 s, 1460 w, 1410 w, 1390 w, 1365 w, 1335 m, 1320 w, 1275 w, 1250 m, 1195 w, 1170 m, 1085 m, 1055 w, 1045 w. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.4 Hz, 3 H, 2′-H_3), 1.46 [s, 9 H, $C(CH_3)_3$], superimposes 1.45−1.55 (m, 1 H, 4-H_A), 1.90−2.02 and 2.16−2.39 (m, 1 H and m, 2 H, 3-H_2 and 4-H_B), 2.83 (d, *J* = 6.4 Hz, 3 H, NMe), 3.62−3.77 (m, 2 H, 5-H, 1′-H), 4.41 (dd, *J* = 3.5, 8.4 Hz, 1 H, 2-H), 4.71 (br. d, *J* = 8.1 Hz, 1 H, N*H*Boc), 8.06 (br. s, 1 H, N*H*Me). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (C-2′), 25.6 (N−CH_3), 28.3 [$C(CH_3)_3$], 28.7 (C-4), 30.6 (C-3), 51.4 (C-1′), 79.0 (C-2), 79.7 [$C(CH_3)_3$], 85.7 (C-5), 156.8 (Boc−CO), 174.2 (CONH). − $C_{13}H_{24}N_2O_4$ (272.344): calcd. C 57.33, H 8.88, N 10.29; found C 57.08, H 8.55, N 10.07.

(2*R*,5*S*,1′*S*)-5-{1′-[(Benzoyl)amino]ethyl}tetrahydrofuran-2-carboxylic Acid Methyl Amide (34): A solution of methyl amide **33** (250 mg, 0.918 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (1.2 mL) and allowed to stir for 4 h at room temperature. The solution was concentrated in vacuo and residual TFA was removed by codistillation with toluene (2 × 10 mL). The crude ammonium salt was dissolved in THF (5 mL), saturated aqueous $NaHCO_3$ solution (2 mL) and water (2 mL). Benzoyl chloride (0.21 mL, 0.26 g, 1.8 mmol) was added at 0°C. The solution was allowed to stir for 1 h at room temperature before the organic solvent was removed in vacuo. The aqueous layer was extracted with EtOAc (2 × 15 mL), washed with saturated NaCl solution (20 mL) and dried with Na_2SO_4. Concentration in vacuo and column chromatography (EtOAc, 20 g of silica) yielded **34** × 0.3 H_2O (232 mg, 0.822 mmol, 90%) as white solid. Crystals of **34** × H_2O suitable for X-ray-structural analysis were obtained by slow evaporation of a solution of **34** in acetone. − m.p.* 86−88°C (acetone). − R_f = 0.21 (EtOAc). − $[\alpha]_D$ = +107.3, $[\alpha]_{578}$ = +112.8, $[\alpha]_{546}$ = +129.5, $[\alpha]_{436}$ = +233.9, $[\alpha]_{365}$ = +405.5 [*c* = 0.96* ($CHCl_3$); *T* = 20°C]. − IR (KBr): $\tilde{\nu}$ = 3480 cm^{-1} m, 3410 m (NH), 3310 s (NH), 3010 w, 2980/2940/2900 w (CH), 1665 s (C=O), 1630 s, 1575 m, 1560 m, 1495 w, 1445 w. − ^1H NMR (600 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.8 Hz, 3 H, 2′-H_3), 1.47 (m_c, 1 H, 4-H_A), 2.01 (dddd, *J* = 2.1, 5.4, 7.4, 12.4 Hz, 1 H, 4-H_B), 2.22 (dddd, *J* = 7.5, 8.6, 11.5, 12.6 Hz, 1 H, 3-H_A), 2.35 (ddd, *J* = 2.5, 7.5, 12.7 Hz, 1 H, 3-H_B), 2.90 (d, *J* = 4.8 Hz, 3 H, NMe), 3.87 (dt, *J* = 5.8, 9.0 Hz, 1 H, 5-H), 4.26 (ddq, *J* = 6.8, 8.9, 8.9 Hz, 1 H, 1′-H), 4.39 (dd, *J* = 2.6, 8.8 Hz, 1 H, 2-H), 6.50 (d, *J* = 8.9 Hz, 1 H, N^1′H), 7.44 (m_c, 2 H, 2 × *m*-ArH), 7.51 (m_c, 1 H, *p*-ArH), 7.82 (m_c, 2 × *o*-ArH), 8.10 (br. s, 1 H, N*H*Me). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7 (C-2′), 25.9 (N−CH_3), 28.7 (C-4), 30.7 (C-3), 50.4 (C-1′), 79.0 (C-2), 85.3 (C-5), 127.0, 128.5, 131.5 and 134.4 (phenyl), 168.3 and 174.3 (2 × CONH). − $C_{15}H_{20}N_2O_3 \times H_2O$* (293.34): calcd. C 61.21 H 7.53 N 9.52; found C 61.73 H 7.45 N 9.46. *Analytical data from **34** × H_2O.

Conformational Analysis of 34 in $CDCl_3$ Solution: Interproton distances of **34** were obtained from a 600-MHz NOESY experiment with a mixing time of 500 ms. The peak volumes were integrated on both sides of the diagonal. The integrals between geminal protons served as a reference for calibration.

Table 3. NOESY data from **34** in $CDCl_3$

	Crosspeak	Rel. integral	Distance [Å]
(1)	1′-H × 4-H_A	17.1	2.2
(2)	3-H_A × 5-H	7.0	2.6
(3)	1′-H × NHMe	10.4	2.4
(4)	3-H_A × 3-H_B	58.0	1.74
(5)	4-H_A × 4-H_B	84.2	reference

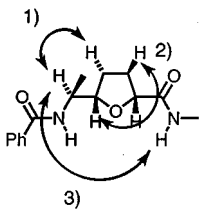


Figure 6. Selected NOESY crosspeaks found for **34** in $CDCl_3$ and used as input for the MD calculations

The calculations were done with "Insight Discover 97" on a Silicon Graphics workstation (Octane) using the forcefield *cvff*. Following a simulated annealing protocol (1000 K, 1.0 ps in steps of 1.0 fs and minimization of the frozen structures at 200 K steepest descent → conjugate gradient → BFGS) with a dieelectric constant of 1.00 and the distances 1−3 (Table 2) as experimental restraints (calculated value ± 0.4 Å) we found the structure displayed in Figure 5c) to be the minimum. The calculated structure was fully consistent with all NOESY-derived distances. The 600-MHz ^{1}H-NMR, 75-MHz APT spectrum and the aliphatic region of the NOESY spectrum of **34** in $CDCl_3$ solution are included as Supporting Information.

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