Preparation of 2,3,4-Trisubstituted Piperidines by a Formal Hetero-Ene Reaction of Amino Acid Derivatives†

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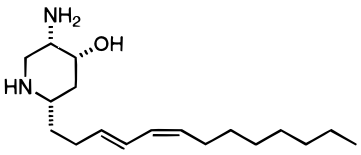
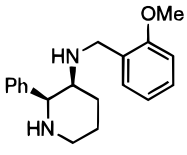
N-Benzyl- or *N*-tosyl-*N*-(4-methyl-3-pentenyl)amino aldehyde benzylimines, which are obtained from alanine, leucine, or phenylalanine methyl esters in five steps, can be cyclized diastereoselectively in the presence of Lewis acids to give 3-amino-2,4-dialkyl-substituted piperidines. The product distribution and diastereoselectivity depends on the type of Lewis acid and nitrogen-protecting group. Benzyl-protected imines give 2-alkyl-3-(benzylamino)-4-isopropenyl piperidines with $FeCl_3$ and 2-alkyl-3-(benzylideneamino)-4-isopropylpiperidines with $TiCl_4$. Tosyl-protected imines show a decreased level of selectivity. The relative configurations of the piperidines were established by NMR and X-ray crystal structure analyses. Iminium ion cyclization followed by two competitive ionic pathways, i.e. either proton elimination or hydride transfer are discussed for these reactions.

Introduction

The piperidine ring is one of the most abundant skeletons in natural products and synthetic compounds with biological activity.[1] Therefore a large amount of synthetic effort has been spent on the stereoselective construction of piperidines, for example the intramolecular nucleophilic substitution of imines,[2] hetero-Diels−Alder reactions using imines either as dienophiles[3] or as dienes,[4] addition of organometallic reagents to pyridines followed by photooxygenation,[5] Eschenmoser contraction,[6] electrophile- or Lewis acid-induced cyclizations of imines (or iminium ions).[7−10] The 3-aminopiperidine system has received increasing attention due to its significant pharmacological properties. For example, the piperidine alkaloid pseudodistomin A **1**, which was isolated from tunicates, exhibits calmodulin antagonistic activity, and therefore strongly depresses tumor growth in vitro.[11] The racemic compound CP-99,994 **2** was recently discovered as the most potent antagonist of substance P,[12] an undecapeptide, which acts as a neurotransmitter in the central and peripheral nervous system and is involved in smooth muscle contraction and regulation of immune responses.[13] During our ongoing



pseudodistomine A (**1**)



CP-99,994 (±)-(**2**)

investigations on Lewis acid-catalyzed hetero-ene reactions of prolinal-derived *N*-benzylimines toward α-amino-substituted indolizidines,[14] we were interested in whether this reaction type could be extended to the syntheses of 2,3,4-trisubstituted piperidines **3** bearing an amino group at C-3 (Scheme 1). In order to achieve that goal, imines **4** derived from various acyclic amino acids **5** had to be used as precursors. Although the cyclization can be formally considered as a hetero-ene reaction,[15,16] it was shown by previous mechanistic studies in the indolizidine

† Dedicated to Prof. Siegfried Hünig, Univ. Würburg, on the occasion of his 75th birthday.

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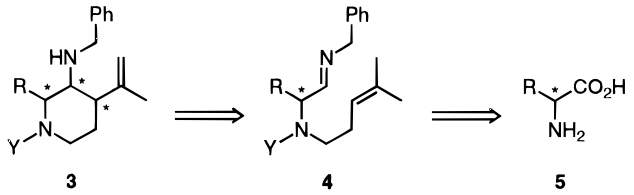
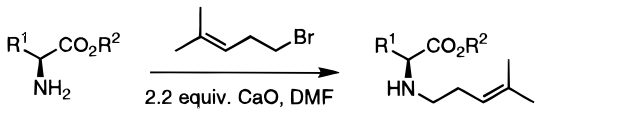
Scheme 1



Scheme 2



	6	R^1	R^2	yield of **7** [%]
Ala	**a**	Me	*n*-Bu	42
Leu	**b**	*i*-Bu	Me	73
Phe	**c**	Bn	Me	60

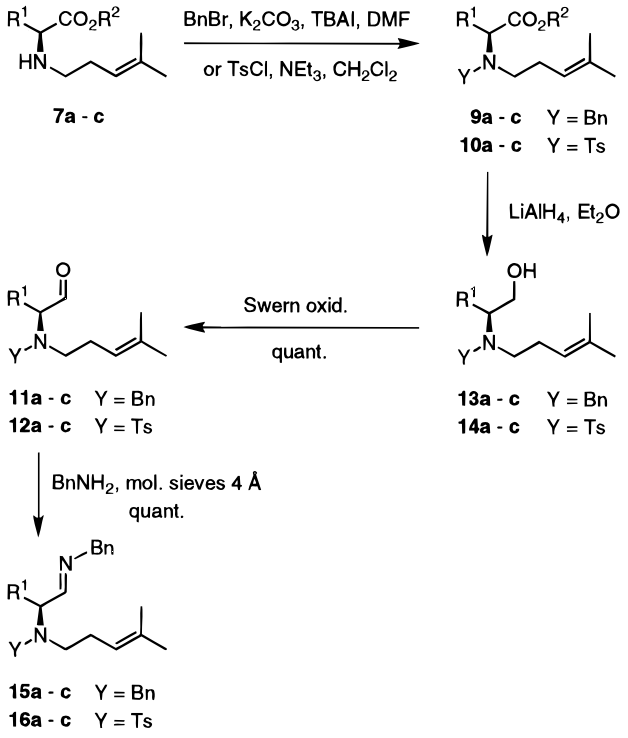
8 R = Bn 5 %

series that the reaction proceeds by a stepwise iminium ion cyclization followed by either proton elimination or intermolecular hydride migration depending on the type of Lewis acid used.[14] In this paper we describe the diastereoselective synthesis of 3-aminopiperidines **3**. In addition the acyclic precursor **4** presents the opportunity to study the influence of the electronic nature of the second nitrogen atom on the stereoselectivity of the cyclization. The results concerning the "mechanistic tuning" by proper choice of the protecting group Y are also presented here.

Results and Discussion

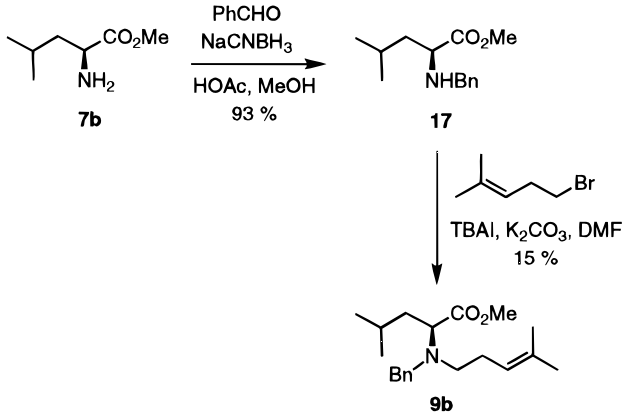
As was mentioned above the use of acyclic amino acids **5** for the imino ene cyclization required the introduction of a protecting group Y on nitrogen, which should be stable to Lewis acid conditions. For this purpose *N*-benzyl and *N*-tosyl groups were chosen. Thus, amino acid esters **6** were *N*-alkylated with 4-methyl-3-pentenyl bromide in DMF in the presence of CaO to afford monoalkylated esters **7** in moderate to good yields (Scheme 2).[17] In the case of the phenylalanine derivative **6c**, 5% of the transesterification product **8** was also obtained. The esters **7** were then treated with benzyl bromide under phase transfer conditions to give *N*-benzyl-protected compounds **9** or reacted with tosyl chloride/triethylamine to give *N*-tosyl derivatives **10** (Scheme 3). Reduction with $LiAlH_4$ of **9** and **10** gave the corresponding alcohols **13** and **14**, respectively. Swern oxidation[18] of **13** and **14** followed by treatment with benzylamine gave the desired imines **15** and **16**. It was anticipated that the yields could be improved by reversing the reaction sequence. Therefore *N*-benzylleucine methyl ester **17** was cleanly prepared by reductive amination (Scheme 4).[19] However this approach turned out to be unsuccessful, because the corresponding *N*-alkylation with K_2CO_3 gave **9b** in only 15% yield. When CaO or other bases were used, none of the desired product **9b** was obtained.

Scheme 3



	9, **10**	R^1	R^2	Y	yield [%]	**13**, **14**	yield [%]
Ala	**9a**	Me	*n*-Bu	Bn	84	**13a**	88
Leu	**9b**	*i*-Bu	Me	Bn	96	**13b**	97
Phe	**9c**	Bn	Me	Bn	90	**13c**	99
Ala	**10a**	Me	*n*-Bu	Ts	88	**14a**	100
Leu	**10b**	*i*-Bu	Me	Ts	100	**14b**	92
Phe	**10c**	Bn	Me	Ts	90	**14c**	100

Scheme 4



As outlined in Scheme 5 and Table 1, Lewis acid-catalyzed cyclization of *N*-benzylimines **15** gave two *cis*-configurated 2-alkyl-3-*(N*-benzylamino)-4-isopropenylpiperidines **18**, **19**, and two *cis*-configurated 2-alkyl-3-*(N*-benzylidene)amino-4-isopropylpiperidines **20**, **21**. Concerning both diastereoselectivity and yields, $FeCl_3$ and $TiCl_4$ showed the best results. $FeCl_3$ favors the formation of product **18** (entries 2, 7, 11), whereas $TiCl_4$ favors the formation of **20** (entries 6, 10, 14). Thus the same reversal of the constitution is observed in the piperidine synthesis as was already discovered in the indolizidine series.[14] However, contrary to the indolizidines, the relative configuration between the newly formed stereocenters at C-3 and C-4 in products **18**−**21** is always *cis*.

(17) Alanine butyl ester **6a** was used instead of the corresponding methyl ester for synthetic convenience, because the latter is both volatile and water soluble.

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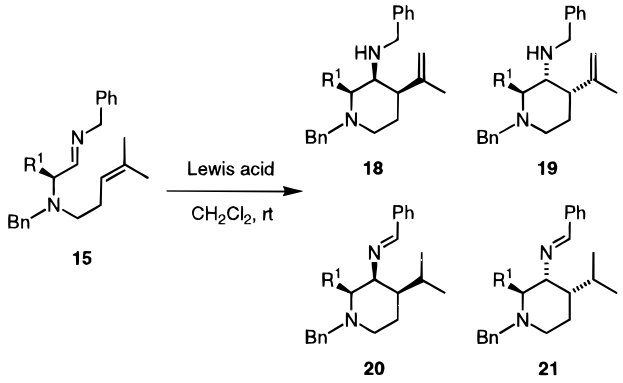
Table 1. Cyclization of *N*-Benzyl-Protected Imines 15 with Various Lewis Acids[a]

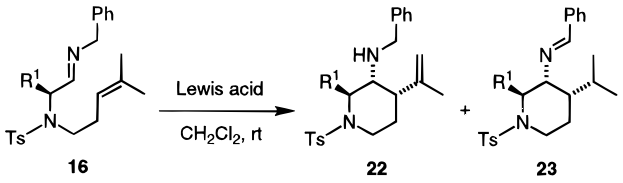
entry	amino acid	imine **15**	R^1	Lewis acid	time [h]	conversion [%]	ratio of products[b] **18**	**19**	**20**	**21**	yield[c] [%]	
1	Ala	**a**	Me	$SnCl_4$	16	62	27.5	–	72.5	–	–	
2		**a**	Me	$FeCl_3$	19	79	62.2	3.0	28.8	7.0	60	(**18a**)
3		**a**	Me	TMSOTf	144	5	90.4	–	9.4	–	–	
4		**a**	Me	$EtAlCl_2$	22	96	0.4	0.7	75.3	23.6	–	
5		**a**	Me	Et_2AlCl	18	98	–	–	82.7	17.3	58	(**20a**)
6		**a**	Me	$TiCl_4$	21	98	–	–	96.6	3.4	80	(**20a**)
7	Leu	**b**	*i*-Bu	$FeCl_3$	17	89	69.1	8.9	13.1	8.9	66	(**18b**)
8		**b**	*i*-Bu	$EtAlCl_2$	19	93	1.3	0.7	46.6	51.4	–	
9		**b**	*i*-Bu	Et_2AlCl	19	86	10.5	3.7	85.8	–	–	
10		**b**	*i*-Bu	$TiCl_4$	18	92	1.2	1.8	97.0	–	56	(**20b**)
11	Phe	**c**	Bn	$FeCl_3$	19	100	75.2	–	13.1	11.7	41	(**18c**)
12		**c**	Bn	$EtAlCl_2$	19	86	–	–	64.6	35.4	–	
13		**c**	Bn	Et_2AlCl	16	73	–	–	65.7	34.3	–	
14		**c**	Bn	$TiCl_4$	21	92	–	–	75.4	24.6	50, 17	(**20c**, **21c**)

[a] Reaction conditions: 2.5 equiv of Lewis acid, CH_2Cl_2, rt. [b] Conversion and product ratios were determined by capillary GC of the crude mixtures. [c] Yields of isolated products.

Scheme 5



Scheme 6



The results in Table 1 follow a general trend; an increase in diastereoselectivity occurs with the increasing size of the R^1 substituents (e.g. entries 2, 7, 11). In addition, monodentate Lewis acids such as TMSOTf gave only very low conversions (entry 3).

When *N*-tosylimines **16** were treated with Lewis acids, a mixture of 3-aminopiperidine **22** and the 3-iminopiperidine **23** (Scheme 6, Table 2) was obtained. Regardless of the amino acid, the ratio of **22**:**23** remained almost constant at 4:1 → 7:1 for both $TiCl_4$ (entries 4, 7, 10) and $FeCl_3$ (entries 1, 5, 8). When $EtAlCl_2$ was employed the diastereoselectivity was low (entries 3, 6, 9). Remarkably, both *N*-tosylpiperidines **22**, **23** were *trans*-configurated at C-2/C-3 and *cis*-configurated at C-3/C-4, whereas the corresponding *N*-benzylpiperidines **18**, **20** show an *all-cis*-configuration at C-2/C-3/C-4.

The relative configuration of the *N*-benzylpiperidines **18**, **20** was determined by 1D NOE experiments on the alanine-derived cyclization products **18a**, **20a** (Figure 1). The NOE enhancement between 2-H and 4-H in both isomers supports the axial orientation of the benzylamino (or benzylideneamino) group. The corresponding chair conformer with the benzylamino group equatorial should be strongly disfavored due to the 1,3-diaxial interaction between methyl and isopropenyl group.

Fortunately, X-ray crystal structure analyses were obtained for both phenylalanine-derived *N*-tosylpiperidines **22c**, **23c** (Figures 2, 3).[20] In addition to the relative configuration of C-2/C-3/C-4 being established, the structures revealed some important features. Both *N*-tosylpiperidines **22c**, **23c** adopt a chair conformation in the solid state in which the benzylamino (or benzylideneamino) group at C-3 and the benzyl group at C-2 are axial. The reason for this conformation might be that the number of favourable *gauche* interactions N−C−C−C and N−C−C−N is maximized.[21] The same stereoelectronic effect might be operating in the *N*-benzylpiperidine series. In addition, the dihedral angle N2−C20−C21−C26 is 173.0(0.2)° [N2−C20−C21−C22 10.4(0.3)°], suggesting that the phenyl ring and the imino group of the benzylideneamino moiety are slightly twisted by about 7−10°. This small twist, which can be explained by the preferred overlap of the aromatic π-system with the lone-pair on nitrogen, is in good agreement with X-ray crystal structure analyses and calculations by Bürgi and Dunitz on benzylidene aniline.[22]

With these results in hand, the mechanistic scheme previously proposed[14] must be modified for acyclic imines **15**, **16** in the following way (Scheme 7). Addition of the Lewis acid to imines **15**, **16** results in the formation of the iminium ions **24**, which cyclize to the tertiary cations **25**, **26** depending on the protecting group on nitrogen. Thus **25** is formed for Y = Bn, whereas **26** is formed for Y = Ts. The cation **25** (or **26** respectively) can undergo two competing pathways, i.e. proton elimination followed by cleavage of the Lewis acid (path A) and reprotonation to give **18** (or **22** respectively), or an intermolecular hydride migration followed by cleavage of the Lewis acid

(20) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(21) Ab initio calculations by Wiberg and Murcko on 1,2-dihaloethanes and 1,2-haloethanols showed that the *gauche* conformation of X−C−C−Y systems is about 1−2 kcal/mol more stable than the *antiperiplanar* conformation. A similar preference for the *gauche* orientation of the C−C−C−O and C−C−O−C fragment contributes to the anomeric effect in 2-methoxytetrahydropyran and related systems. (a) Wiberg, K. B.; Murcko, M. A. *J. Mol. Struct.* **1988**, *163*, 1. (b) Wiberg, K. B.; Murcko, M. A. *J. Phys. Chem.* **1987**, *91*, 3616. (c) Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821. For a general discussion of stereoelectronic effects and the anomeric effect see: (d) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 302. (e) Graczyk, P. P.; Mikolajczyk, M. *Top. Stereochem.* **1994**, *21*, 159.

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Table 2. Cyclization of *N*-Tosyl-Protected Imines 16 with Various Lewis Acids[a]

						ratio of products[b]			
entry	amino acid	imine **16**	R^1	Lewis acid	time [h]	**22**	**23**	yield[c] [%]	
1	Ala	**a**	Me	$FeCl_3$	62	87.8	12.2	–	
2		**a**	Me	Et_2AlCl	64	67.2	32.8	–	
3		**a**	Me	$EtAlCl_2$	64	73.2	26.7	–	
4		**a**	Me	$TiCl_4$	63	82.1	17.9	42	(**22a**)
5	Leu	**b**	*i*-Bu	$FeCl_3$	87	82.3	17.7	76	(**22b**)
6		**b**	*i*-Bu	$EtAlCl_2$	22	73.7	26.5	41, 12	(**22b**, **23b**)
7		**b**	*i*-Bu	$TiCl_4$	25	81.3	18.7	58	(**22b**)
8	Phe	**c**	Bn	$FeCl_3$	17	82.7	17.3	52	(**22c**)
9		**c**	Bn	$EtAlCl_2$	19	49.4	50.6	44	(**23c**)
10		**c**	Bn	$TiCl_4$	18	81.9	18.1	48	(**22c**)

[a] See Table 1, footnote a. [b] Ratio of products was determined by ^1H NMR of the crude products. [c] See Table 1, footnote c.

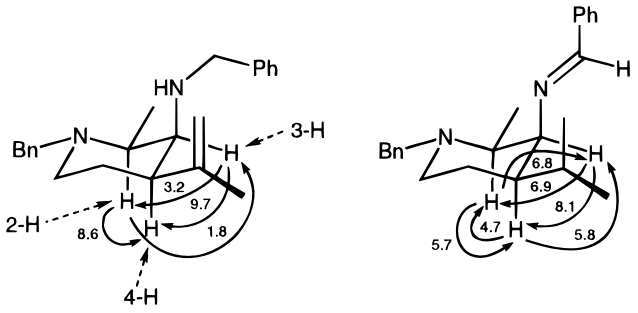


Figure 1.

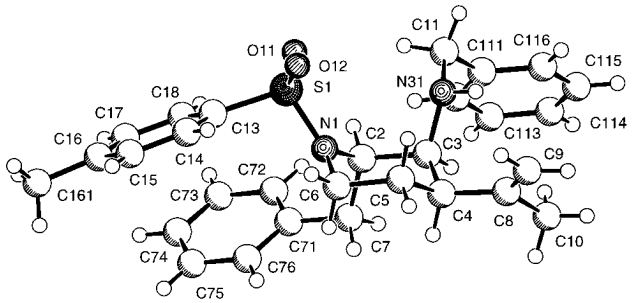


Figure 2. X-ray crystal structure of *N*-tosylpiperidine **22c**.

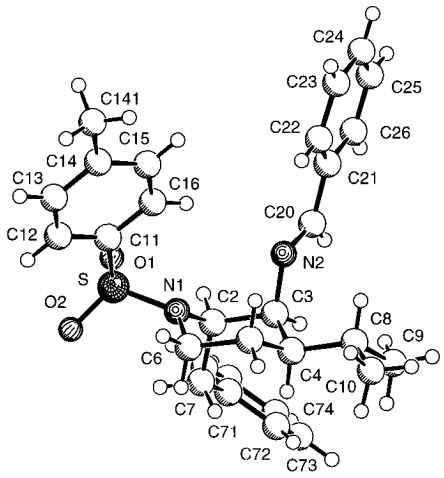


Figure 3. X-ray crystal structure of *N*-tosylpiperidine **23c**.

(path B) to give **20** (or **23** respectively). For the *N*-benzyl protected cation **25** the Lewis acid determines which pathway is preferred. $FeCl_3$ favors path A, whereas $TiCl_4$ favors path B. However in the case of the *N*-tosyl protected cation **26**, both $FeCl_3$ and $TiCl_4$ show a preference for path A. That means, that the Lewis acid-determined reaction pathways A and B are strongly influenced by the stereoelectronic effect of nitrogen. The hydride migration requires the presence of a second electron-rich nitrogen atom, which chelates the Lewis acid and thus reduces the electron withdrawal of the Lewis acid from the $N-CH_2Bn$ bond.[23,24] As soon as the donor ability of the piperidino nitrogen atom is decreased, e.g. by the electron-withdrawing tosyl group, the electron density of the $N-CH_2Bn$ bond is decreased as well and the hydride is less likely to be abstracted. The origin of the different stereocontrol in these acyclic imines **15**, **16** depends on the protecting group Y, but still remains unclear. Factors, such as forming chelate complexes whenever possible, maximizing the number of C–C–C–N (and C–C–N–C and N–C–C–N) *gauche* interactions may contribute to the observed results.

As mentioned above, the *N*-benzyl protected imines **15** were used initially because the electron density of the nitrogen atom is not decreased by the benzyl group, thus allowing a chelation-control of the diastereoselectivity. In addition, the *N*-benzyl group provides the opportunity to remove both protecting groups from the piperidines **18**–**21** simultaneously. Such a hydrogenation/hydrogenolysis sequence could be achieved by treatment with $PdCl_2$ in methanol under 1 atm of hydrogen. For example, if a (1:1) mixture of piperidines **18b**, **20b** was subjected to these conditions, the fully deprotected 2-isobutyl-3-amino-4-isopropylpiperidine (**27**) was obtained in almost quantitative yield (Scheme 8).[25,26]

In conclusion, a diastereoselective Lewis acid-catalyzed cyclization of acyclic amino acid-derived benzylimines toward 2,3,4-trisubstituted piperidines was developed. Although the reaction can be formally treated as a hetero-ene reaction, it probably follows two stepwise competetive pathways. The type of Lewis acid and the electronic nature of the nitrogen atom play a role in which pathway is preferred.

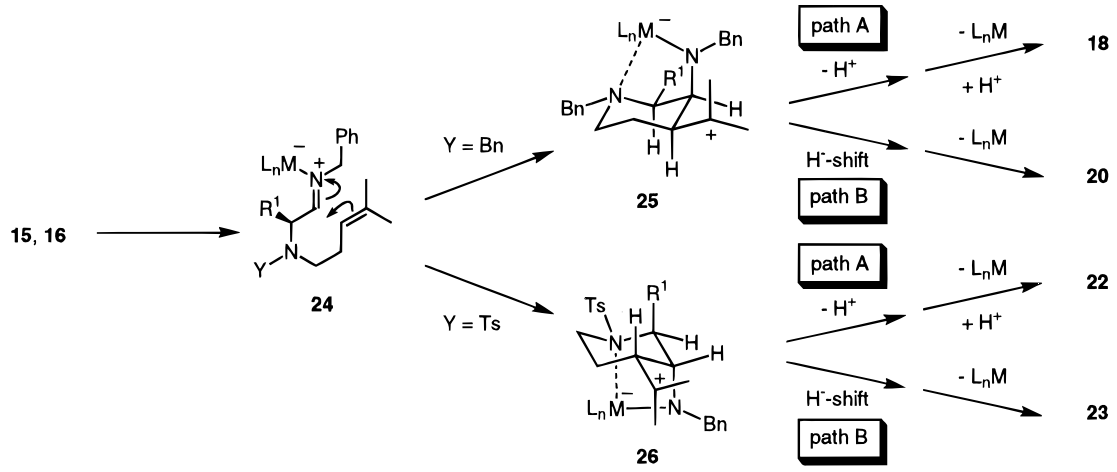
(23) In order to further support this hypothesis 3,3,7-trimethyl-6-octenal benzylimine was treated with various Lewis acids under the above mentioned conditions. In all cases *N*-benzyl-3,3-dimethyl-6-isopropenylcyclohexylamine (*trans*/*cis* ratios: $FeCl_3$ 98.3/1.7, $TiCl_4$ 97.2/2.8, $SnCl_4$ 97.4/2.6) was observed as the only product. No traces of the corresponding *N*-benzylidene-3,3-dimethyl-6-isopropylcyclohexylamine could be detected. See also: (a) Demailly, G.; Solladie, G. *Tetrahedron Lett.* **1977**, *18*, 1885. (b) Demailly, G.; Solladie, G. *J. Org. Chem.* **1981**, *46*, 3102.

(24) The question, why $TiCl_4$ and $FeCl_3$ favor different pathways, remains unsolved. One reason might be the stronger Lewis acidity of $TiCl_4$ compared to $FeCl_3$.

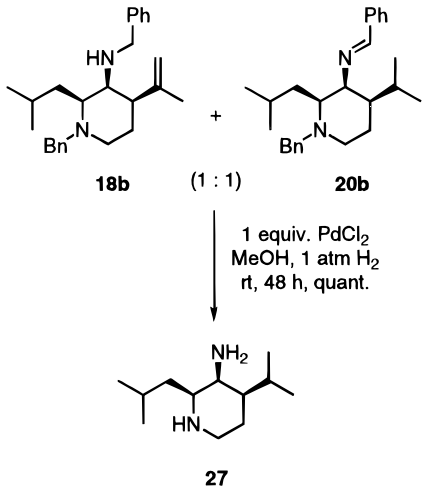
(25) *N*-Tosyl groups might be cleaved with sodium or lithium in liquid ammonia or with sodium naphthalenide: (a) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396. (b) Schultz, A. G.; Mc Closkey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493. (c) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(26) For a detailed discussion concerning removal of *N*-tosyl and *N*-benzyl groups see: Kocienski, P. J. *Protecting Groups*, Thieme Verlag: Stuttgart, 1994; p 212.

Scheme 7



Scheme 8



Experimental Section

General Experimental.[14b] All reactions were carried out under an argon atmosphere using standard Schlenk technique. Solvents were dried and deoxygenated by standard procedures. Analytical TLC was performed on precoated Merck Si 254 F plates (0.25 mm thickness) and visualized with a solution of phosphomolybdic acid in EtOH (5%, v/v). Flash chromatography was carried out with Merck silica gel 60 (230−400 mesh). NMR spectra were performed at 200 and 300 MHz (^{1}H), 50 and 75 MHz (^{13}C). Multiplets in ^{13}C NMR spectra were determined by DEPT and APT experiments. Melting points were uncorrected. Optical rotations: 1 dm-cells, 1 mL capacity, room temp. Mass spectra (EI and CI) were obtained at 70 eV, NH_3 was used as reactant gas for CI spectra. GC analysis: HP5 fused silica capillary column (ID 0.32 mm, length 25 m), a temperature program was run from 80 °C with 8 °C min^{-1} up to 280 °C. Amino acid methyl esters **6b**,**c** and *n*-butyl ester **6a** were obtained by esterification with thionyl chloride/methanol or *n*-butanol respectively according to literature procedures.[27] Signals in the ^{13}C NMR spectra of compounds **7b**, **10b**, **17** with * refer to a second rotamer.

General Procedure for the *N*-Alkylation of Amino Acid Esters 6. To a solution of ester **6** (20.0 mmol) in DMF (40 mL) were subsequently added CaO (2.47 g, 44.0 mmol) and 4-methyl-3-pentenyl bromide (3.26 g, 20.0 mmol), and the resulting suspension was heated at 60 °C for 62 h. After dilution with Et_2O (40 mL), Celite was poured under vigorous stirring into the mixture, which was then filtered through a short column (eluent: Et_2O). The combined filtrates and washings were poured into ice−water (200 mL). Extraction with Et_2O (4 × 100 mL), followed by drying over $MgSO_4$ and evaporation of the solvent yielded a yellow oil, which was purified by flash chromatography on SiO_2 (hexanes/ethyl acetate 10:1 → 4:1).

***(S)-N*-(4-Methyl-3-pentenyl)alanine Butyl Ester (7a):** 2.87 g (12.6 mmol, 42%) of a colorless oil (99% pure by GC, t_R = 16.4 min); $[\alpha]^{22}_D$ −10.6 (c = 1.00; $CHCl_3$); IR (film) 3323, 1734, 1177 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.03 (dd, J = 7.0 Hz, 1 H), 4.06 (dd, J = 6.5 Hz, 1 H), 3.26 (ddd, J = 7.0 Hz, 1 H), 2.54−2.37 (m, 2 H), 2.28−2.06 (m, 2 H), 1.63 (s, 3 H), 1.56 (s, 3 H), 1.49−1.02 (m, 5 H), 1.22 (d, J = 7.0 Hz, 3 H), 0.87 (dd, J = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.7, 133.4, 121.5, 64.3, 56.6, 47.7, 30.6, 28.8, 25.6, 19.0, 18.9, 17.7, 13.5; MS (EI) m/z 227 (M, 3), 158 (32), 126 (33), 102 (30), 83 (43), 56 (100); HRMS (CI) calcd for $C_{13}H_{25}NO_2 + H^+$ 228.1963, found 228.1982. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 10.08; N, 6.16. Found: C, 68.68; H, 10.14; N, 6.17.

***(S)-N*-(4-Methyl-3-pentenyl)leucine Methyl Ester (7b):** 3.31 g (14.6 mmol, 73%) of a colorless oil (98% pure by GC, t_R = 16.2 min); $[\alpha]^{22}_D$ −4.6 (c = 1.00; $CHCl_3$); IR (film) 3335, 1738, 1167 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.04 (dd, J = 7.1 Hz, 1 H), 3.67 (s, 3 H), 3.24 (dd, J = 7.2 Hz, 1 H), 2.57−2.37 (m, 2 H), 2.10 (ddd, J = 7.4 Hz, 2 H), 1.65 (d, J = 1.2 Hz, 3 H), 1.57 (d, J = 0.7 Hz, 3 H), 1.69−1.60 (m, 1 H), 1.45−1.39 (m, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.85 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.4, 133.3, 121.9, 121.5*, 60.1, 51.6, 51.2*, 48.0, 42.8*, 28.9, 25.7, 24.9, 22.6, 22.4, 22.3, 17.8, 17.7*; MS (EI) m/z 228 (M + H$^+$, 6), 212 (6), 168 (36), 158 (66), 130 (40), 102 (100), 83 (40); HRMS (DCI, NH_3) 228.1964 calcd for $C_{13}H_{25}NO_2$ + H$^+$, found 228.1897. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 10.08; N, 6.16. Found: C, 68.70; H, 10.05; N, 6.19.

***(S)-N*-(4-Methyl-3-pentenyl)phenylalanine Methyl Ester (7c):** 3.13 g (12.0 mmol, 60%) of a colorless oil (99% pure by GC, t_R = 21.4 min); $[\alpha]^{22}_D$ +14.2 (c = 1.00; $CHCl_3$); IR (film) 3324, 1737, 1454, 1200, 1169, 745, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27−7.10 (m, 5 H), 4.98 (dd, J = 7.2 Hz, 1 H), 3.58 (s, 3 H), 3.49 (dd, J = 7.0 Hz, 1 H), 2.90 (d, J = 7.0 Hz, 1 H), 2.59−2.36 (m, 2 H), 2.09 (ddd, J = 7.1 Hz, 2 H), 1.61 (d, J = 0.8 Hz, 3 H), 1.55 (s, 3 H), 1.50 (s, broad, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.8, 137.2, 133.3, 128.9, 128.2, 126.5, 121.4, 62.9, 51.3, 47.8, 39.5, 28.6, 25.5, 17.6; MS (EI) m/z 261 (M, 31), 202 (62), 192 (50), 178 (44), 165 (43), 98 (76), 91 (C_7H_7, 68), 83 (100); HRMS calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1724. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.54; H, 8.91; N, 5.28.

***(S)-N*-(4-Methyl-3-pentenyl)phenylalanine 4-Methyl-3-pentenyl Ester (8):** 330 mg (1.00 mmol, 5%) of a yellow oil (98% pure by GC, t_R = 27.1 min); $[\alpha]^{22}_D$ +11.8 (c = 1.00; $CHCl_3$); IR (film) 3324, 1733, 1454, 1170, 746, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25−7.13 (m, 5 H), 5.01−4.96 (m, 2 H), 3.97 (dd, J = 7.1 Hz, 2 H), 3.48 (dd, J = 7.1 Hz, 1 H), 2.94−2.89 (m, 2 H), 2.61−2.43 (m, 2 H), 2.21−2.05 (m, 5 H), 1.66 (d, J = 1.0 Hz, 3 H), 1.63 (d, J = 1.0 Hz, 3 H), 1.57 (s, 6

(27) Brenner, M.; Müller, H. R.; Pfister, R. W. *Helv. Chim. Acta* **1950**, *33*, 568.

H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 137.3, 134.5, 133.4, 129.1, 128.3, 126.6, 121.5, 119.1, 64.1, 63.0, 47.8, 39.7, 28.7, 27.5, 25.6, 17.7; MS (EI) *m*/*z* 330 (M + 1, 3), 290 (9), 260 (21), 202 (21), 178 (21), 91 (22), 83 (100), 55 (100); HRMS (DCI) calcd for $C_{21}H_{31}NO_2 + H^+$ 330.2433, found 330.2454. Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.70; H, 9.49; N, 4.20.

General Procedure for the *N*-Benzylation of Amino Acid Esters 7. To a solution of ester **7** (1.00 mmol) in DMF (1 mL) were sucessively added K_2CO_3 (138 mg, 1.00 mmol), tetrabutylammonium iodide (369 mg, 1.00 mmol), and then benzyl bromide (171 mg, 1.00 mmol). The resulting mixture was stirred at room temperature for 4 h and then heated to 100 °C for 48 h. The dark brown mixture was then diluted with toluene (10 mL) and azeotropically codistilled (3×) under high vacuum. The remaining brown solid was diluted in pentane (10 mL) and purified by flash chromatography over SiO_2 (hexanes/ethyl acetate 25:1).

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)alanine Butyl Ester (9a):** 1.39 g (4.37 mmol, 84%) of a colorless oil (98% pure by GC, t_R = 25.0 min); $[\alpha]^{22}_D$ −80.3 (*c* = 1.00; $CHCl_3$); IR (film) 1732, 1144, 730, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25−7.07 (m, 5 H), 4.95 (dd, *J* = 7.0 Hz, 1 H), 3.98 (dd, *J* = 6.5 Hz, 2 H), 3.75 (d, *J* = 14.3 Hz, 1 H), 3.52 (d, *J* = 14.3 Hz, 1 H), 3.38 (ddd, *J* = 7.2 Hz, 1 H), 2.59−2.33 (m, 2 H), 2.07−1.91 (m, 2 H), 1.53 (s, 3 H), 1.42 (s, 3 H), 1.58−1.37 (m, 2 H), 1.36−1.19 (m, 2 H), 1.15 (d, *J* = 7.2 Hz, 3 H), 0.82 (dd, *J* = 7.3 Hz, 3 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 174.1, 140.5, 132.2, 128.4, 128.0, 126.6, 122.2, 63.9, 57.5, 55.1, 50.7, 30.8, 27.5, 25.6, 19.2, 17.6, 15.4, 13.6; MS (EI) *m*/*z* 317 (M, 1), 274 (6), 248 (35), 220 (9), 192 (7), 117 (20), 91 (100), 83 (17); HRMS (CI) calcd for $C_{20}H_{31}NO_2$ 318.2433, found 318.2442. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.68; H, 9.81; N, 4.45.

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)leucine Methyl Ester (9b):** 280 mg (0.88 mmol, 96%) of a pale yellow oil (99% pure by GC, t_R = 25.2 min); $[\alpha]^{22}_D$ −97.2 (*c* = 1.00; $CHCl_3$); IR (film) 1735, 1147, 733, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.13 (m, 5 H), 5.02 (dd, *J* = 7.2 Hz, 1 H), 3.90 (d, *J* = 14.2 Hz, 1 H), 3.65 (s, 3 H), 3.50 (d, *J* = 14.2 Hz, 1 H), 3.38 (dd, *J* = 8.8, 6.4 Hz, 1 H), 2.63−2.54 (m, 1 H), 2.47−2.39 (m, 1 H), 2.17−1.96 (m, 2 H), 1.62 (d, *J* = 1.2 Hz, 3 H), 1.51 (s, 3 H), 1.78−1.37 (m, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.69 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 140.4, 132.3, 128.7, 128.1, 126.7, 122.3, 60.3, 55.2, 50.7, 39.0, 27.5, 25.6, 24.5, 23.1, 21.7, 17.7; MS (DCI, NH_3) *m*/*z* 318 (M + 1, 100), 261 (4), 248 (13), 190 (44), 170 (11); HRMS (DCI) calcd for $C_{20}H_{31}NO_2 + H^+$ 318.2433, found 318.2457. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.69; H, 9.87; N, 4.35.

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)phenylalanine Methyl Ester (9c):** 1.45 g (4.11 mmol, 90%) of a colorless oil (99% pure by GC, t_R = 30.1 min); $[\alpha]^{22}_D$ −102.9 (*c* = 1.00; $CHCl_3$); IR (film) 1733, 735, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17−6.96 (m, 10 H), 4.92 (dd, *J* = 7.1 Hz, 1 H), 3.87 (d, *J* = 14.4 Hz, 1 H), 3.55 (s, 3 H), 3.54 (dd, *J* = 6.9 Hz, 1 H), 3.47 (d, *J* = 14.4 Hz, 1 H), 2.98 (dd, *J* = 13.8, 7.5 Hz, 1 H), 2.80 (dd, *J* = 13.8, 7.5 Hz, 1 H), 2.66−2.32 (m, 2 H), 2.04−1.91 (m, 2 H), 1.55 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 139.8, 138.5, 132.3, 129.3, 128.5, 128.1, 127.9, 126.6, 126.1, 122.0, 64.0, 55.1, 50.9, 50.5, 36.1, 27.1, 25.6, 17.6; MS (EI) *m*/*z* 351 (M, 1), 282 (38), 260 (12), 222 (19), 91 (100), 83 (16); HRMS (DCI) calcd for $C_{23}H_{29}NO_2 + H^+$ 352.2276, found 352.2293. Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.98. Found: C, 78.62; H, 8.33; N, 4.02.

General Procedure for the *N*-Tosylation of Amino Acid Esters 7. A solution of ester **7** (1.00 mmol) and NEt_3 (111 mg, 1.10 mmol) in CH_2Cl_2 (2 mL) was treated with tosyl chloride (200 mg, 1.05 mmol) and then stirred at room temperature for 22 h. Evaporation of the solvent gave an oily residue, which was purified by flash chromatography on SiO_2 (hexanes/ethyl acetate 10:1).

***(S)*-*N*-(4-Methyl-3-pentenyl)-*N*-tosylalanine Butyl Ester (10a):** 1.74 g (4.57 mmol, 88%) of a colorless oil; $[\alpha]^{22}_D$ −52.1 (*c* = 1.00; $CHCl_3$); IR (film) 1738, 1341, 1175, 1154, 729, 655 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.3 Hz, 2 H), 7.23 (d, *J* = 7.3 Hz, 2 H), 4.99 (dd, *J* = 7.3 Hz, 1 H), 4.60 (ddd, *J* = 7.3 Hz, 1 H), 3.89 (dd, *J* = 6.5 Hz, 2 H), 3.24−2.92 (m, 2 H), 2.38 (s, 3 H), 2.46−2.11 (m, 2 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.40 (d, *J* = 7.3 Hz, 3 H), 1.53−1.19 (m, 4 H), 0.86 (dd, *J* = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5, 143.1, 137.3, 134.3, 129.4, 127.3, 120.1, 65.0, 55.3, 45.4, 30.3, 30.0, 25.6, 21.4, 19.0, 17.7, 16.9, 13.6; MS (EI) *m*/*z* 380 (M, 6), 312 (14), 280 (7), 225 (21), 198 (31), 155 (39), 91 (79), 83 (100), 56 (97); HRMS calcd for $C_{20}H_{31}NO_4S$ 381.1974, found 381.1982. Anal. Calcd for $C_{20}H_{31}NO_4S$: C, 62.96; H, 8.19; N, 3.67. Found: C, 62.78; H, 8.25; N, 3.66.

***(S)*-*N*-(4-Methyl-3-pentenyl)-*N*-tosylleucine Methyl Ester (10b):** 382 mg (1.00 mmol, quant) of a colorless oil; $[\alpha]^{22}_D$ −58.3 (*c* = 1.00; $CHCl_3$); IR (KBr) 1749, 1730, 1338, 1147, 731, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 5.00 (dd, *J* = 7.4 Hz, 1 H), 4.53 (dd, *J* = 9.1, 5.7 Hz, 1 H), 3.40 (s, 3 H), 3.22−3.11 (m, 1 H), 3.06−2.93 (m, 1 H), 2.49−2.35 (m, 1 H), 2.37 (s, 3 H), 2.23−2.09 (m, 1 H), 1.77−1.55 (m, 3 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 143.0, 136.8, 134.3, 129.2, 127.4, 120.2, 120.1*, 57.9, 51.7, 51.6*, 45.4, 39.4, 30.1, 25.5, 24.3, 22.7, 21.4, 17.7; MS (EI) *m*/*z* 381 (M, 3), 322 (22), 312 (37), 284 (35), 256 (87), 186 (39), 155 (68), 91 (100); HRMS (DCI) calcd for $C_{20}H_{31}NO_4S + H^+$, 382.2052 found 382.2071. Anal. Calcd for $C_{20}H_{31}NO_4S$: C, 62.96; H 8.19; N 3.67. Found: C, 63.08; H, 8.24; N, 3.90.

***(S)*-*N*-(4-Methyl-3-pentenyl)-*N*-tosylphenylalanine Methyl Ester (10c):** 1.71 g (4.11 mmol, 90%) of a colorless oil; $[\alpha]^{22}_D$ −40.6 (*c* = 1.00; $CHCl_3$); IR (film) 1742, 1455, 1436, 1342, 1221, 1204, 1161, 1092, 727, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2 H), 7.27−7.16 (m, 7 H), 5.01 (dd, *J* = 7.3 Hz, 1 H), 4.78 (dd, *J* = 8.2, 7.0 Hz, 1 H), 3.46 (s, 3 H), 3.34−3.12 (m, 3 H), 2.98−2.87 (dd, *J* = 13.9, 7.0 Hz, 1 H), 2.38 (s, 3 H), 2.37−2.12 (m, 2 H), 1.67 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9, 143.1, 137.0, 136.6, 134.4, 129.3, 129.0, 128.5, 127.3, 126.7, 119.9, 60.8, 51.8, 45.4, 36.8, 29.3, 25.5, 21.3, 17.7; MS (EI) *m*/*z* 415 (M, 11), 356 (19), 346 (33), 286 (88), 259 (26), 155 (71), 130 (69), 91 (100), 83 (51), 55 (86); HRMS calcd for $C_{23}H_{28}NO_4S$ (M − H^+) 414.1731, found 414.1739. Anal. Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.39; H, 7.21; N, 3.36.

General Procedure for $LiAlH_4$ Reduction of Esters 9, 10. To an ice-cooled suspension of $LiAlH_4$ (44 mg, 1.14 mmol) in Et_2O (1 mL) was added dropwise *N*-benzyl or *N*-tosyl ester **9** or **10**, respectively (1.04 mmol), in Et_2O (2 mL). Then the ice-bath was removed, and the resulting suspension was stirred at room temperature for 4 h and then carefully hydrolyzed by the addition of ethyl acetate (5 mL) and H_2O (2.5 mL). Stirring was continued for 1 h and then were added H_2O (50 mL) and Et_2O (50 mL). After separation of the organic layer, the aqueous layer was extracted with Et_2O (50 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated to yield an oil, which was used without further purification.

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)alaninol (13a):** 217 mg (0.88 mmol, 88%) of a colorless oil (98% pure by GC, t_R = 23.0 min); $[\alpha]^{22}_D$ +53.1 (*c* = 1.00; $CHCl_3$); IR (film) 3440, 1452, 1375, 1145, 1074, 1041, 1030, 731, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28−7.17 (m, 5 H), 4.96 (dd, *J* = 5.7 Hz, 1 H), 3.77 (d, *J* = 13.6 Hz, 1 H), 3.31 (d, *J* = 13.6 Hz, 1 H), 3.31 (m, 2 H), 3.18 (s, broad, 1 H), 2.98−2.87 (m, 1 H), 2.52−2.27 (m, 2 H), 2.07 (ddd, broad, *J* = 7.0 Hz, 2 H), 1.63 (d, *J* = 1.1 Hz, 3 H), 1.52 (s, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 132.9, 128.7, 128.2, 126.9, 122.0, 62.6, 55.3, 53.4, 48.4, 27.2, 25.5, 17.7, 8.8; MS (EI) *m*/*z* 229 (M − 1 − H_2O, 5), 216 (4), 205 (7), 178 (40), 160 (35), 146 (21), 134 (20), 91 (100), 83 (75); HRMS (DCI) calcd for $C_{16}H_{25}NO + H^+$ 248.2014, found 248.2020. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.69; H, 10.22; N, 5.43.

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)leucinol (13b):** 246 mg (0.85 mmol, 97%) of a colorless oil (99% pure by GC, t_R = 25.9 min); $[\alpha]^{22}_D$ +77.0 (*c* = 1.00; $CHCl_3$); IR (film) 3428, 1096, 1071, 1028, 730, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.17 (m, 5 H), 4.95 (dd, *J* = 7.1 Hz, 1 H), 3.77 (d, *J* = 13.6 Hz, 1 H), 3.71 (s, broad, 1 H), 3.43 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.32

(d, J = 13.6 Hz, 1 H), 3.26 (dd, J = 10.5, 10.5 Hz, 1 H), 2.82−2.75 (m, 1 H), 2.55−2.45 (m, 1 H), 2.40−2.32 (m, 1 H), 2.07 (ddd, broad, J = 6.9 Hz, 2 H), 1.63 (d, J = 1.2 Hz, 3 H), 1.51 (s, 3 H), 1.49−1.32 (m, 2 H), 1.09−1.00 (m, 1 H), 0.87 (d, J = 6.4 Hz, 3 H), 0.83 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 133.0, 128.8, 128.2, 126.9, 122.0, 61.1, 58.1, 53.7, 48.8, 34.3, 25.5, 25.3, 23.8, 22.0, 17.7; MS (DCI, NH_3) m/z 290 (M + 1, 100), 258 (1), 220 (7), 200 (1); HRMS (DCI) calcd for $C_{19}H_{31}NO + H^+$ 290.2484, found 290.2463. Anal. Calcd for $C_{19}H_{31}NO$: C, 78.84; H, 10.79; N, 4.84. Found: C, 78.83; H, 10.85; N, 4.76.

***(S)-N*-Benzyl-*N*-(4-methyl-3-pentenyl)phenylalaninol (13c):** 1.33 g (4.12 mmol, 99%) of a yellow oil (99% pure by GC, t_R = 32.5 min); $[\alpha]^{22}_D$ +23.0 (c = 1.00; $CHCl_3$); IR (film) 3442, 1495, 1454, 1039, 1029, 731, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23−6.99 (m, 10 H), 4.95 (dd, J = 7.0 Hz, 1 H), 3.83 (d, J = 13.5 Hz, 1 H), 3.36 (d, J = 13.5 Hz, 1 H), 3.35−3.22 (m, 2 H), 3.01−2.85 (m, 2 H), 2.62−2.33 (m, 3 H), 2.26 (dd, J = 13.0, 9.6 Hz, 1 H), 2.07 (ddd, J = 7.0 Hz, 2 H), 1.61 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.4, 139.2, 133.2, 128.8, 128.4, 128.3, 127.0, 126.0, 121.9, 62.2, 60.3, 53.9, 48.7, 31.9, 27.4, 25.6, 17.7; MS (EI) m/z 323 (M, 4), 305 (M − H_2O, 13), 292 (20), 254 (54), 232 (28), 117 (50), 91 (100), 83 (32); HRMS calcd for $C_{22}H_{27}N$ (M − H_2O) 305.2143, found 305.2136. Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.70; H, 9.10; N, 4.29.

***(S)-N*-(4-Methyl-3-pentenyl)-*N*-tosylalaninol (14a):** 1.13 g (3.64 mmol, quant) of a colorless oil; $[\alpha]^{22}_D$ +39.7 (c = 1.00; $CHCl_3$); IR (film) 3520, 1334, 1151, 1091, 656 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 5.02 (dd, J = 7.3 Hz, 1 H), 3.97−3.81 (m, 1 H), 3.61−3.44 (m, 3 H), 3.20−2.84 (m, 2 H), 2.36 (s, 3 H), 2.31 (ddd, J = 7.7 Hz, 2 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 0.85 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 137.6, 134.7, 129.5, 127.0, 120.1, 64.6, 55.5, 43.3, 30.2, 25.5, 21.3, 17.7, 14.2; MS (EI) m/z 312 (M + 1, 2), 280 (4), 242 (45), 155 (43), 91 (75), 83 (22), 70 (100); HRMS (CI) calcd for $C_{16}H_{25}NO_3S + H^+$ 312.1633, found 312.1584. Anal. Calcd for $C_{16}H_{25}NO_3S$: C, 61.71; H, 8.09; N, 4.50. Found: C, 61.78; H, 7.97; N, 4.53.

***(S)-N*-(4-Methyl-3-pentenyl)-*N*-tosylleucinol (14b):** 1.13 g (3.21 mmol, 92%) of a colorless oil; $[\alpha]^{22}_D$ +10.5 (c = 1.00; $CHCl_3$); IR (KBr) 3526, 1332, 1151, 1092, 756, 658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.6 Hz, 2 H), 7.24 (d, J = 8.6 Hz, 2 H), 5.00 (dd, J = 7.4 Hz, 1 H), 3.82−3.72 (m, 1 H), 3.51−3.43 (m, 2 H), 3.15−2.96 (m, 2 H), 2.37 (s, 3 H), 2.36−2.23 (m, 3 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 1.44−1.29 (m, 1 H), 1.25−1.06 (m, 2 H), 0.73 (d, J = 6.7 Hz, 3 H), 0.70 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2 137.8, 134.5, 129.5, 127.3, 120.1, 63.6, 58.2, 43.7, 38.6, 30.1, 25.5, 24.6, 22.5, 22.4, 21.4, 17.7; MS (DCI) m/z 371 (M + NH_4^+, 9), 354 (M + H^+, 100), 196 (93), 168 (100), 130 (100); HRMS (DCI) calcd for $C_{19}H_{31}NO_3S + H^+$ 354.2103, found 354.2121. Anal. Calcd for $C_{19}H_{31}NO_3S$: C, 64.55; H, 8.84; N, 3.96. Found: C, 64.46; H, 8.80; N, 3.92.

***(S)-N*-(4-Methyl-3-pentenyl)-*N*-tosylphenylalaninol (14c):** 1.59 g (4.12 mmol, quant) of a pale yellow oil; $[\alpha]^{22}_D$ −45.1 (c = 1.00; $CHCl_3$); IR (film) 3526, 1324, 1153, 1092, 700, 658 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2 H), 7.23−7.16 (m, 5 H), 7.01−6.96 (m, 2 H), 5.03 (dd, J = 6.0 Hz, 1 H), 4.12−3.85 (m, 1 H), 3.59−3.54 (m, 2 H), 3.33−3.02 (m, 2 H), 2.75−2.54 (m, 2 H), 2.37 (s, 3 H), 2.34 (ddd, J = 7.7 Hz, 2 H), 1.10 (s, broad, 1 H), 1.67 (d, J = 0.9 Hz, 3 H), 1.62 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 137.6, 134.7, 129.5, 128.9, 128.5, 127.2, 126.5, 120.1, 62.4, 62.0, 44.5, 36.2, 29.9, 25.6, 21.4, 17.8; MS (EI) m/z 387 (M, 9), 372 (15), 356 (22), 318 (37), 300 (35), 155 (91), 91 (100), 55 (99); HRMS (DCI) calcd for $C_{22}H_{29}NO_3S + H^+$ 388.1946, found 388.1936. Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.61. Found: C, 68.05; H, 7.51; N, 3.72.

Swern Oxidation of Alcohols 13, 14. A solution of DMSO (907 mg, 11.6 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 30 min at −45 °C to a solution of oxalyl chloride (737 mg, 5.80 mmol) in CH_2Cl_2 (8 mL). After stirring the mixture for 15 min a solution of the alcohol **13**, **14** (3.36 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 30 min, and the resulting mixture was stirred for another 8 h at −45 °C. Then NEt_3 (3 mL) was added over 30 min, and the mixture was warmed to room temperature and stirred for another 1 h. The mixture was subsequently washed with H_2O (3 × 50 mL), dried with Na_2SO_4, and concentrated to yield a crude oil (>95% pure by ^{13}C NMR), which was immediately used without further purification.

***(S)-N*-Benzyl-*N*-(4-methyl-3-pentenyl)alaninal (11a):** 246 mg (1.00 mmol, quant) of a yellow oil; $[\alpha]^{22}_D$ −28.3 (c = 1.00; $CHCl_3$); IR (film) 1730, 1452, 1376, 909, 735, 698 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 9.69 (s, 1 H), 7.38−7.18 (m, 5 H), 5.14 (dd, J = 7.2 Hz, 1 H), 3.66 (d, J = 14.1 Hz, 1 H), 3.42 (d, J = 14.1 Hz, 1 H), 3.13 (ddd, J = 6.9 Hz, 1 H), 2.54−2.42 (m, 2 H), 2.12 (ddd, broad, J = 7.2 Hz, 2 H), 1.72 (s, 3 H), 1.57 (s, 3 H), 1.04 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 203.1, 140.0, 132.4, 128.9, 128.5, 127.4, 122.4, 64.3, 55.8, 51.1, 27.8, 25.7, 17.7, 7.6; MS (EI) m/z 245 (M, 5), 216 (M − CHO, 26), 177 (23), 160 (20), 148 (38), 109 (36), 91 (100); HRMS calcd for $C_{16}H_{23}NO$ 245.1780, found 245.1774.

***(S)-N*-Benzyl-*N*-(4-methyl-3-pentenyl)leucinal (11b):** 761 mg (2.65 mmol, quant) of a brown oil; $[\alpha]^{22}_D$ +64.6 (c = 1.00; $CHCl_3$); IR (film) 1729, 736, 698 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 9.55 (s, 1 H), 7.29−7.06 (m, 5 H), 5.04 (dd, J = 7.1 Hz, 1 H), 3.64 (d, J = 14.0 Hz, 1 H), 3.50 (d, J = 14.0 Hz, 1 H), 3.02 (dd, J = 7.0 Hz, 1 H), 2.54−2.31 (m, 2 H), 2.09−1.98 (ddd, J = 7.2 Hz, 2 H), 1.74−1.13 (m, 3 H), 1.58 (s, 3 H), 1.46 (s, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.70 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 202.9, 140.3, 132.4, 129.0, 128.6, 127.5, 122.5, 66.5, 55.9, 51.1, 33.8, 28.2, 25.3, 22.8, 22.6, 17.7; MS (EI) m/z 287 (M, 3), 266 (8), 258 (M − CHO, 34), 218 (36), 190 (28), 176 (26), 91 (100), 83 (47); HRMS calcd for $C_{19}H_{29}NO$ 287.2249, found 287.2242.

***(S)-N*-Benzyl-*N*-(4-methyl-3-pentenyl)phenylalaninal (11c):** 1.31 g (4.08 mmol, quant) of a brown oil; $[\alpha]^{22}_D$ −115.8 (c = 1.00; $CHCl_3$); IR (film) 1730, 1453, 910, 742, 698 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 9.49 (s, 1 H), 7.16−7.02 (m, 10 H), 5.01 (dd, J = 7.1 Hz, 1 H), 3.62 (d, J = 14.0 Hz, 1 H), 3.41 (d, J = 14.0 Hz, 1 H), 3.31 (dd, J = 6.7, 7.1 Hz, 1 H), 3.00 (dd, J = 13.8, 7.1 Hz, 1 H), 2.61 (dd, J = 13.8, 6.0 Hz, 1 H), 2.51−2.37 (m, 2 H), 2.01 (ddd, J = 7.2 Hz, 2 H), 1.60 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 201.0, 140.0, 139.9, 132.5, 129.7, 128.9, 128.6, 128.5, 127.4, 126.3, 122.4, 70.3, 55.8, 51.0, 30.6, 28.0, 25.8, 17.7; MS (EI) m/z 321 (M, 2), 292 (M − CHO, 24), 252 (51), 224 (24), 202 (34), 91 (100), 83 (45); HRMS calcd for $C_{21}H_{26}N$ (M − CHO) 292.2065, found 292.2057.

***(S)-N*-(4-Methyl-3-pentenyl)-*N*-tosylalaninal (12a):**[28] 1.10 g (3.57 mmol, quant) of a pale brown oil; $[\alpha]^{22}_D$ −3.5 (c = 1.00; $CHCl_3$); IR (film) 1736, 1337, 1155, 1092, 815, 732, 658 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 9.46 (s, 1 H), 7.60 (d, J = 8.3 Hz, 2 H), 6.90 (d, J = 8.3 Hz, 2 H), 4.87 (dd, J = 7.2 Hz, 1 H), 4.66−4.57 (m, 1 H), 3.04−2.78 (m, 2 H), 2.10 (ddd, J = 7.5 Hz, 2 H), 2.00 (s, 3 H), 1.53 (s, 3 H), 1.43 (s, 3 H), 0.89 (d, J = 7.7 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 199.0, 142.9, 137.8, 134.1, 129.4, 127.0, 119.9, 61.7, 45.4, 28.9, 25.2, 20.7, 17.2, 11.7; MS (EI) m/z 309 (M, 5), 281 (6), 280 (M − CHO, 19), 240 (30), 212 (26), 155 (41), 91 (73), 83 (57), 55 (100); HRMS (CI) calcd for $C_{16}H_{23}NO_3S + H^+$ 310.1477, found 310.1435.

***(S)-N*-(4-Methyl-3-pentenyl)-*N*-tosylleucinal (12b):** 1.13 g (3.21 mmol, quant) of a yellow oil; $[\alpha]^{22}_D$ −115.4 (c = 1.00; $CHCl_3$); IR (film) 1735, 1339, 1156, 736, 659 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 9.34 (s, 1 H), 7.67 (d, J = 8.4 Hz, 2 H), 6.79 (d, J = 8.4 Hz, 2 H), 4.93 (dd, J = 7.3 Hz, 1 H), 4.25 (dd, J = 9.3, 4.6 Hz, 1 H), 3.15−3.07 (m, 1 H), 2.99−2.91 (m, 1 H), 2.25−2.09 (m, 2 H), 1.69−1.43 (m, 2 H), 1.35−1.18 (m, 1 H), 1.91 (s, 3 H), 1.56 (d, J = 1.0 Hz, 3 H), 1.50 (s, 3 H), 0.77 (d, J = 6.3 Hz, 3 H), 0.72 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 199.6, 143.2, 138.4, 134.6, 129.7, 127.6, 120.4, 65.0, 46.7, 36.1, 30.1, 25.6, 24.5, 23.0, 21.5, 21.1, 17.7; MS (EI) m/z 351 (M, 2), 322 (M − CHO, 8), 226 (27), 196 (10), 155 (35), 91 (100), 83 (73), 55 (100); HRMS calcd for $C_{19}H_{29}NO_3S$ 351.1868, found 351.1861.

***N*-(4-Methyl-3-pentenyl)-*N*-tosylphenylalaninal (12c):**[28] 1.58 g (4.12 mmol, quant) of a brown oil; $[\alpha]^{22}_D$ −1.5 (c =

(28) Unexpectedly, almost complete racemization of the N-tosyl-protected aldehydes **12a**,**c** occurred during Swern oxidation. This was determined by NMR as described in ref 29.

1.00; $CHCl_3$); IR (film) 1737, 1338, 1156, 1092, 737, 660 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 9.75 (d, J = 0.6 Hz, 1 H), 7.69 (d, J = 8.2 Hz, 2 H), 7.19−7.07 (m, 5 H), 6.93 (d, J = 8.2 Hz, 2 H), 5.04 (dd, J = 6.9 Hz, 1 H), 4.52 (dd, J = 7.6, 6.1 Hz, 1 H), 3.46 (dd, J = 14.5, 6.1 Hz, 1 H), 3.25−3.03 (m, 2 H), 2.82 (dd, J = 14.5, 8.0 Hz, 1 H), 2.31 (ddd, J = 7.6 Hz, 2 H), 1.96 (s, 3 H), 1.71 (s, 3 H), 1.62 (s, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 198.3, 143.2, 138.4, 137.9, 129.8, 129.4, 128.8, 127.6, 126.7, 120.3, 68.2, 46.6, 33.5, 29.3, 25.7, 17.7, 12.3; MS (EI) m/z 385 (M, 4), 356 (M − CHO, 19), 316 (25), 155 (37), 91 (100), 83 (99), 55 (93); HRMS (DCI) calcd for $C_{22}H_{27}NO_3S + H^+$ 386.1790, found 386.1796.

General Procedure for the Preparation of Benzylimines 15, 16. To a solution of aldehyde **15**, **16** (1.00 mmol) and *N*-benzylamine (1.00 mmol) in CH_2Cl_2 (10 mL) was added powdered, freshly activated 4 Å molecular sieves (500 mg), and the mixture was stirred at room temperature for 12−24 h. The mixture was then filtered via a fritted funnel through Celite, and the resulting filtrate was concentrated at room temperature to give an oil (>95% pure by ^{13}C NMR), which was used immediately without further isolation or purification.

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)alaninal Benzylimine (15a):** 335 mg (1.00 mmol, quant) of a pale yellow oil; $[\alpha]^{22}_D$ −59.4 (c = 1.00; $CHCl_3$); IR (film) 1667, 1494, 1452, 1375, 1028, 733, 698 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.70−7.67 (ddd, J = 3.2, 1.4, 1.4 Hz, 1 H), 7.39−7.06 (m, 10 H), 5.11 (dd, J = 7.1, 1.4 Hz, 1 H), 4.42 (s, 2 H), 3.67 (d, J = 14.1 Hz, 1 H), 3.46 (d, J = 14.1 Hz, 1 H), 3.49−3.42 (m, 1 H), 2.54−2.37 (m, 2 H), 2.14−2.05 (ddd, J = 7.1 Hz, 2 H), 1.63 (d, J = 1.0 Hz, 3 H), 1.47 (s, 3 H), 1.19 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 167.7, 141.1, 140.3, 132.0, 128.9, 128.6, 128.5, 128.1, 127.1, 126.9, 123.0, 65.0, 58.6, 55.3, 50.6, 27.9, 25.8, 17.8, 11.3; MS (EI) m/z 334 (M, 13), 263 (15), 188 (19), 173 (19), 147 (19), 120 (20), 91 (100), 83 (24); HRMS calcd for $C_{23}H_{30}N_2$ 334.2409, found 334.2394.

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)leucinal Benzylimine (15b):** 996 mg (2.65 mmol, quant) of a yellow oil; $[\alpha]^{22}_D$ −33.7 (c = 1.00; $CHCl_3$); IR (film) 1665, 1495, 1452, 733, 697 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.63 (d, J = 4.8 Hz, 1 H), 7.43−7.08 (m, 10 H), 5.15 (dd, J = 7.2 Hz, 1 H), 4.48 (s, 2 H), 3.73 (d, J = 14.0 Hz, 1 H), 3.67 (d, J = 14.0 Hz, 1 H), 3.46 (ddd, J = 4.8 Hz, 1 H), 2.59 (d, J = 7.5 Hz, 2 H), 2.19 (ddd, J = 7.5 Hz, 2 H), 1.92−1.71 (m, 1 H), 1.64 (s, 3 H), 1.64−1.45 (m, 2 H), 1.50 (s, 3 H), 0.87 (d, J = 6.1 Hz, 3 H), 0.80 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 166.1, 141.1, 140.4, 132.1, 129.1, 128.6, 128.4, 128.1, 127.1, 127.0, 123.0, 65.3, 60.8, 55.4, 50.7, 37.7, 28.1, 25.8, 25.1, 23.0, 22.9; MS (EI) m/z 376 (M, 3), 307 (19), 285 (4), 188 (17), 146 (26), 91 (100), 83 (23); HRMS calcd for $C_{26}H_{36}N_2$ 376.2878, found 376.2870.

***(S)*-*N*-Benzyl-*N*-(4-methyl-3-pentenyl)phenylalaninal Benzylimine (15c):** 1.67 g (4.08 mmol, quant) of a pale brown oil; $[\alpha]^{22}_D$ −35.4 (c = 1.00; $CHCl_3$); IR (film) 1666, 1495, 1453, 733, 697 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.61 (d, J = 3.8 Hz, 1 H), 7.32−7.08 (m, 15 H), 5.12 (dd, J = 7.4 Hz, 1 H), 4.36 (s, 2 H), 3.75 (d, J = 14.2 Hz, 1 H), 3.72−3.66 (m, 1 H), 3.62 (d, J = 14.2 Hz, 1 H), 3.25 (dd, J = 13.7, 7.9 Hz, 1 H), 2.89 (dd, J = 13.7, 5.8 Hz, 1 H), 2.69−2.59 (m, 2 H), 2.15 (ddd, J = 7.4 Hz, 2 H), 1.66 (s, 3 H), 1.50 (s, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 165.1, 140.8, 140.7, 140.1, 132.1, 128.9, 128.6, 128.4, 128.4, 128.1, 127.1, 126.9, 126.0, 122.9, 65.1, 64.7, 55.3, 50.6, 33.7, 28.1, 25.8, 17.8; MS (EI) m/z 410 (M, 20), 341 (28), 319 (24), 292 (23), 250 (36), 188 (31), 159 (47), 91 (100); HRMS calcd for $C_{29}H_{34}N_2$ 410.2722, found 410.2711.

(±)-*N*-(4-Methyl-3-pentenyl)-*N*-tosylalaninal Benzylimine (16a): 400 mg (1.00 mmol, quant) pale brown oil; IR (film) 1669, 1495, 1453, 1382, 1338, 1155, 1092, 814, 734, 699, 659 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.76 (d, J = 8.3 Hz, 2 H), 7.57−7.56 (m, 1 H), 7.19−7.01 (m, 5 H), 6.83 (d, J = 8.3 Hz, 2 H), 5.13 (dd, J = 7.2 Hz, 1 H), 4.62 (ddd, J = 6.9 Hz, 1 H), 4.31 (s, 2 H), 3.31−2.90 (m, 2 H), 2.41−2.18 (m, 2 H), 1.95 (s, 3 H), 1.61 (d, J = 0.9 Hz, 3 H), 1.49 (s, 3 H), 1.14 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 164.6, 142.8, 140.8, 138.9, 134.1, 129.7, 129.2, 128.6, 128.1, 127.4, 120.8, 64.5, 56.6, 51.4, 44.5, 25.7, 21.1, 17.7; MS (EI) m/z 398 (M, 3), 329 (6), 243 (21), 173 (43), 91 (100), 83 (61); HRMS calcd for $C_{23}H_{30}N_2O_2S$ 398.2028, found 398.2019.

***(S)*-*N*-(4-Methyl-3-pentenyl)-*N*-tosylleucinal Benzylimine (16b):** 1.41 g (3.21 mmol, quant) of a yellow oil; $[\alpha]^{22}_D$ −57.7 (c = 1.00; $CHCl_3$); IR (film) 1668, 1340, 1155, 733, 698, 659 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.80 (d, J = 8.3 Hz, 2 H), 7.51−7.48 (m, 1 H), 7.20−7.09 (m, 5 H), 6.79 (d, J = 8.3 Hz, 2 H), 5.04 (dd, J = 7.3 Hz, 1 H), 4.78−4.67 (m, 1 H), 4.29 (s, 2 H), 3.25−3.12 (m, 2 H), 2.69−2.31 (m, 2 H), 1.93 (s, 3 H), 1.98−1.72 (m, 2 H), 1.65−1.22 (m, 1 H), 1.61 (d, J = 0.7 Hz, 3 H), 1.57 (s, 3 H), 0.90 (d, J = 6.3 Hz, 3 H), 0.86 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 163.9, 142.7, 139.2, 139.0, 134.2, 129.5, 128.6, 128.1, 127.8, 127.1, 120.9, 64.7, 59.4, 45.2, 39.1, 30.8, 25.7, 24.6, 23.0, 22.2, 21.1, 17.8; MS (EI) m/z 440 (M, 1), 285 (7), 215 (28), 125 (17), 91 (100), 83 (35); HRMS (DCI) calcd for $C_{26}H_{36}N_2O_2S$ + H 441.2575, found 441.2560.

***(S)*-*N*-(4-Methyl-3-pentenyl)-*N*-tosylphenylalaninal Benzylimine (16c):** 1.95 g (4.12 mmol, quant) of a yellow oil; $[\alpha]^{22}_D$ −1.4 (c = 1.00; $CHCl_3$); IR (film) 1668, 1599, 1495, 1453, 1338, 1158, 1092, 735, 698, 660 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.64 (d, J = 8.2 Hz, 2 H), 7.21−7.03 (m, 11 H), 6.75 (d, J = 8.2 Hz, 2 H), 5.13−4.88 (m, 2 H), 3.50 (dd, J = 14.0, 8.0 Hz, 1 H), 3.27−3.17 (m, 2 H), 2.82 (dd, J = 14.0, 6.4 Hz, 1 H), 2.52−2.28 (m, 4 H), 1.94 (s, 3 H), 1.61 (d, J = 0.8 Hz, 3 H), 1.53 (d, J = 0.7 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 162.9, 142.7, 139.3, 138.8, 138.7, 134.2, 129.8, 129.6, 128.5, 128.2, 127.6, 127.1, 126.4, 120.8, 64.6, 62.5, 45.2, 35.9, 30.3, 25.7, 21.1, 17.8; MS (EI) m/z 474 (M, 2), 405 (17), 383 (12), 319 (22), 249 (42), 158 (30), 91 (100), 81 (39); HRMS calcd for $C_{29}H_{34}N_2O_2S$ 474.2341, found 474.2351.

***(S)*-*N*-Benzylleucine Methyl Ester (17).** To an ice-cooled solution of leucine methyl ester **7b** (795 mg, 5.48 mmol) in MeOH (2 mL) were added $NaCNBH_3$ (314 mg, 5.00 mmol) and freshly distilled benzaldehyde (636 mg, 6.00 mmol), and the pH was adjusted to 6 by careful addition of acetic acid. The resulting mixture was stirred at room temperature for 17 h, cooled with a MeOH/ice bath, and hydrolyzed by careful addition of K_2CO_3 (20 mL of a 40% solution in H_2O). Extraction with Et_2O (3 × 50 mL), washing of the combined organic layers with brine (2 × 50 mL), and drying over Na_2SO_4 yielded a colorless oil, which was purified by flash chromatography on SiO_2 (hexanes/ethyl acetate 7.5:1) to give 1.20 g (93%) of a colorless oil (99% pure by GC, t_R = 19.9 min); $[\alpha]^{22}_D$ −40.7 (c = 1.00, $CHCl_3$); IR (film) 3333, 1736, 1196, 1171, 1152, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.15 (m, 5 H), 3.73 (d, J = 12.9 Hz, 1 H), 3.63 (s, 3 H), 3.53 (d, J = 12.9 Hz, 1 H), 3.23 (dd, J = 7.3 Hz, 1 H), 1.77−1.65 (m, 2 H), 1.40 (dd, J = 7.3 Hz, 2 H), 0.83 (d, J = 6.7 Hz, 3 H), 0.77 (d, J = 6.7 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.4, 139.9, 128.2, 126.9, 59.2, 59.1*, 52.1, 51.5, 51.4 *, 42.8, 24.8, 22.7, 22.0; MS (EI) m/z 235 (M, 3), 176 (49), 106 (16), 91 (100); HRMS (DCI) calcd for $C_{14}H_{21}NO_2 + H^+$ 236.1651, found 236.1621. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.44; H, 8.90; N, 5.93.

Preparation of 9b from 17. To a solution of **17** (235 mg, 1.00 mmol) in DMF (1 mL) were sucessively added K_2CO_3 (138 mg, 1.00 mmol), tetrabutylammonium iodide (369 mg, 1.00 mmol), and then 4-methyl-3-pentenyl bromide (163 mg, 1.00 mmol), and the resulting mixture was stirred at room temperature for 4 h and then heated to 100 °C for 48 h. The reaction mixture was then diluted with toluene (10 mL) and azeotropically codistilled (3×) under high vacuum. The remaining brown solid was diluted in pentane (10 mL) and purified by flash chromatography on SiO_2 (hexanes/ethyl acetate 10:1 → 4:1) to give 48 mg (15%) of a pale yellow oil.

General Procedure for the Lewis Acid-Catalyzed Cyclization of Benzylimines 15, 16.[29] To an ice-cooled solution of imine **15**, **16** (1.00 mmol) were added dropwise in CH_2Cl_2 (28 mL) and the Lewis acid (2.50 mmol), and the mixture was stirred at room temperature (see Tables 1, 2) for 24 h. Then 2 N NaOH (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). After drying the combined organic

(29) The enantiomeric purity of the cyclization products **18a**−**c**, **20a**−**c**, **22a**,**b**, and **23b** (>98% ee) was determined by ^1H NMR (200 MHz) using 1 mol equiv of (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as shift reagent: Pirkle, W. H., Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.

layers with $MgSO_4$ and evaporation of the solvent, the crude products were purified by flash chromatography on SiO_2 (hexanes/ethyl acetate/NEt_3, 97:3:1).

(2*S*,3*S*,4*R*)-*N*-Benzyl-3-(*N*-benzylamino)-4-isopropenyl-2-methylpiperidine (18a): 200 mg (0.60 mmol, 60%) of a yellow oil; $[\alpha]^{22}_D$ +35.9 (*c* = 1.00; $CHCl_3$); IR (film) 3432, 1495, 734, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45−7.22 (m, 10 H, 2 x Ph), 4.85 (dd, *J* = 2.0, 0.6 Hz, 1 H, 9a-H), 4.77 (d, *J* = 0.6 Hz, 1 H, 9b-H), 4.04 (d, *J* = 13.5 Hz, 1 H, NHC*H*$_2$Ph), 3.86 (d, *J* = 11.1 Hz, 1 H, NC*H*$_2$Ph), 3.76 (d, *J* = 11.1 Hz, 1 H, NC*H*$_2$Ph), 3.09 (d, *J* = 13.5 Hz, 1 H, NHC*H*$_2$Ph), 2.81 (d, broad, *J* = 1.7 Hz, 2 H, 4a-H, 1-H), 2.44 (ddd, *J* = 6.5, 6.5, 2.0 Hz, 1 H, 2-H), 1.93−1.88 (m, 4 H, 6-H, 4b-H, 5a-H, NH), 1.78 (s, 3 H, 10-H), 1.37−1.28 (m, 1 H, 5b-H), 1.32 (d, *J* = 6.5 Hz, 3 H, 7-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.5 (C-8), 141.5 (C-1″), 139.8 (C-1′), 128.8, 128.4, 128.2, 128.0, 126.6, 110.3 (C-9), 62.8 (C-2), 60.6 (C-1), 57.5 (NH*C*H$_2$Ph), 55.5 (N*C*H$_2$Ph), 53.3 (C-4), 49.1 (C-6), 25.0 (C-5), 22.5 (C-10), 19.1 (C-7); MS (EI) *m*/*z* 334 (M, 25), 319 (6), 289 (24), 200 (35), 188 (41), 173 (40), 105 (35), 91 (100); HRMS calcd for $C_{23}H_{30}N_2$ 334.2409, found 334.2401. Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.54; H, 9.12; N, 8.34.

(2*S*,3*S*,4*R*)-*N*-Benzyl-3-(*N*-benzylamino)-3-isopropenyl-2-(2-methylpropyl)piperidine (18b): 329 mg (0.88 mmol, 66%) of a yellow oil; $[\alpha]^{22}_D$ +16.3 (*c* = 1.00; $CHCl_3$); IR (film) 3322, 1456, 738, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28−7.07 (m, 10 H, 2 x Ph), 4.77 (s, broad, 1 H, 12a-H), 4.63 (s, broad, 1 H, 12b-H), 3.68 (d, *J* = 13.3 Hz, 1 H, NHC*H*$_2$Ph), 3.56 (d, broad, *J* = 3.5 Hz, 2 H, NC*H*$_2$Ph), 3.45 (d, *J* = 13.3 Hz, 1 H, NHC*H*$_2$Ph), 2.89−2.81 (m, 1 H, 2-H), 2.55−2.41 (m, 2 H), 2.12 (d, broad, *J* = 13.8 Hz, 1 H), 1.87−1.63 (m, 1 H), 1.51 (s, 3 H, 13-H), 1.40−1.23 (m, 5 H), 0.77 (d, *J* = 6.0 Hz, 3 H, 9-H), 0.68 (d, *J* = 6.0 Hz, 3 H, 10-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.6 (C-11) 141.2, 140.0, 128.5, 128.2, 128.0, 126.7, 126.5, 110.2 (C-12), 58.7 (NH*C*H$_2$Ph), 56.3 (C-2), 55.3 (C-3), 52.1 (N*C*H$_2$Ph), 45.6 (C-6), 40.6 (C-4), 31.8 (C-8), 25.8 (C-5), 24.4 (C-7), 23.8 (C-9), 22.0 (C-10), 21.9 (C-13); MS (EI) *m*/*z* 376 (M, 5), 238 (14), 202 (17), 188 (18), 158 (20), 91 (100), 83 (23); HRMS calcd for $C_{26}H_{36}N_2$ 376.2878, found 376.2866. Anal. Calcd for $C_{26}H_{36}N_2$: C, 82.93; H, 9.64; N, 7.44. Found: C, 82.88; H, 9.60; N, 7.52.

(2*S*,3*S*,4*R*)-*N*-Benzyl-2-(2-benzyl)-3-(*N*-benzylamino)-3-isopropenylpiperidine (18c): 168 mg (0.41 mmol, 41%) of a yellow oil; $[\alpha]^{22}_D$ −15.7 (*c* = 1.00; $CHCl_3$); IR (film) 3317, 1494, 1453, 736, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39−7.16 (m, 8 H), 7.06−7.03 (m, 3 H), 6.94−6.89 (m, 2 H), 6.78−6.75 (m, 2 H, 3 x Ph), 4.78 (s, 1 H, 9a-H), 4.66 (s, 1 H, 9b-H), 3.75 (s, broad, 2 H, NC*H*$_2$Ph), 3.40 (d, *J* = 13.2 Hz, 1 H, NHC*H*$_2$Ph), 3.08 (d, *J* = 13.2 Hz, 1 H, NHC*H*$_2$Ph), 3.12−3.05 (m, 1 H, 2-H), 2.92 (dd, *J* = 13.1, 3.7 Hz, 1 H, 6eq-H), 2.70−2.60 (m, 3 H, NH, 7-H), 2.41 (s, broad, 1 H, 3-H), 2.32 (d, broad, *J* = 13.0 Hz, 1 H, 5eq-H), 1.97−1.75 (m, 2 H, 4-H, 6ax-H), 1.45 (d, broad, *J* = 13.0 Hz, 1 H, 5ax-H), 1.28 (s, 3 H, 10-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.4 (C-8), 140.6, 140.2, 139.3 (3 x C-i), 128.7, 128.5, 128.4, 128.3, 128.1, 127.7, 126.9, 126.2, 125.6 (3 x C-p), 109.9 (C-9), 61.8 (C-2), 59.9 (C-2), 58.8 (NH*C*H$_2$-Ph), 51.7 (C-3), 51.3 (N*C*H$_2$Ph), 46.2 (C-6), 40.2 (C-4), 28.4 (C-7), 24.6 (C-5), 21.4 (C-10); MS (EI) *m*/*z* 410 (M, 6), 319 (39), 303 (6), 224 (26), 214 (34), 200 (32), 91 (100), 83 (34); HRMS calcd for $C_{29}H_{34}N_2$ 410.2722, found 410.2711. Anal. Calcd for $C_{29}H_{34}N_2$: C, 84.83; H, 8.35; N, 6.82. Found: C, 84.80; H, 8.39; N, 6.81.

^1H and ^{13}C NMR signals of the minor isomers **19a**−**c**, **21a**,**b**, and **23a** from crude products were only incompletely visible.

(2*S*,3*S*,4*R*)-*N*-Benzyl-3-(*N*-benzylideneamino)-3-isopropyl-2-methylpiperidine (20a): 267 mg (0.80 mmol, 80%) of a yellow oil; $[\alpha]^{22}_D$ −58.3 (*c* = 1.00; $CHCl_3$); IR (film) 1642, 1451, 1384, 757, 732, 706, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1 H, HC═N), 7.67−7.64 (m, 2 H), 7.27−7.03 (m, 8 H), 3.80 (d, *J* = 14.0 Hz, 1 H, NC*H*$_2$Ph), 3.31 (d, *J* = 14.0 Hz, 1 H, NC*H*$_2$Ph), 3.12 (s, broad, 1 H, 3-H), 2.90 (ddd, *J* = 11.4, 3.5, 2.9 Hz, 1 H, 6a-H), 2.60 (dddd, *J* = 6.7, 6.7, 6.7, 2.1 Hz, 1 H, 2-H), 2.20 (ddd, *J* = 12.6, 12.6, 2.8 Hz, 1 H, 6b-H), 1.88 (dddd, *J* = 12.9, 2.4, 2.4, 2.4 Hz, 1 H, 5a-H), 1.33 (dd, *J* = 12.9, 2.4 Hz, 1 H, 5b-H), 1.17−1.02 (m, 2 H, 8-H, 4-H), 0.89 (d, *J* = 6.7 Hz, 3 H, 7-H), 0.67 (d, *J* = 6.4 Hz, 3 H, 9-H), 0.65 (d, *J* = 6.2 Hz, 3 H, 10-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (HC═N), 139.9 (C-1″), 136.6 (C-1′), 130.2, 129.2, 128.5, 128.3, 128.0, 126.5, 73.5 (C-3), 60.3 (C-2), 55.8 (N*C*H$_2$Ph), 52.9 (C-6), 49.2 (C-4), 28.7 (C-8), 23.3 (C-5), 20.4 (C-9), 19.9 (C-7), 18.4 (C-10); MS (EI) *m*/*z* 334 (M, 37), 291 (36), 231 (38), 202 (47), 188 (60), 91 (100), 83 (41); HRMS calcd for $C_{23}H_{30}N_2$ 334.2409, found 334.2401. Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.58; H, 9.10; N, 8.32.

(2*S*,3*S*,4*R*)-*N*-Benzyl-3-(*N*-benzylideneamino)-3-isopropyl-2-(2-methylpropyl)piperidine (20b): 282 mg (0.75 mmol, 56%) of a yellow oil; $[\alpha]^{22}_D$ −61.3 (*c* = 1.00; $CHCl_3$); IR (film) 1644, 1494, 1451, 1384, 1366, 758, 731, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1 H, HC═N), 7.86−7.82 (m, 2 H, 2″-H, 6″-H), 7.48−7.18 (m, 8 H), 4.05 (d, *J* = 14.8 Hz, 1 H, NC*H*$_2$Ph), 3.68 (d, *J* = 14.8 Hz, 1 H, NC*H*$_2$Ph), 3.42 (s, 1 H, 3-H), 3.15−3.06 (m, 2 H, 2-H, 6eq-H), 2.73 (dd, *J* = 12.5 Hz, 1 H, 6ax-H), 2.21−2.05 (m, 1 H), 1.82−1.79 (m, 1 H), 1.51−1.44 (m, 1 H), 1.37−1.31 (m, 4 H, 4-H, 5-H, 7-H, 8-H, 11-H), 1.00 (d, *J* = 6.7 Hz, 3 H, 12-H), 0.92 (d, *J* = 6.7 Hz, 3 H, 13-H), 0.90 (d, *J* = 6.0 Hz, 3 H, 9-H), 0.87 (d, *J* = 6.0 Hz, 3 H, 10-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4 (HC═N), 141.9, 136.7 (2 x C-i), 128.6, 128.1, 126.3, 71.8 (C-3), 62.3 (C-2), 51.8 (N*C*H$_2$-Ph), 50.9 (C-6), 49.9 (C-4), 39.8 (C-5), 29.1 (C-11), 24.1, 23.4, 22.4, 20.4, 19.8 (C-12, C-13, C-8, C-9, C-10), 19.8 (C-7); MS (EI) *m*/*z* 376 (M, 8), 333 (6), 319 (8), 272 (7), 238 (13), 91 (100); HRMS calcd for $C_{26}H_{36}N_2$ 376.2878, found 376.2866. Anal. Calcd for $C_{26}H_{36}N_2$: C, 82.93; H, 9.64; N, 7.44. Found: C, 82.94; H, 9.61; N, 7.51.

***N*-Benzyl-2-(2-benzyl)-3-(*N*-benzylideneamino)-3-isopropylpiperidine (20c, 21c):** 70 mg (0.17 mmol, 17%) of a yellow oil as first fraction (95.2% **21c** by GC, t_R = 31.3 min) and 205 mg (0.50 mmol, 50%) of a yellow oil as second fraction (98.7% **20c** by GC, t_R = 34.7 min). GC conditions: isotherm at 280 °C.

(2*S*,3*S*,4*R*)-Isomer 20c: $[\alpha]^{22}_D$ −8.0 (*c* = 1.00; $CHCl_3$); IR (film) 1642, 1494, 1451, 732, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.01 (s, broad, 1 H, HC═N), 7.77−7.73 (m, 2 H), 7.40−7.35 (m, 3 H), 7.26−7.06 (m, 10 H, 3 x Ph), 4.03 (d, *J* = 14.5 Hz, 1 H, NC*H*$_2$Ph), 3.70 (d, *J* = 14.5 Hz, 1 H, NC*H*$_2$Ph), 3.29 (s, broad, 1 H, 3-H), 3.23 (dd, *J* = 8.2 Hz, 1 H, 2-H), 3.01 (dd, *J* = 13.4, 3.4 Hz, 1 H), 2.88 (dd, *J* = 14.2, 6.2 Hz, 1 H), 2.63−2.47 (m, 2 H), 2.08−1.84 (m, 1 H), 1.66−1.47 (m, 1 H), 1.31−1.14 (m, 3 H), 0.71 (d, *J* = 5.8 Hz, 3 H, 9-H), 0.65 (d, *J* = 5.8 Hz, 3 H, 10-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.7 (HC═N), 141.0, 139.4, 136.5 (3 x C-i), 130.3, 129.3, 128.9, 128.6, 128.3, 128.1, 128.0, 126.4, 125.9, 69.9 (C-3), 65.6 (C-2), 53.4 (C-6), 51.5 (N*C*H$_2$Ph), 49.6 (C-4), 37.2 (C-7), 28.9 (C-8), 20.4 (C-5), 20.3 (C-9), 19.9 (C-10); MS (EI) *m*/*z* 410 (M, 3), 365 (4), 319 (37), 214 (29), 202 (15), 91 (100); HRMS calcd for $C_{29}H_{34}N_2$ 410.2722, found 410.2711. Anal. Calcd for $C_{29}H_{34}N_2$: C, 84.83; H, 8.35; N, 6.82. Found: C, 84.83; H, 8.40; N, 6.77.

(2*S*,3*R*,4*S*)-Isomer 21c: $[\alpha]^{22}_D$ −83.4 (*c* = 1.00; $CHCl_3$); IR (film) 1643, 732, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.86 (s, broad, 1 H, HC═N), 7.63−7.58 (m, 2 H), 7.27−6.94 (m, 13 H, 3 x Ph), 3.78 (s, broad, 1 H, NC*H*$_2$Ph), 3.76 (s, broad, 1 H, NC*H*$_2$Ph), 3.24 (s, broad, 2 H, 7-H), 3.20−2.45 (m, 3 H), 1.96 (ddd, *J* = 12.9, 12.9, 4.8 Hz, 2 H), 1.57−1.13 (m, 3 H), 0.78 (d, *J* = 6.4 Hz, 3 H, 9-H), 0.62 (d, *J* = 6.4 Hz, 3 H, 10-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.4 (HC═N), 140.8, 140.2, 137.0 (3 x C-i), 130.0, 129.1, 128.6, 128.4, 128.2, 128.0, 127.9, 126.5, 125.7, 67.4 (C-3), 66.9 (C-2), 59.3 (C-6), 46.8 (N*C*H$_2$Ph), 42.3 (C-4), 32.8 (C-7), 28.8 (C-8), 23.4 (C-5), 20.6 (C-9), 19.9 (C-10); MS (EI) *m*/*z* 410 (M, 4), 367 (3), 319 (41), 214 (31), 202 (14), 158 (24), 91 (100); HRMS calcd for $C_{29}H_{34}N_2$ 410.2722, found 410.2711. Anal. Calcd for $C_{29}H_{34}N_2$: C, 84.83; H, 8.35; N, 6.82. Found: C, 84.87; H, 8.38; N, 6.75.

(2*SR*,3*RS*,4*SR*)-3-(*N*-Benzylamino)-2-(2-methyl)-3-isopropenyl-*N*-tosylpiperidine (22a): 167 mg (0.42 mmol, 42%) of an orange oil; IR (film) 3397, 1456, 1336, 1156, 1095, 667, 657 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 2 H, 2′-H, 6′-H), 7.16−7.04 (m, 7 H, 3′-H, 5′-H, Ph), 4.74 (s, broad, 1 H, 9a-H), 4.51 (s, broad, 1 H, 9b-H), 4.28 (ddd, *J* = 6.8 Hz, 1 H, 2-H), 3.73 (d, *J* = 13.3 Hz, 1 H, HNC*H*$_2$Ph), 3.53 (dd, *J* = 12.6, 12.6 Hz, 1 H, H-6eq), 3.41 (d, *J* = 13.3 Hz, 1 H, HNC*H*$_2$-Ph), 3.67−3.36 (m, 1 H, 3-H), 3.27−2.94 (m, 2 H, 6ax-H, NH),

2.85 (ddd, J = 13.1, 13.1, 2.8 Hz, 1 H, 4-H), 2.52−2.22 (m, 1 H, 5eq-H), 2.21 (s, 3 H, tosyl-CH_3), 1.81−0.80 (m, 1 H, 5ax-H), 1.40 (s, 3 H, 10-H), 0.93 (d, J = 6.8 Hz, 3 H, 7-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.7 (C-8), 142.6, 140.2 (2 x C-i), 138.3, 129.3, 128.2, 128.1, 127.0, 126.7, 111.6 (C-9), 56.2 (C-2), 51.1 (HNCH_2Ph), 49.6 (C-3), 40.0 (C-4), 39.5 (C-6), 23.7 (C-5), 21.6 (Tosyl-CH_3), 21.3 (C-10), 14.7 (C-7); MS (EI) m/z 398 (M, 7), 375 (4), 360 (6), 321 (5), 243 (37), 200 (39), 155 (27), 138 (53), 91 (100); HRMS calcd for $C_{23}H_{30}N_2O_2S$ 398.2028, found 398.2019. Anal. Calcd for $C_{23}H_{30}N_2O_2S$: C, 69.31; H, 7.59; N, 7.03. Found: C, 69.52; H, 7.50; N, 7.11.

(2*S*,3*R*,4*S*)-3-(*N*-Benzylamino)-2-(2-methylpropyl)-3-isopropenyl-*N*-tosylpiperidine (22b): 334 mg (0.76 mmol, 76%) of a yellow oil; $[\alpha]^{22}_D$ +60.1 (c = 1.00; $CHCl_3$); IR (film) 3330, 1336, 1154, 1094, 736, 667, 663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2 H, 2′-H, 6′-H), 7.41−7.09 (m, 5 H, Ph), 7.16 (d, J = 8.3 Hz, 2 H, 3′-H, 5′-H), 4.86 (dd, J = 1.2, 1.5 Hz, 1 H, 12a-H), 4.60 (d, J = 1.4 Hz, 1 H, 12b-H), 4.37 (dd, broad, J = 6.7 Hz, 1 H, 2-H), 3.92 (d, J = 13.3 Hz, 1 H, NHCH_2Ph), 3.60 (d, J = 13.3 Hz, 1 H, NHCH_2Ph), 2.97 (ddd, J = 10.5, 10.5, 2.9 Hz, 1 H, 6eq-H), 2.61 (dd, J = 2.2 Hz, 1 H, 6ax-H), 2.35 (s, 3 H, tosyl-CH_3), 1.81−1.53 (m, 3 H, 3-H, 4-H, NH), 1.53 (s, 3 H, 13-H), 1.33−1.21 (m, 2 H, 7-H), 1.09−0.97 (m, 2 H, 8-H, 5eq-H), 0.94 (d, J = 6.6 Hz, 3 H, 9-H), 0.88 (d, J = 6.6 Hz, 3 H, 10-H), 0.78 (dd, J = 8.6 Hz, J = 6.7 Hz, 1 H, 5ax-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8 (C-11), 142.5, 140.3 (2 x C-i), 138.6, 129.2, 128.2, 127.3, 126.7, 111.4 (C-12), 68.6 (C-2), 58.7 (C-3), 54.4 (C-4), 52.7 (NCH_2Ph), 40.6 (tosyl-CH_3), 40.0 (C-6), 38.3 (C-5), 25.1 (C-8), 23.3 (C-7), 22.7 (C-9, C-10), 21.6 (C-13); MS (EI) m/z 440 (M, 6), 383 (4), 285 (19), 200 (33), 180 (53), 91 (100); HRMS calcd for $C_{26}H_{36}N_2O_2S$ 440.2497, found 440.2487. Anal. Calcd for $C_{26}H_{36}N_2O_2S$: C, 70.87; H, 8.23; N, 6.36. Found: C, 70.90; H, 8.25; N, 6.32.

(2*SR*,3*RS*,4*SR*)-2-(2-Benzyl)-3-(*N*-benzylamino)-3-isopropenyl-*N*-tosylpiperidine (22c): 247 mg (0.52 mmol, 52%) of a yellow oil; $[\alpha]^{22}_D$ −0.8 (c = 1.00; $CHCl_3$); IR (film) 3318, 1304, 1279, 1266, 1156, 1149, 1093, 816, 752, 716 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2 H, 2′-H, 6′-H), 7.19−6.99 (m, 10 H, 2 x Ph), 6.71−6.69 (m, 2 H, 3′-H, 5′-H), 4.70 (s, broad, 1 H, 9a-H), 4.48 (s, broad, 1 H, 9b-H), 4.35 (dd, J = 7.5 Hz, 1 H, 2-H), 3.66−3.50 (m, 1 H), 3.53 (d, J = 13.7 Hz, 1 H, HNCH_2Ph), 3.09 (d, J = 13.7 Hz, 1 H, HNCH_2-Ph), 2.97 (dd, J = 10.5 Hz, 1 H), 2.79 (s, broad, 1 H, 7a-H), 2.75 (s, broad, 1 H, 7b-H), 2.43 (s, broad, 1 H, 4-H), 2.30−2.19 (m, 1 H), 1.66 (ddd, J = 13.0, 13.0, 4.6 Hz, 1 H), 1.55−1.08 (m, 2 H), 1.14 (s, 3 H, 10-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.8 (C-8), 142.7, 140.0 (2 x C-i), 138.4, 129.4, 129.1, 128.7, 128.4, 127.9, 127.2, 126.5, 111.4 (C-9), 56.2 (C-2), 50.6 (HNCH_2Ph), 50.6 (C-3), 40.5 (C-7), 40.4 (C-4), 35.9 (C-6), 23.4 (C-5), 21.4 (tosyl-CH_3), 21.2 (C-10); MS (EI) m/z 474 (M, 14), 383 (20), 319 (28), 214 (67), 200 (57), 155 (29), 91 (100); HRMS calcd for $C_{29}H_{34}N_2O_2S$ 474.2341, found 474.2351. Anal. Calcd for $C_{29}H_{34}N_2O_2S$: C, 73.38; H, 7.22; N, 5.90. Found: C, 73.41; H, 7.23; N, 5.88.

(2*S*,3*R*,4*S*)-3-(*N*-Benzylideneamino)-3-isopropyl-2-(2-methylpropyl)-*N*-tosylpiperidine (23b): 52 mg (0.12 mmol, 12%) of a colorless oil; $[\alpha]^{22}_D$ +66.5 (c = 1.00; $CHCl_3$); IR (film) 1645, 1150, 715, 696, 656 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (s, 1 H, HC=N), 7.76 (d, J = 8.2 Hz, 2 H, 2″-H, 6″-H), 7.42−7.39 (m, 2 H), 7.25−7.24 (m, 3 H), 7.11 (d, J = 8.2 Hz, 2 H, 3″-H, 5″-H), 3.96 (dd, J = 7.3 Hz, 1 H, 2-H), 3.60 (dd, J = 13.5, 3.3 Hz, 1 H, 6eq-H), 3.38 (s, broad, 1 H, 3-H), 3.16 (dt, J = 13.3, 3.0 Hz, 1 H, 7b-H), 2.35 (s, 3 H, tosyl-CH_3), 1.85−1.07 (m, 7 H), 1.00 (d, J = 6.2 Hz, 3 H, 12-H), 0.97 (d, J = 6.2 Hz, 3 H, 13-H), 0.78 (dd, J = 6.4 Hz, 6 H, 9-H, 10-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.9 (HC=N), 142.2, 138.6 (2 x C-i), 136.3, 130.5, 129.2, 128.5, 128.4, 127.7, 68.6 (C-3), 58.7 (C-2), 41.6 (tosyl-CH_3), 40.8 (C-6), 39.6 (C-5), 28.3 (C-4), 24.9 (C-11), 23.9 (C-7), 22.8, 21.5 (C-8, C-9, C-10), 20.4 (C-12), 19.8 (C-13); MS (EI) m/z 440 (M, 7), 383 (15), 285 (95), 182 (100), 155 (32), 100 (55), 91 (96), 83 (30); HRMS calcd for $C_{26}H_{36}N_2O_2S$ 440.2497, found 440.2487. Anal. Calcd for $C_{26}H_{36}N_2O_2S$: C, 70.87; H, 8.23; N, 6.36. Found: C, 70.85; H, 8.27; N, 6.39.

(2*SR*,3*RS*,4*SR*)-2-(2-Benzyl)-3-(*N*-benzylideneamino)-3-isopropyl-*N*-tosylpiperidine (23c): 209 mg (0.44 mmol, 44%) of a yellow, amorphous solid; $[\alpha]^{22}_D$ −1.3 (c = 1.00; $CHCl_3$); IR (film) 1644, 1320, 1157, 1093, 696, 687, 656 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (s, broad, 1 H, HC=N), 7.58 (d, J = 8.3 Hz, 2 H, 2′-H, 6′-H), 7.47−7.42 (m, 2 H), 7.29−6.94 (m, 8 H, 2 x Ph), 6.98 (d, J = 8.3 Hz, 2 H, 3′-H, 5′-H), 4.02−3.94 (m, 1 H, 3-H), 3.64 (dd, J = 13.4, 2.6 Hz, 1 H, 2-H), 3.28 (m, 1 H), 3.24−3.11 (m, 1 H), 3.03−2.91 (m, 2 H), 2.19 (s, 3 H, tosyl-CH_3), 1.78 (ddd, J = 12.8, 12.8, 4.7 Hz, 1 H), 1.54−1.40 (m, 3 H), 0.73 (d, J = 6.6 Hz, 3 H, 9-H), 0.59 (d, J = 6.6 Hz, 3 H, 10-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.1 (HC=N), 142.3, 138.3, 136.2 (3 x C-i), 130.4, 129.4, 129.1, 128.6, 128.3, 128.2, 127.3, 126.5, 65.2 (C-3), 62.1 (C-2), 41.2 (C-4), 41.2 (C-7), 37.3 (C-6), 28.1 (C-8), 23.9 (C-5), 21.4 (tosyl-CH_3), 19.7 (C-9), 17.7 (C-10); MS (EI) m/z 474 (M, 7), 459 (8), 383 (69), 319 (35), 266 (33), 227 (51), 91 (100), 83 (48); HRMS calcdfor $C_{29}H_{34}N_2O_2S$ 474.2341, found 474.2351. Anal. Calcd for $C_{29}H_{34}N_2O_2S$: C, 73.38; H, 7.22; N, 5.90. Found: C, 73.39; H, 7.30; N, 5.92.

(2*S*,3*S*,4*R*)-3-Amino-4-isopropyl-2-(2-methylpropyl)piperidine (27). To a (1:1) mixture of piperidines **18b** and **20b** (400 mg, 1.06 mmol) in MeOH (10 mL) was added under argon $PdCl_2$ (188 mg, 1.06 mmol), and the remaining mixture was presaturated (3×) with H_2 and then stirred under H_2 at 1 atm for 48 h at room temperature. The mixture was filtered through Celite via a fritted funnel, and the solvent was evaporated to yield 210 mg (quant) of a pale yellow oil; $[\alpha]^{22}_D$ −3.7 (c = 1.00; MeOH); IR (film) 3381, 1469, 1027 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 5.26 (s, 3 H), 3.68−3.62 (m, 1 H), 3.51−3.14 (m, 2 H), 3.08−2.95 (m, 1 H), 2.14−2.01 (m, 1 H), 1.87−1.52 (m, 5 H), 1.28−1.20 (m, 1 H), 0.99−0.89 (m, 9 H) 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (50 MHz, CD_3OD) δ 54.1, 50.8, 40.9, 38.7, 37.8, 28.3, 25.6, 23.1, 22.6, 21.6, 21.1, 20.7; MS (EI) m/z 198 (M, 41), 170 (64), 141 (60), 128 (66), 114 (81), 99 (81), 83 (81), 56 (100). In order to obtain correct elemental analysis the amine **27** was converted to the corresponding hydrobromide. Anal. Calcd for $C_{12}H_{27}N_2Br$: C, 51.61; H, 9.75; N, 10.03. Found: C, 51.68; H, 9.71; N, 10.14.

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Supporting Information Available: ^{13}C NMR (APT) spectra of compounds **11a**−**c**, **12a**−**c**, **15a**−**c**, and **16a**−**c** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, see any current masthead page for ordering information.

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