Synthesis of Peptidosulfinamides and Peptidosulfonamides: Peptidomimetics Containing the Sulfinamide or Sulfonamide Transition-State Isostere

Wilna J. Moree,† Gijs A. van der Marel, and Rob J. Liskamp*,‡

Department of Organic Chemistry, Gorlaeus Laboratories, University of Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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Synthetic routes are described toward the preparation of α- as well as β-substituted aminoethanesulfinyl chlorides, starting from either an aldehyde or from an amino acid derivative. The sulfinyl chlorides are used as building blocks for the preparation of homochiral α- or β- substituted sulfinamide and sulfonamide transition-state isosteres. The methodology has been applied to the synthesis of peptidosulfonamide peptidomimetics such as a hapten needed for the generation of antibodies and potential HIV protease inhibitors. In addition, the β-substituted aminoethanesulfinyl chlorides were used as building blocks for the preparation of a tetrapeptidosulfonamide, which can be considered as a biopolymer mimetic, employing a repetition of a cycle of three reactions: coupling of the sulfinyl chloride to the N-terminus of the growing peptidosulfonamide, oxidation to the sulfonamide, and deprotection of the N-terminus.

Introduction

Transition-state isosteres of the hydrolysis of the amide bond are very important in the design of protease inhibitors[1] with the aim to develop therapeutic agents as well as for the generation of catalytic antibodies.[2] For these purposes a wide variety of transition-state isostere-containing peptides have been described.[1-3] Surprisingly, peptides containing the sulfinamide or sulfonamide transition-state isosteres, *i.e.*, peptidosulfinamides and peptidosulfonamides, respectively (Figure 1), had never been used in approaches toward the development of, *e.g.*, HIV protease inhibitors or catalytic antibodies. Another emerging important application is the replacement of all amide bonds in a peptide by a transition-state isostere leading to "unnatural biopolymers" or "biopolymer mimetics",[4] which can be used for the development of libraries of peptidosulfonamide peptidomimetics.[4]

In previous papers, we have described a route for the synthesis of peptides containing an aminoethanesulfonyl (tauryl: Tau) or aminoethanesulfinyl (hypotauryl) moiety in order to mimic the hydrolysis transition-state of the Gly-Xxx bond,[5,6] in which "Xxx" is, *e.g.*, Pro and Phe (Figure 1). In addition, we found that sulfonamide mimics of other peptide bonds, such as the Phe-Pro bond, were accessible by alkylation of the α-carbon atom next to the sulfonamide moiety.[6] Unfortunately, this alkylation procedure turned out to be limited to tertiairy sulfonamides such as Tau-Pro-containing peptides (Scheme 1). α-Substituted secondary sulfonamides as well as α-substituted sulfinamides mimicking peptide bonds other than that in a Xxx-Pro peptide were not accessible by this route.[7]

† Present address: Scripps Research Institute, Department of Chemistry, 10666 North Torrey Pines Road, La Jolla, CA 92037.

‡ Present address: Utrecht Institute for Pharmaceutical Sciences, Department of Pharmaceutics, Section of Organic and Medicinal Chemistry, Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands. E-mail: R.M.J.Liskamp@FAR.RUU.NL.

* To whom correspondence should be addressed.

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(4) (a) Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303–1305. (b) Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 633–636.

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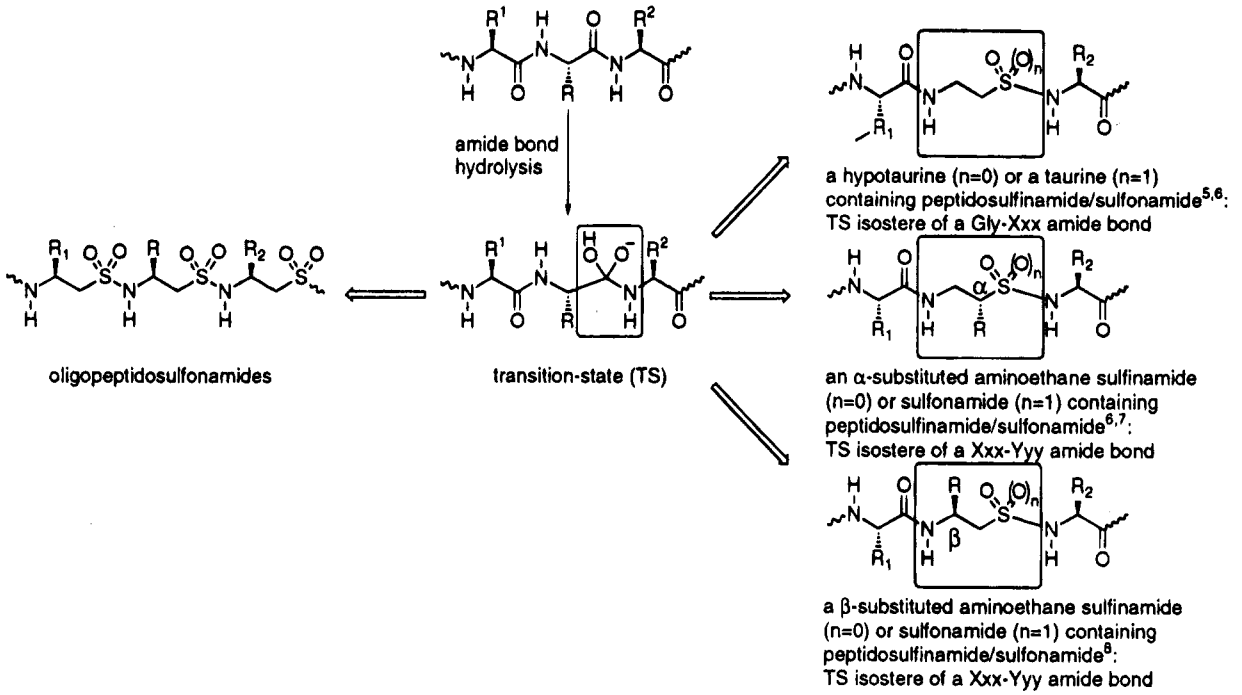
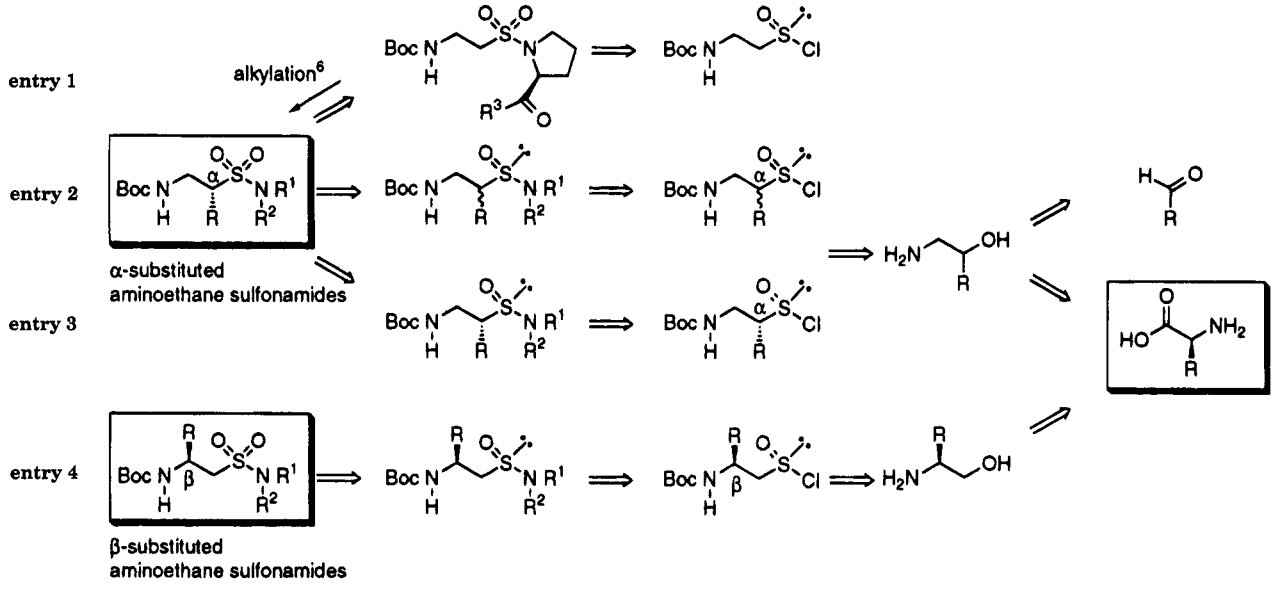


Figure 1. Sulfinamide (n = 0) and sulfonamide (n = 1) transition-state (TS) isosteres of the amide bond incorporated into peptidosulfinamides and peptidosulfonamides.

Scheme 1. Retrosyntheses of α- and β-substituted sulfonamides: via alkylation (entry 1),[6] going back to an aldehyde (entry 2) or to an α-amino acid (entries 3 and 4)



In order to be able to prepare sulfonamide-containing peptidomimetics of, in principle, every possible dipeptide we have complemented the α-alkylation route (Scheme 1) with two additional routes for the synthesis of α-substituted sulfonamides. These routes (retrosyntheses: Scheme 1) feature an α-substituted sulfinyl chloride as a crucial synthon which was derived from an amino alcohol, which in turn was accessible starting from either an aldehyde or an α-amino acid.

α-Amino acids could also be used as the starting material for the synthesis of β-substituted aminoethanesulfinyl chlorides (retrosynthesis: Scheme 1), which were applied as building blocks for various peptidosulfinamides and peptidosulfonamides containing a β-substituted aminoethanesulfinamide and -sulfonamide moiety.[8]

These methods were applied to the syntheses of hapten **38** (Scheme 3), which was used for the generation of antibodies and of sulfonamide-based potential HIV protease inhibitors **44**–**46** based on the structure of Ro 31-8959(*R*) **47** synthesized by Hoffmann-LaRoche.[9] In the structure of these sulfonamide analogs the hydroxyethylamine moiety in the Roche compound is replaced by the

(7) When Pro is another amino acid, a sulfonamide NH is present as part of the transition-state isostere. This NH is deprotonated much easier than the α-carbon adjacent to the sulfonamide. Therefore, the second deprotonation necessary for α-alkylation becomes less likely or at least more difficult. Indeed, we found that treatment with excess of base under various conditions only gave rise to N-alkylated products, in low yields, in addition to mostly starting material.

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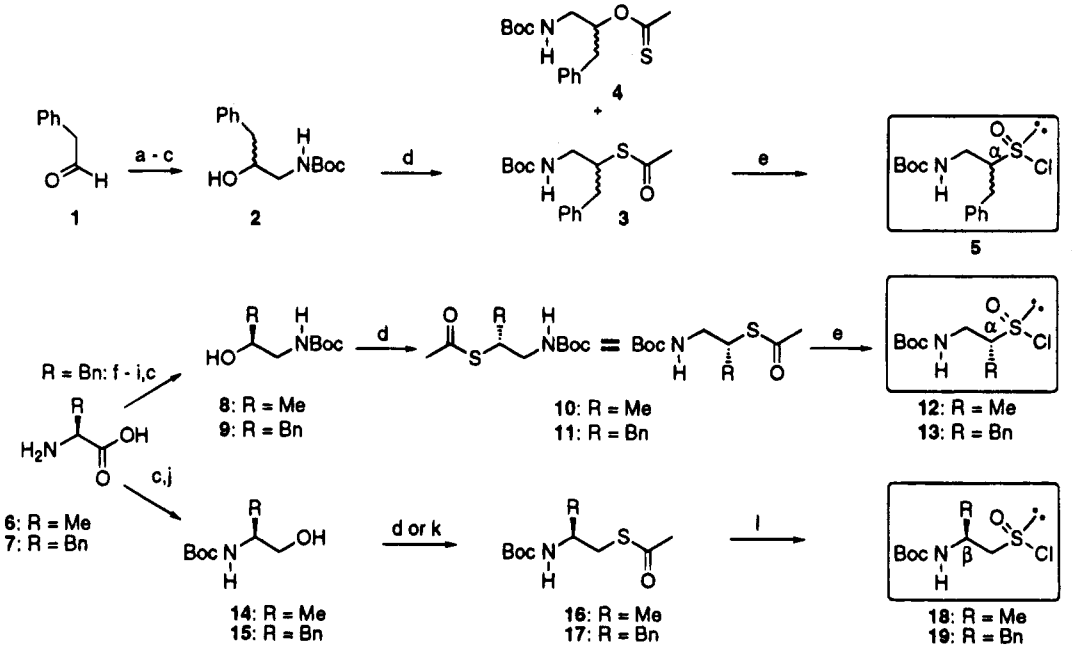
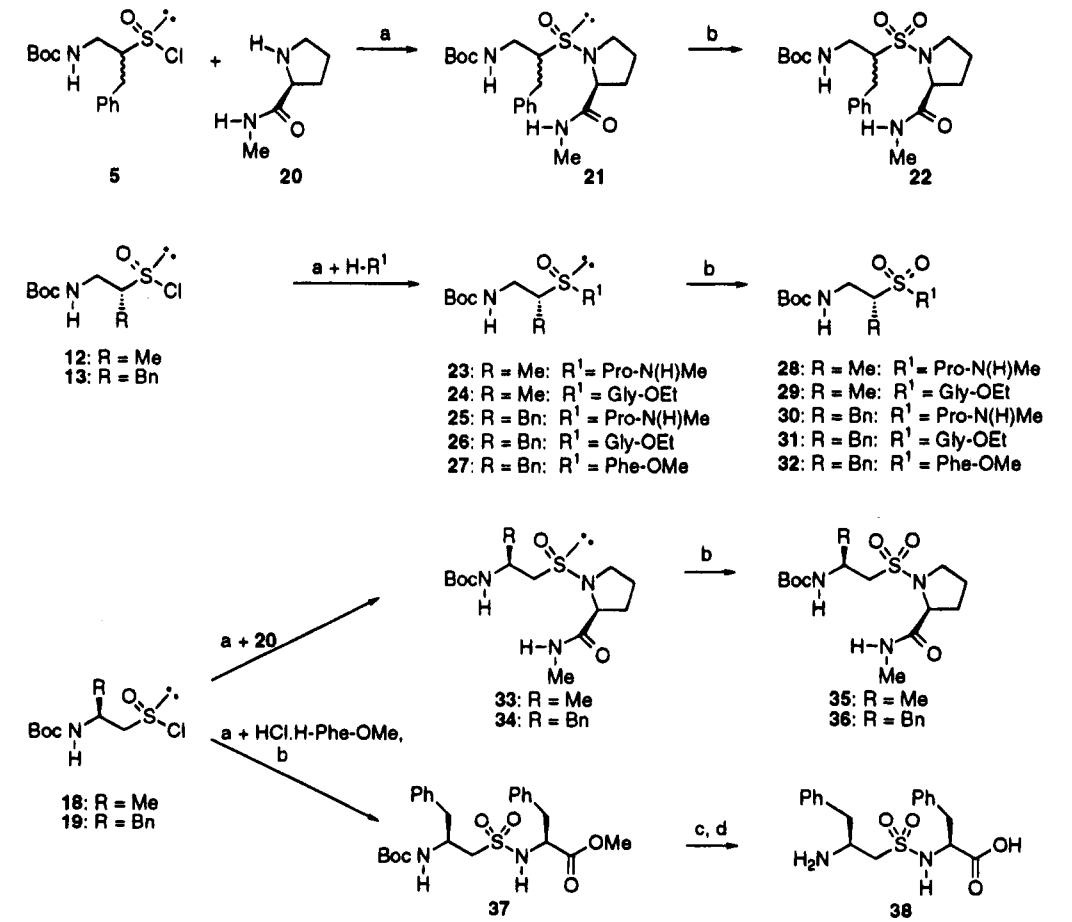
Scheme 2[a]



[a] Key: (a) TMSCN, ZnI_2; (b) $LiALH_4$; (c) Boc_2O; (d) DIAD or DEAD, Ph_3P, MeC(O)SH; (e) SO_2Cl_2, Ac_2O; (f) $NaNO_2$, H_2SO_4; (g) $SOCl_2$, MeOH; (h) NH_3, MeOH; (i) BH_3.THF Δ; (j) (1) Et_3N, ethyl chloroformate, (2) $NaBH_4$, MeOH; (k) (1) MsCl, Et_3N, (2) Cs_2CO_3, MeC(O)SH; (l) 2 equiv of Cl_2, 1 equiv of Ac_2O.

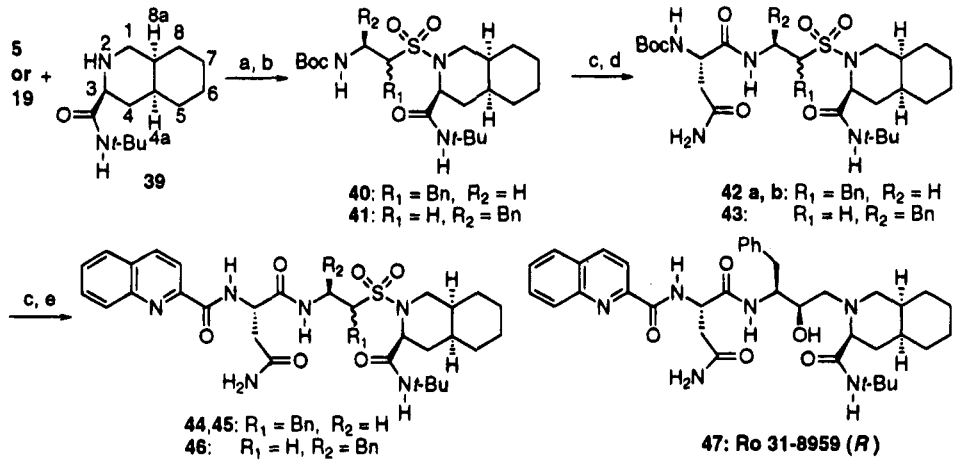
Scheme 3[a]



[a] Key: (a) NMM; (b) $NaIO_4$, $RuCl_3$ aq; (c) LiOH, MeOH, H_2O; (d) (1) TFA, CH_2Cl_2, (2) ion exchange chromatography (Dowex H^+).

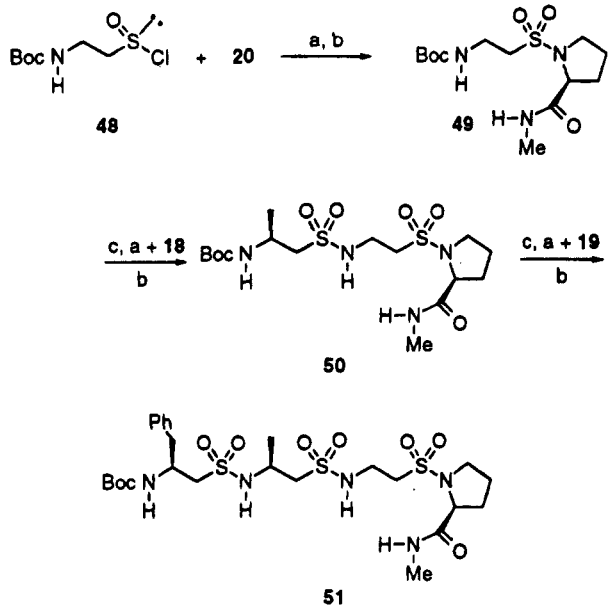
sulfonamide moiety (Scheme 4). The last application concerned construction of the peptidosulfonamide **51** (Scheme 5). The synthesis of such a biopolymer mimetic in solution is a necessary exercise before extending the methodology to a solid-phase synthesis approach in view of the preparation of combinatorial libraries. Combinatorial libraries of biopolymer mimetics, such as the peptidosulfonamides, offer a promising opportunity to obtain new lead compounds for drug development. Biopolymer mimetics may also lead to new insights in

Scheme 4[a]



[a] Key: (a) NMM; (b) $NaIO_4$, $RuCl_3$ aq; (c) (1) TFA, CH_2Cl_2, (2) Dowex OH^-; (d) Boc-Asn-OH, DCC, HOBt, NMM; (e) quinaldic acid, DCC, HOBt, NMM.

Scheme 5[a]



[a] Key: (a) NMM; (b) $NaIO_4$, $RuCl_3$ aq; (c) (1) TFA, CH_2Cl_2, (2) Dowex OH^-.

protein structure and folding. The number of examples of biopolymer mimetics described in the literature[4a] is still limited, although several types have been suggested.[4b] The sulfonamide moiety possesses some features, which may make it especially attractive for incorporation into a biopolymer mimetic. It is more resistant to degradation by proteases and more flexible than the amide bond. It is also more polar, and its more acidic N–H may give rise to stronger hydrogen bonds.

Results and Discussion

As was described earlier[5] the sulfinyl chloride **48** leading to taurine-containing peptides (Figure 1, Scheme 5) can be easily obtained by treatment of *N,N'*-bis(*tert*-butoxycarbonyl)cystamine with chlorine in the presence of acetic anhydride. The corresponding α- and β-substituted sulfinyl chlorides (Scheme 1 and 2) were directly accessible from the corresponding thioacetates. In the route where we start from an aldehyde to prepare the amino alcohol necessary for synthesis of the thioacetate, we chose phenylacetaldehyde (**1**) as starting material, since this would ultimately lead to sulfinamide and sulfonamide mimics of Phe-Xxx bonds, which are of interest in the development of potential HIV protease inhibitors. Thus, phenylacetaldehyde (**1**) was converted to the amino alcohol in 51% yield by treatment with (trimethylsilyl)cyanide in the presence of ZnI_2 followed by reduction with $LiAlH_4$[10,11] (Scheme 2). Protection of the amino function with a Boc group afforded the Boc-amino alcohol **2** in 89% yield, which was predominantly (82% yield) converted to the thioacetate **3** in a Mitsunobu displacement reaction using diisopropyl azodicarboxylate (DIAD), triphenylphosphine, and thioacetic acid.[12] The thioester **4** was formed as a byproduct in 13% yield. Thioacetate **3** was subsequently treated with sulfuryl chloride[13] in the presence of acetic anhydride to afford the sulfinyl chloride **5**, which was used without further purification. Surprisingly, treatment of thioacetate **3** with Cl_2 in the presence of acetic anhydride as was employed for the synthesis of unsubstituted[5,6] and β-substituted sulfinyl chlorides[8] (*vide infra*), resulted in a mixture of both the sulfinyl chloride and the sulfenyl chloride.[14]

Although in principle it is possible to carry out the above-described route using enantiopure amino alcohols, which are directly accessible from aldehydes using, *e.g.*, the enzyme oxynitrilase,[15] we thought that using, *e.g.*, amino acids as a chiral pool for homochiral amino alcohols might also be an attractive alternative. In order to obtain an amino alcohol with the substituent on the proper position, the amino group in the amino acid precursor has to be converted to a hydroxyl, whereas the carboxyl function has to be converted to an amine. This can be achieved by diazotization, aminolysis, and reduction (Scheme 2). To illustrate this approach (*S*)-phenylalanine (**7**) was transformed into (*S*)-phenyllactic acid

(10) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914–917.
(11) Bol, K. M.; Liskamp, R. M. J. *Tetrahedron* **1992**, *48*, 6425–6438.
(12) Volante, R. P. *Tetrahedron Lett.* **1984**, *22*, 3119–3122.
(13) Youn, J.-H.; Herrmann, R. *Synth.* **1987**, 72–73.
(14) Thioacetate **3** can be converted to only the sulfenyl chloride using sulfuryl chloride in the absence of acetic anhydride. Upon treatment of this with H-Pro-N(H)Me the sulfenamide is formed. Attempted oxidation using either $NaIO_4/RuCl_3$ or $NCS/NaHCO_3$ did not afford sulfinamide **21** or the sulfonamide **22** but instead resulted in decomposition.
(15) See, e.g.: Effenberger, F.; Ziegler, T.; Förster, S. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 458. Niedermeyer, U.; Kula, M.-R. *Ibid.* **1990**, *29*, 386. Brussee, J.; Dofferhoff, F; Kruse, C. G.; Van der Gen, A. *Tetrahedron* **1990**, *46*, 1653.

with retention of configuration using diazotation.[16] Treatment with thionyl chloride in methanol gave (*S*)-methylphenyl lactate. Aminolysis of the methylester with saturated ammonia in MeOH afforded the corresponding amide in quantitative yield. Reduction of the phenyllactamide using $LiAlH_4$ in THF or $NaBH_4$ in dioxane was very slow and afforded low yields of the amino alcohol, whereas BH_3[17] in THF as a reducing agent gave the highest yield of the amino alcohol with the highest optical purity. Although the amino alcohol could be isolated it was preferred, in order to simplify purification, to protect the amino alcohol immediately after the reduction with a Boc group to give **9** (average yield of 70%). Conversion of the (*S*)-amino alcohol **9** to the (*R*)-thioacetate **11** with inversion of configuration was carried out as was described above for the synthesis of the racemic thioacetate **3**. The α-substituted sulfinyl chloride **13** was prepared using sulfuryl chloride/acetic anhydride and used without further purification. A few α-hydroxy carboxylic acids, including lactic acid, malic acid, and mandelic acid, are available as a chiral pool and can be commercially obtained. Therefore, we have used the methyl ester of lactic acid to prepare the sulfinyl chloride containing an α-methyl substituent. After aminolysis, reduction, and protection the Boc-protected amino alcohol **8** was obtained in 60% yield. Subsequently, the thioacetate **10** was obtained in a comparable yield (74%) as **11** from **9** and converted to the sulfinyl chloride **12** according to the previously described procedure (Scheme 2).

The β-substituted sulfinyl chlorides, crucial synthons in the preparation of peptidosulfonamides containing a β-substituted aminoethanesulfonamide moiety, were prepared from alanine and phenylalanine, which were converted to the corresponding amino alcohols **14** and **15** by reduction of the *in situ* prepared mixed anhydrides of the Boc-amino acid derivatives in 68% and 67% yield, respectively, according to the method of Kokotos.[18] The alaninol derivative **14** was converted to the thioester **16** in 85% yield using Mitsunobu conditions as was described above[12] according to Higashiura and Ienaga.[19] Application of this reaction to the phenylalaninol derivative **15** gave the desired product **17** from which, unfortunately, triphenylphosphine oxide could not be completely separated. Therefore, **17** was prepared by a two-step procedure, *i.e.*, formation of the mesylate (96% yield) followed by substitution with cesium thioacetate (93% yield).[20] The sulfinyl chlorides **18** and **19** were prepared by treatment of the thioesters **16** and **17** with chlorine (approximately 2 equiv) in the presence of acetic anhydride (1 equiv)[21,22] and were used without further purification (Scheme 2).

The thus obtained sulfinyl chlorides (**5**, **12**, **13**, **18**, and **19**) were coupled to various amino acid derivatives in the presence of *N*-methylmorpholine (NMM) to afford the corresponding peptidosulfinamides. These could be oxidized using $NaIO_4/RuCl_3$[23] to the sulfonamides (Scheme 3). For example, upon coupling of α-substituted racemic sulfinyl chloride **5** to H-Pro-N(H)Me **20**, the sulfinamides **21** were isolated in 64% yield. The two pairs of diastereomers of **21** could be separated using column chromatography. After oxidation the sulfonamides **22** were isolated as a mixture of two diastereomers. Naturally, the homochiral α-substituted aminoethane sulfinyl chlorides derived from amino acids gave, upon coupling to an amino acid derivative, only one pair of diastereomeric sulfinamides **23-27** in overall yields ranging from 57 to 74%. After oxidation the homochiral α-substituted sulfonamides **28–32** in an average yield of 90% (Scheme 3). From the NMR spectra it was apparent that the sulfinyl chloride coupling was stereospecific, and ultimately only one isomer of the sulfonamide was formed.[24]

The β-substituted aminoethanesulfinyl chlorides **18** and **19** were coupled to H-Pro-N(H)Me **20** to give the sulfinamides **33** and **34**[25] in 72% and 75% yield, respectively, and subsequently oxidized to afford the homochiral β-substituted aminoethane sulfonamides **35** and **36** in 95% and 96% yield, respectively (Scheme 3).

The sulfonamide-containing hapten **38** was synthesized according to the same methodology (Scheme 3); coupling of the sulfinyl chloride **19** to HCl·H-Phe-OMe gave the peptidosulfinamide in 66% yield.[26] Oxidation using $RuCl_3/NaIO_4$ afforded the sulfonamide-containing dipeptide **37** in 79% yield. Deprotection was achieved by saponification of the methyl ester followed by removal of the Boc group using trifluoroacetic acid (TFA) in dichloromethane. Purification by ion exchange chromatography afforded the sulfonamide isostere **38** of Phe-Phe in 91% yield. This compound was conjugated to either KLH or BSA via a glutaryl linker and used for the production of monoclonal antibodies by Janda and co-workers (Scripps Research Institute, La Jolla). The thus obtained antibodies were investigated in his laboratory for possible amidase activity using a furyl acrolein derivative of Gly-Phe-Phe-NH_2 as a substrate in a chromogenic assay. Esterase activity was examined in an experiment using Ac-Phe esters as acyl donors and Phe as amine substrate, allowing detection of Phe-Phe by HPLC analysis. Unfortunately, the antibodies did not show any amidase or esterase activity.

The methodology was also applied to the synthesis of potential HIV protease inhibitors **44–46** based on the inhibitor Ro 31-8959(*R*) **47**[9] (Scheme 4). The α-benzylated sulfinyl chloride **5** (Scheme 2) was coupled to (4a*S*,8a*S*)-decahydro-3(*S*)-isoquinoline-*tert*-butylamide (**39**) to afford the corresponding sulfinamide as a mixture of four diastereomers in 54% yield. Subsequent oxidation gave the sulfonamides **40** in 85% yield as a mixture of two diastereomers which could not be separated. After removal of the Boc group using TFA in dichloromethane,

(16) This method can be applied to various amino acids; see, *e.g.*: Dakin, H. D.; Dudley, H. W. *J. Biol. Chem.* **1914**, *18*, 29–51. Cohen, S. G.; Weinstein, S. Y. *J. Am. Chem. Soc.* **1964**, *86*, 5326–5330. Brewster, P.; Hiron, F.; Hughes, E. D.; Ingold, C. K.; Rao, P. A. D. S. *Nature* **1950**, *166*, 179–180. Reference 36. Lok, C. M.; Ward, J. P.; van Dorp, D. A. *Chem. Phys. Lipids* **1976**, *16*, 115–122. Tabuchi, H.; Ichihara, A. *Tetrahedron Lett.* **1992**, *33*, 4933–4936. (g) Mori, K. *Tetrahedron* **1976**, *32*, 1101–1106. Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547–3552.

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(22) Van den Broek, L. A. G. M.; Lázaro, E.; Zylicz, Z.; Fennis, P. J.; Missler, F. A. N.; Lelieveld, P.; Garzotto, M.; Wagener, D. J. T.; Ballesta, J. P. G; Ottenheijm, H. C.J. *J. Med. Chem.* **1989**, *32*, 2002–2015.

(23) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.

(24) Since apparently no racemization of the α-carbon takes place during the substitution reaction of the sulfinyl chloride leading to sulfinamide and, after oxidation, to the sulfonamide, we assume that direct subtitution of the chlorine occurs and no intermediate sulfine is formed.

(25) The diastereomeric sulfinamides derived were separated by column chromatography and isolated in approximately equal amounts.

(26) Here the diastereomeric sulfinamides were obtained in a ratio of 1 to 1.6.

the diastereomeric amines were coupled to Boc-Asn-OH using the DCC/HOBt method yielding the diastereomers **42a,b** in 90% yield, which could be separated by flash chromatography. Removal of the Boc groups followed by coupling to quinaldic acid using the DCC/HOBt method afforded the potential HIV protease inhibitors **44** and **45** in a combined yield of 98%

Similarly, coupling of sulfinyl chloride **19** to **39** afforded the sulfinamide in 76% yield, which was further oxidized to the sulfonamide **41** in 98% yield. After removal of the Boc group and subsequent liberation of the amine from its TFA-salt with Dowex OH^-, the resulting amine was coupled to Boc-Asn-OH using the DCC/HOBt method to afford **43** in 84% yield. Deprotection and coupling (DCC/HOBt) to quinaldic acid gave the sulfonamide containing potential HIV protease inhibitor **46** in 86% yield (Scheme 4). Compounds **44**–**46** were evaluated in a HIV protease assay by Martin and co-workers (Roche Products Ltd., U.K.) using a colorimetric assay with Succ-Val-Ser-Gln-Asn-Phe-Pro-Ile-N(H)iBu as a substrate. Disappointingly, the compounds did not achieve an IC_{50} value at 1 μM. We were rather surprised by these negative results since AMPAC calculations had indicated a clear similarity of the sulfonamide moiety, both from a steric and electronic point of view, to the phosphonamidate moiety and the transition-state of the hydrolysis of the amide bond.[5,6] The similarity to the phosphonamidate is particularly noteworthy since this moiety has been used with success to prepare (HIV) protease inhibitors.[3b,s] These data have led to the proposal of the sulfonamide as a new transition-state isostere.[5,6,8] Recently, Houk and coworkers carried out more sophisticated calculations (RHF/6-31+G*) and compared the tetrahedral intermediate, resulting from attack of a hydroxide on a peptide carbonyl, to the phosphonamidate and the sulfonamide moiety.[27] Two minima of similar energy (within 1 kcal/mol) were found for the tetrahedral intermediate, one of which closely resembles both the phosphonamidate and the sulfonamide moiety, thus supporting the concept that the sulfonamide should be at least qualitatively similar and therefore a good transition-state isostere. Neither the sulfonamide nor the phosphonamidate have an OH like the tetrahedral intermediate, and all three of them have NH groups. These calculations also showed that the phosphonamidate is charged more like the tetrahedral intermediate than the sulfonamide moiety, being somewhat detrimental for the sulfonamide transition-state concept.[27,28] However, *e.g.*, the Roche inhibitor **47** (*vide infra*) only contains a secondary alcohol functionality as a transition-state isostere, having completely different charges than the tetrahedral intermediate, and still it is a very active compound.[9]

Since in principle all kinds of α-amino acids[29] can be used as a starting material for the preparation of homochiral α- and β-substituted sulfonamides, it was almost imperative to use the sulfinylchloride synthons as building blocks for the peptidosulfonamide peptidomimetics in which several amide bonds are replaced by a sulfonamide moiety. These "unnatural biopolymers" or "biopolymer mimetics" hold considerable promise (*vide supra*). As an illustration the tetrapeptidosulfonamide **51** was synthesized (Scheme 5).[30] Starting from the sulfinyl chloride **48**, coupling with H-Pro-N(H)Me **20** and subsequent oxidation gave Boc-tauryl-proline methylamide **49**.[31] Subsequently, the Boc group was removed using TFA in dichloromethane, and after liberation from its salt, the amine was coupled to the sulfinyl chloride **18** as described previously. The thus formed sulfinamide, isolated in 70% yield, was oxidized to the sulfonamide **50** using $NaIO_4/RuCl_3$ in 91% yield. Repetition of the deprotection and coupling procedure, this time using sulfinyl chloride **19**, gave the sulfinamide in 64% yield, which was oxidized to the corresponding tetrapeptidosulfonamide **51** in 90% yield.[32]

Conclusions

In conclusion, we have described straightforward methods for the synthesis of peptidomimetics containing the sulfonamide transition-state isostere as part of a homochiral α- or β-substituted aminoethanesulfonamide system. These methods feature the preparation of α- or β-substituted sulfinyl chlorides, starting from amino acids. These sulfinyl chlorides were coupled to various amino acid (derivatives) and subsequently oxidized. In this way, in principle the amide function in any dipeptide can be mimicked by either a sulfinamide or a sulfonamide transition-state isostere, and a whole array of peptidosulfinamide and peptidosulfonamide peptidomimetics becomes accessible. In addititon, α-substituted aminoethanesulfinamides and -sulfonamides could also be derived from aldehydes. Since approaches to prepare homochiral amino alcohols from aldehydes[15] are described, this route is a suitable alternative of the former route, which uses α-amino acids as a starting material.

The described routes were illustrated with the syntheses of a sulfonamide-based hapten used for the generation of catalytic antibodies and the syntheses of sulfonamide-containing potential HIV protease inhibitors, derived from the inhibitor Ro 31-8959(*R*) developed by Hoffmann-LaRoche. Disappointingly, neither of these compounds turned out to be significantly biologically active. We still do not have an unambiguous explanation as to why the sulfonamide is not an effective transition-state isostere in these cases. Perhaps the sulfonamide charges are too different from those of the tetrahedral intermediate (*vide supra*).[27,28] Alternatively, a hydrogen-bond donor-containing transition-state isostere (OH in, *e.g.*, the Roche inhibitor) may be essential for obtaining biologically very active compounds. Another aspect concerns the presence of an additional methylene in the sulfonamide. The β-methylene is necessary to obtain stable sulfonamides[6] and although not directly part of the transition-state isostere, it may cause a "frameshift" or displacement of the backbone together with the side chains. Nevertheless, a recent example shows that the sulfonamide moiety can be employed as a good transition-state isostere leading to effective phospholipase A_2 inhibitors.[33] Inves-

(27) In collaboration with Professor Dr. K. N. Houk, Department of Chemistry and Biochemistry, University of California, Los Angeles: Radkiewicz, M.; McAllister, J.; Goldstein, E.; Houk, K. N.; Liskamp, R. M. J. Manuscript in preparation.

(28) RHF/6-31+G* Chelpg charges: tetrahedral intermediate: C(1.27), O1(−1.11), O2(−0.86), N(−1.02); phosphonamidate: P(1.57), O1(−0.99), O2(−0.96), N(−0.91); sulfonamide S(1.33), O1(−0.62), O2(−0.66), N(−0.69).

(29) Except for amino acids containing oxidizable side chains *e.g.* methionine and tryptophane.

(30) An arbitrary sequence was chosen, mainly based on the direct availability of the sulfinyl chlorides, merely to illustrate the method.

(31) The synthesis of this compound has been described earlier[5,6].

(32) Examples of α-β unsaturated oligopeptidosulfonamides, designated as sulfonamide−pseudopeptides, have recently been described: Gennari, C; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2067−2069.

(33) Pisabarro, M. T.; Ortiz, A. R.; Palomer, A.; Cabré, F; Carcía, L.; Wade, R. C.; Cago, F.; Mauleón, D.; Carganico, G. *J. Med. Chem.* **1994**, *37*, 337−341.

tigations aimed at explaining the rather unexpected behavior of the sulfonamide transition-state isostere containing compounds are continuing.

Finally, we have described an approach to the synthesis of a new biopolymer mimetic, the peptidosulfonamide.[30] A tetrapeptidosulfonamide consisting of unsubstituted and β-substituted aminoethanesulfonamide units was assembled. In an analogous way peptidosulfonamides consisting of α-substituted aminoethane sulfonamides, using the α-substituted aminoethanesulfinyl chlorides, can be prepared.

Under present investigation is the application of these methods to the synthesis of potential inhibitors of other proteases. Experiments toward the solid-phase synthesis of peptidosulfonamides, as well as the construction of combinatorial libraries of peptidosulfonamides, are also in progress.

Experimental Section

General Methods. Dioxane and THF were dried by refluxing on $LiAlH_4$ and distilled immediately prior to use. DMF was stirred with CaH_2 for 16 h and then distilled under reduced pressure. Ethanol-free dichloromethane used for synthesis of the sulfinyl chlorides and sulfinamides was purchased from Baker, dried by refluxing on CaH_2, and distilled directly prior to use. *N*-methylmorpholine (NMM) was distilled from calcium hydride, and isobutyl chloroformate (IBCF) was distilled under argon atmosphere. All monoprotected amino acids were purchased from Bachem. Quinaldic acid and (4a*S*,8a*S*)-decahydro-(*S*)-3-isoquinoline-*tert*-butylamide (DIQ-NH*t*-Bu) were gifts from Roche Products, Ltd. (Hertfordshire, England).

Melting points are uncorrected. TLC analysis was performed on Merck precoated silica gel 60 F-254 plates. Spots were visualized with UV light, ninhydrin (after treatment with HCl), or Cl_2-TDM.[34] Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh, ASTM). For flash chromatography Merck kieselgel (60 H) was used. Sephadex LH-20 (Pharmacia) was used for gel filtration. ^1H NMR and ^{13}C NMR spectra were recorded on a 200 MHz or, when indicated, on a 300 MHz or 400 MHz spectrometer operating in the Fourier transform mode. The chemical shifts are given in ppm (δ) relative to TMS or TSP (^1H) or to $CDCl_3$ or MeOD (^{13}C) as internal standard. The numbering of the carbon atoms in the amino acids is according to IUPAC recommendations.[35] Optical rotations were measured at 20 °C and 589 nm using a automatic polarimeter. For fast atom bombardment (FAB) mass spectrometry the samples were loaded in a glycerol/thioglycerol/nitrobenzyl alcohol (NBA) solution onto a stainless steel probe and bombarded with Xenon atoms with an energy of 8 keV. During the high resolution FABMS measurements a resolving power of 10 000 (10% valley definition) was used. Glycerol was used to calibrate the mass spectrometer. The compounds were homogeneous according to NMR and TLC.

(*RS*)-2-[(*tert*-Butoxycarbonyl)amino]-1-benzylethanol (2). The procedure described by Evans *et al.*[10] for the preparation of β-amino methyl alcohols was used with the modifications described by Bol and Liskamp.[11] Phenylacetaldehyde (**1**) (11.7 mL, 100 mmol) was converted to the cyanohydrin using TMSCN (13.7 mL, 110 mmol) and a catalytic amount of ZnI_2. Reduction with $LiAlH_4$ (4.14 g, 110 mmol) in ether (110 mL) afforded (*RS*)-2-amino-1-benzyl ethanol, which was crystallized from ether and obtained in 51% yield: mp 77–79 °C; ^1H NMR ($CDCl_3$) δ 2.00 (br, 2H, NH_2), 2.54, 2.76 (two dd, 2H, AB of ABX, J_{AX} = 8.1 Hz, J_{BX} = 3.3 Hz, J_{AB} = 12.7 Hz), 2.67–2.73 (m, 1H), 2.70 (d, 2H, J = 6.4 Hz), 3.64–3.76 (m, 1H), 7.13–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 41.5, 46.8, 72.9, 126.0, 128.2, 129.2, 138.6.

To a cooled solution of this amino alcohol (3.02 g, 20.0 mmol) in CH_2Cl_2 (50 mL) was added di-*tert*-butyl dicarbonate (4.50 g, 20.6 mmol), and the pH of the reaction mixture was kept between 7 and 8 using NMM. After being stirred for 0.5 h at rt, the mixture was diluted with CH_2Cl_2 (50 mL), washed with 5% citric acid (2 × 10 mL) and brine (1 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (125 g silica, eluent: ether/petroleum ether, 1/1, v/v) afforded **2** as an oil in 89% yield: R_f 0.23 (eluent: ether/petroleum ether, 1/1, v/v); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.44 (br, 1H), 2.71, 2.81 (two dd, 2H, AB of ABX, J_{AX} = 8.0 Hz, J_{BX} = 5.7 Hz, J_{AB} = 13.8 Hz), 3.07, 3.38 (eight lines (H_a), eight lines (H_b), 2H, AB of ABXY, J_{AX} = 5.4 Hz, J_{AY} = 7.6, J_{BX} = 2.8 Hz, J_{BY} = 6.7, J_{AB} = 14.0 Hz), 3.80–3.94 (m, 1H), 4.93 (br, 1H), 7.19–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.1, 41.0, 45.7, 71.8, 79.2, 126.2, 128.2, 129.1, 137.7, 156.5.

Thioacetates 3, 10, 11, and 16. Typical Procedure: (*RS*)-2-[(*tert*-Butoxycarbonyl)amino]-1-phenylpropyl Thioacetate (3). The Boc-amino alcohol **2** was converted to **3** according to the procedure described by Volante.[12] The alcohol **2** (2.19 g, 8.71 mmol) and thioacetic acid (1.25 mL, 17.5 mmol) were added to the complex of triphenylphosphine (4.57 g, 17.4 mmol) and DIAD (3.42 mL, 17.4 mmol) formed in THF (30 mL) at 0 °C. Upon completion of the reaction (1 h at 0 °C and 1 h at rt), the mixture was concentrated *in vacuo*. The triphenylphosphineoxide was crystallized upon addition of a mixture of EtOAc/petroleum ether, removed by filtration, and washed with petroleum ether. The combined filtrates were concentrated *in vacuo* and subjected to column chromatography (150 g of silica, eluent: gradient of petroleum ether to petroleum ether/ether, 9/1, v/v) to give **3** as an oil in 82% yield, which solidified upon standing, and **4** (oil, 13%) as a byproduct.

3: R_f 0.66 (eluent: ether/petroleum ether, 1/4, v/v); ^1H NMR (MeOD) δ 1.43 (s, 9H), 2.23 (s, 3H), 2.77, 2.97 (two dd, 2H, AB of ABX, J_{AX} = 8.3 Hz, J_{BX} = 6.3 Hz, J_{AB} = 14.0 Hz), 3.14, 3.34 (two dd, 2H, AB of ABX, J_{AX} = 7.2 Hz, J_{BX} = 5.5 Hz, J_{AB} = 14.0 Hz), 3.76-3.92 (m, 1H), 7.12–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.1, 30.5, 38.0, 43.5, 46.0, 79.0, 126.4, 128.1, 128.9, 137.8, 155.6, 195.0.

(*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1-methylethyl Thioacetate (10). Column chromatography (eluent: gradient of petroleum ether to EtOAc/petroleum ether, 1/2, v/v) gave the thioacetate **10** as an oil in 74% yield, which solidified upon standing: R_f 0.32 (eluent: ether/petroleum ether, 1/2, v/v); $[\alpha]^{20}_D$ = +35.6° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (d, 3H, J = 7.2 Hz), 1.44 (s, 9H), 2.33 (s, 3H), 3.12–3.36 (m, 2H), 3.56–3.69 (m, 1H), 4.76 (br, 1H); ^{13}C NMR ($CDCl_3$) 17.9, 28.1, 30.5, 39.8, 45.3, 79.0, 155.7, 195.3.

(*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1-phenylpropyl Thioacetate (11). The NMR data are identical to those described for **3**: $[\alpha]^{20}_D$ = +5.2° (c = 1.0, $CHCl_3$).

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]propyl Thioacetate (16). Instead of DIAD, DEAD was used according to the procedure described by Higashiura and Ienaga.[19] Column chromatography (eluent: petroleum ether/ether, 4/1, v/v) gave **16** as an oil in 85% yield, which solidified upon standing: R_f 0.25 (eluent: petroleum ether/ether, 4/1, v/v); ^1H NMR ($CDCl_3$) δ 1.17 (d, 3H, J = 6.7 Hz), 1.44 (s, 9H), 2.36 (s, 3H), 3.01, 3.05 (two dd, 2H, AB of ABX, J_{AX} = 6.4 Hz, J_{BX} = 5.4 Hz, J_{AB} = 13.0 Hz), 3.76–3.90 (m, 1H), 4.57 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7, 27.2, 29.3, 33.8, 45.2, 78.4, 154.0, 194.0.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropyl Thioacetate (17). Boc-phenylalaninol **15** (1.28 g, 5.09 mmol) was converted to the mesylate according to the procedure described by Higashiura and Ienaga,[19] using MsCl (0.42 mL, 5.3 mmol) and Et_3N (0.78 mL, 5.6 mmol). After aqueous workup and column chromatography (30 g of silica, eluent: CH_2Cl_2) the mesylate was obtained as a white solid in 96% yield: R_f 0.44 (eluent: CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.85–2.96 (m, 2H), 3.01 (s, 3H), 4.11–4.29 (m, 3H), 4.77 (br, 1H), 7.21–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.1, 37.0, 37.1, 50.7, 69.8, 79.7, 126.7, 128.5, 129.1, 136.5, 155.0.

To a solution of Cs_2CO_3 (0.426 g, 1.31 mmol) in DMF (2 mL) under argon atmosphere was added thioacetic acid (0.195 mL, 2.73 mmol) followed by addition of a solution of the mesylate (0.726 g, 2.20 mmol) in DMF (2 mL). After being stirred overnight at rt, the mixture was concentrated *in vacuo*. The

(34) Von Arx, E.; Faupel, M.; Brugger, M. *J. Chromatogr.* **1976**, *120*, 224–228.

(35) IUPAC-IUB Nomenclature and Symbolism for Amino Acids and Peptides. Recommendations 1983. *J. Biol. Chem.* **1985**, *260*, 14–42.

residue was treated with CH_2Cl_2 (50 mL) and water (10 mL). The separated organic layer was washed with water (2 × 5 mL) and brine (5 mL) and dried (Na_2SO_4). Column chromatography (25 g of silica, eluent: gradient of petroleum ether to petroleum ether/ether, 8/1, v/v) gave **17** as a white solid in 93% yield: R_f 0.41 (eluent: petroleum ether/ether, 2/1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.35 (s, 3H), 2.77, 2.85–2.96 (dd (H_a), m (H_b), 2H, AB of ABX, J_{AX} = 7.2 Hz, J_{AB} = 13.6 Hz), 2.93, 3.08 (two dd, 2H, AB of ABX, J_{AX} = 7.7 Hz, J_{BX} = 4.9 Hz, J_{AB} = 13.9 Hz), 3.85–4.07 (m, 1H), 4.64 (br, 1H), 7.16–7.37 (m, 5H); ^{13}C NMR δ ($CDCl_3$) 28.1, 30.3, 32.6, 40.1, 51.5, 78.9, 126.3, 128.2, 129.0, 137.2, 155.0, 195.3.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-methylethanol (8). Lactic amide was prepared from (*S*)-3-methyl lactate (4.92 g, 47.2 mmol) analogous to the procedure described below for the synthesis of **9** (*vide infra*), except for the reaction time, which was 4 h. The amide was obtained as an oil in quantitative yield: $[\alpha]^{20}_D$ = −17.3° (*c* = 1.1, dioxane); ^{1}H NMR (MeOD) δ 1.35 (d, 3H, *J* = 6.9 Hz), 4.10 (q, 1H, *J* = 6.9 Hz); ^{13}C NMR (MeOD) δ 21.1, 68.7, 181.0.

Subsequently, the amide (0.337 g, 3.79 mmol) was converted to the Boc-aminoethanol **8** analogous to the procedure described for the synthesis of **9**. Purification by column chromatography (20 g of silica, eluent: EtOAc) gave **8** as an oil in 60% yield: R_f 0.70 (eluent: EtOAc/MeOH, 95/5, v/v); $[\alpha]^{20}_D$ = +21.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3H, *J* = 6.4 Hz), 1.45 (s, 9H), 2.92–3.32 (m, 3H), 3.80–3.92 (m, 1H), 5.12 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 28.1, 47.7, 67.0, 79.2, 156.6.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-benzylethanol (9). Nitrous acid deamination of (*S*)-Phe **7** (13.95 g, 84.4 mmol) was carried out according to the protocol described by Linstromberg and Baumgarten[36] and afforded 3-phenyllactic acid in 68% yield: $[\alpha]^{20}_D$ = −20.7° (*c* = 1, water); mp 122–123 °C; ^{1}H NMR (MeOD) 2.88, 3.10 (two dd, 2H, AB of ABX, J_{AX} = 8.1 Hz, J_{BX} = 4.4 Hz, J_{AB} = 13.7 Hz), 4.33 (dd, 1H, X of XAB, J_{XA} = 8.1 Hz, J_{XB} = 4.4 Hz), 7.13–7.34 (m, 5H); ^{13}C NMR (MeOD) 41.3, 72.5, 127.3, 129.0, 130.3, 138.6, 176.9.

Thionyl chloride (12.3 mL, 171 mmol) was added dropwise to methanol (47 mL), cooled to −20 °C (acetone, liquid N_2). Phenyllactic acid (7.81 g, 47.0 mmol) was added, and the mixture was stirred for 2 h at rt and concentrated *in vacuo*. Crystallization from ether afforded the corresponding ester in 85% yield: mp 42–43 °C; R_f 0.45 (eluent: ether/petroleum ether, 1/1, v/v); $[\alpha]^{20}_D$ = −7.3° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.58 (br, 1H), 2.95, 3.12 (two dd, 2H, AB of ABX, J_{AX} = 6.7 Hz, J_{BX} = 4.5 Hz, J_{AB} = 13.9 Hz), 3.76 (s, 3H), 4.45 (dd, 1H, X of ABX, J_{XA} = 6.7 Hz, J_{XB} = 4.5 Hz), 7.18–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 40.4, 52.2, 71.2, 126.7, 128.2, 129.3, 136.2, 174.4.

The thus obtained ester of phenyllactic acid (3.79 g, 21.0 mmol) was dissolved in MeOH saturated with NH_3 (70 mL). After the mixture was stirred overnight, the solvent and the ammonia were evaporated *in vacuo* to give phenyllactamide in quantitative yield as a white solid: $[\alpha]^{20}_D$ = −7.2° (*c* = 1, THF); ^{1}H NMR (MeOD) δ 2.81, 3.10 (two dd, 2H, AB of ABX, J_{AX} = 8.2 Hz, J_{BX} = 3.6 Hz, J_{AB} = 13.9 Hz), 4.21 (dd, 1H, X of ABX, J_{XA} = 8.2 Hz, J_{XB} = 3.6 Hz), 7.14–7.27 (m, 5H); ^{13}C NMR (MeOD) δ 41.6, 73.7, 127.3, 129.1, 130.5, 139.0, 179.5.

BH_3·THF (1 M in THF, 12.9 mL, 12.9 mmol) was added dropwise to phenyllactamide (1.425 g, 8.6 mmol). After the mixture was refluxed for 3.5 h additional BH_3·THF (15.0 mL, 15.0 mmol) was gradually added, and refluxing was continued until TLC indicated complete conversion of the amide (overnight). The mixture was then cooled to rt, quenched with MeOH (70 mL), and concentrated *in vacuo*. Di-*tert*-butyl dicarbonate (2.07 g, 9.48 mmol) was added to a cooled (0 °C) solution of the residue in dry CH_2Cl_2 (40 mL). The mixture was stirred for 1 h at rt, diluted with CH_2Cl_2 (40 mL), washed with 5% citric acid (5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL), dried (Na_2SO_4), and evaporated to dryness. Column chromatography (60 g silica, ether/petroleum ether, 1/2, v/v with gradient to ether/petroleum ether, 1/1, v/v) gave the Boc-amino alcohol **9** as an oil (in an average yield of 70%), which solidified upon standing: $[\alpha]^{20}_D$ = +7.4° (*c* = 1, $CHCl_3$). The NMR data are identical to those of of compound **2**.

(*S*)-*N*-(*tert*-Butoxycarbonyl)alaninol (14). Boc-Ala-OH (0.415 g, 2.19 mmol) either commercially obtained or prepared from alanine **6** was used to prepare the alcohol **14** according to the procedure described by Kokotos.[18] Instead of NMM, Et_3N was used to simplify purification of **3**. An activated ester was formed using ECF (0.21 mL, 2.20 mmol) in the presence of Et_3N (0.31 mL, 2.22 mmol), followed by reduction with $NaBH_4$ (0.249 g, 6.58 mmol) in MeOH (22 mL). Column chromatography (25 g of silica, eluent: petroleum ether/ether, 1/1, v/v) afforded **3** as a white solid in 68% yield: R_f 0.12 (eluent: petroleum ether/ether, 1/1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, *J* = 6.7 Hz), 1.43 (s, 9H), 2.93 (br, 1H), 3.48, 3.61 (two dd, 2H, AB of ABX, J_{AX} = 6.0 Hz, J_{BX} = 3.9 Hz, J_{AB} = 10.9 Hz), 3.63–3.80 (m, 1H), 4.74 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 17.1, 28.1, 48.1, 66.0, 79.1, 156.0.

(*S*)-*N*-(*tert*-Butoxycarbonyl)phenylalaninol (15). The above-described procedure was used to prepare Boc-phenylalaninol (**15**). Column chromatography (eluent: gradient of petroleum ether/ether, 3/2, to petroleum ether/ether, 1/1, v/v) gave a white solid in 67% yield: R_f 0.53 (eluent: petroleum ether/ether, 1/1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.50 (br, 1H), 2.83 (d, 2H, *J* = 6.9 Hz), 3.48–3.72 (m, 2H), 3.76–3.96 (m, 1H), 4.80 (d, 1H, *J* = 6.0 Hz), 7.20–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3, 37.4, 53.6, 63.7, 79.5, 126.3, 128.4, 129.2, 138.0, 156.1.

Sulfinyl Chlorides 5, 12, and 13. Typical Procedure: *N*-(*tert*-Butoxycarbonyl)-1-(*RS*)-benzylhypotauryl Chloride (5). Thioacetate **3** (197 mg, 0.64 mmol) was coevaporated in dioxane (3 × 10 mL), dissolved in dry CH_2Cl_2 (1 mL), and cooled to −20 °C (acetone, liquid N_2) under argon atmosphere. Acetic anhydride (60 μL, 0.64 mmol) and sulfuryl chloride (103 μL, 1.27 mmol) were added *via* a syringe. After being stirred for 1 h, during which time the temperature was allowed to rise to −5 °C, the mixture was concentrated and dried *in vacuo* at rt. The thus obtained sulfinyl chloride was used for coupling without purification.

Sulfinyl Chlorides 18 and 19. Typical Procedure: *N*-(*tert*-Butoxycarbonyl)-2(*S*)-methylhypotauryl Chloride (18). To a stirred and cooled (−18 °C, ethanol, liquid N_2) solution of thioacetate **16** (0.364 g, 1.56 mmol) and Ac_2O (0.147 mL, 1.56 mmol) in CH_2Cl_2 (5 mL) was added a cooled (−10 °C) solution of Cl_2 (ca. 0.3 g, 4.2 mmol, dried over concd H_2SO_4) in CH_2Cl_2 (7 mL) *via* a glass connecting tube, and stirring was continued for 1 h at a temperature between −18 and −10 °C. Concentration and removal of residual solvent and acetyl chloride *in vacuo* at rt gave the sulfinyl chloride **7** as a white solid, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.38 (d, 3H, *J* = 6.9 Hz), 1.45 (s, 9H), 3.48–3.72 (m, 2H), 4.08–4.32 (m, 1H), 4.89 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 28.2, 43.5, 71.7, 78.3, 155.1.

General Procedure A. Coupling of a Sulfinyl Chloride to an Amine. A solution of the amino acid derivative (1.05 mmol) in dry CH_2Cl_2 (2 mL) and NMM (0.11 mL, 1.0 mmol) were added simultaneously to a solution of the sulfinyl chloride (1.0 mmol) in CH_2Cl_2 (4 mL) at 0 °C under argon atmosphere. The mixture was stirred overnight at rt and subsequently concentrated *in vacuo*.

General Procedure B. Oxidation of a Sulfinamide to a Sulfonamide. A sulfinamide was oxidized to the corresponding sulfonamide according to the procedure described by Gao and Sharpless,[23] using $RuCl_3$ hydrate and $NaIO_4$ as cooxidant.

General Procedure C. Removal of the Boc Group and Liberation of the Amine from TFA. TFA (1 mL) was added to a cooled solution (0 °C) of the Boc-protected sulfonamide (0.5 mmol) in dry CH_2Cl_2 (1 mL). After being stirred for 30 min at rt, the mixture was concentrated *in vacuo* and coevaporated in dry THF (4 × 30 mL). The TFA salt was dissolved in a mixture of *t*-BuOH/water (4/1, v/v), and Dowex OH^- was added until the pH was 7–8. The Dowex was filtered and the filtrate lyophilized.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*RS*)-benzylhypotauryl]-proline Methylamide (21).** Sulfinyl chloride **5** (0.64 mmol) was coupled to H-Pro-N(H)Me **20** (85 mg, 0.66 mmol) according

(36) Linstromberg, W. W. Baumgarten, H. E. In *Organic Experiments;* D. C. Heath and Co.; Lexington: Massachussets, Toronto, 1987; pp 211–212

to general procedure A. Column chromatography of the residue (15 g of silica, eluent: gradient of EtOAc to EtOAc/MeOH, 95/5, v/v) gave two pairs of diastereomeric sulfinamides **21** in 64% total yield (ratio approximately 1/1).

Higher running diastereomers: R_f 0.24 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$) δ 1.42, 1.43 (two s, 18H), 1.72–2.28 (m, 8H), 2.71, 2.81 (two d, 6H, J = 4.9, 4.9 Hz), 2.88–3.68 (m, 14H), 4.32 (dd, 1H, A of AXY, J_{AX} = 3.2 Hz, J_{AY} = 7.8 Hz), 4.48 (dd, 1H, A of AXY, J_{AX} = 3.6 Hz, J_{AY} = 8.0 Hz), 4.62 (br, 1H), 5.40 (br, 1H), 6.41 (br, 1H), 7.12–7.38 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 25.0, 26.2, 28.2, 31.7, 31.8, 33.0, 33.4, 38.3, 40.2, 51.3, 52.7, 58.0, 58.9, 63.5, 64.2, 79.5, 79.8, 126.9, 128.7, 128.9, 129.1, 129.2, 136.9, 137.1, 155.7, 155.9, 172.8, 173.1.

Lower running diastereomers: R_f 0.19 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H), 1.48–2.20 (m, 8H), 2.81 (d, 6H, J = 4.9 Hz), 2.70–3.12, 3.28–3.48 (m (12 H), m (1H)), 3.60–3.74 (m, 1H), 4.04–4.21 (m, 2H), 4.40 (br, 1H), 4.68 (br, 1H), 5.00 (br, 1H), 7.04–7.32 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.0, 26.2, 28.2, 31.0, 31.3, 33.8, 38.6, 40.2, 41.0, 42.4, 63.9, 65.0, 66.8, 66.9, 79.7, 126.8, 128.8, 129.2, 137.0, 137.3, 156.0, 172.1, 172.8.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*RS*)-benzyltauryl]proline Methylamide (22).** The sulfonamide **22** was prepared from the corresponding sulfinamide **21** (67 mg, 0.16 mmol) according to general procedure B. Column chromatography (10 g of silica, eluent: gradient of CH_2Cl_2 to CH_2Cl_2/MeOH, 99/1, v/v) afforded **22** as an oil in 93% yield as a mixture of diastereomers: R_f 0.36 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 18H), 1.85–2.08 (m, 4H), 2.10–2.25 (m, 4H), 2.81, 2.83 (two d, 6H, J = 4.6 Hz, J = 4.5 Hz), 2.85–2.93 (m, 2H), 3.30–3.52 (m, 11H), 3.59 (dd, 1H, B of ABX, J_{BX} = 7.3 Hz, J_{AB} = 9.7 Hz), 4.35 (dd, 1H, A of AXY, J_{AX} = 4.7 Hz, J_{AY} = 7.5 Hz), 4.41 (dd, 1H, A of AXY, J_{AX} = 4.3 Hz, J_{AY} = 7.8 Hz), 5.42, 5.57 (two br, 2H), 6.67 (br, 2H), 7.20–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.1, 26.4, 26.5, 28.3, 31.0, 32.9, 33.1, 39.3, 49.2, 49.6, 61.8, 62.4, 62.9, 63.2 79.4, 79.6, 127.1, 128.8, 129.0, 129.1, 136.5, 136.7, 155.7, 172.1, 172.3.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-methylhypotauryl]proline Methylamide (23).** Sulfinyl chloride **12** was coupled to H-Pro-N(H)Me **20** (147 mg, 1.14 mmol) according to general procedure A. Column chromatography (25 g of silica, eluent: gradient of CH_2Cl_2 to CH_2Cl_2/MeOH, 98/2, v/v) afforded the sulfinamide **23** as a mixture of diastereomers (ratio 1/1) as an oil in 60% yield: R_f 0.39 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (d, 3H, J = 7.1 Hz), 1.27 (d, 3H, J = 6.9 Hz), 1.44, 1.45 (two s, 18H), 1.80–2.05 (m, 4H), 2.00–2.26 (m, 4H), 2.84 (d, 6H, J = 4.9 Hz), 2.76–3.08 (m, 3H), 3.05 (eight lines, 1H, A of ABXY, J_{AX} = 4.5 Hz, J_{AY} = 7.4 Hz, J_{AB} = 9.8 Hz), 3.30–3.73 (m, 5H), 3.73 (six lines, 1H, B of ABX, J_{BX} = 7.8 Hz, J_{AB} = 9.8 Hz), 4.20 (dd, 1H, A of AXY, J_{AX} = 4.1 Hz, J_{AY} = 8.1 Hz), 4.43 (dd, 1H, A of AXY, J_{AX} = 3.3 Hz, J_{AY} = 8.4 Hz), 5.04 (br, 1H), 5.45 (br, 1H), 6.59 (br, 1H), 7.27 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.1, 12.4, 25.0, 26.0, 26.1, 28.1, 30.9, 31.6, 41.5, 52.6, 57.6, 58.1, 58.2, 66.4, 79.2, 79.5, 155.9, 172.4, 173.1.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-1-methylhypotauryl]glycine Ethyl Ester (24).** Sulfinyl chloride **12** (0.86 mmol) was coupled to H-Gly-OEt·HCl (144 mg, 1.03 mmol) suspended in a mixture of CH_2Cl_2 (1 mL), DMF (3 mL), and NMM (113 μL, 1.03 mmol) according to the general procedure A. Upon column chromatography (20 g of silica, eluent: gradient of CH_2Cl_2 to CH_2Cl_2/MeOH, 98/2, v/v) the diastereomers **24** were separated and obtained as oils (ratio 1/1) in a total yield of 57%.

Higher running diastereomer: R_f 0.31 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 7.2 Hz), 1.30 (d, 3H, J = 7.2 Hz), 1.44 (s, 9H), 2.92 (10 lines, 1H, A of AXYM, J_{AX} = 7.2 Hz, J_{AY} = 6.9 Hz, J_{AM} = 6.9 Hz), 3.37–3.44, 3.54–3.66 (two m, 2H), 3.76, 3.99 (two dd, 2H, AB of ABX, J_{AX} = 5.6 Hz, J_{BX} = 5.4 Hz, J_{AB} = 17.4 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.50 (br, 1H), 5.46 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.7, 14.1, 28.3, 41.7, 42.2, 58.7, 61.8, 79.5, 156.0, 170.3.

Lower running diastereomer: R_f 0.28 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.30 (d, 3H, J = 7.0 Hz), 1.44 (s, 9H), 2.86–3.02 (m, 1H), 3.28–3.44 (m, 2H), 3.83, 3.98 (two dd, 2H, AB of ABX, J_{AX} = 5.5 Hz, J_{BX} = 5.7 Hz, J_{AB} = 17.6 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.61 (br, 1H), 5.30 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.3, 14.0, 28.3, 41.3, 43.1, 58.6, 61.8, 79.7, 155.9, 170.5.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-benzylhypotauryl]proline Methylamide (25).** Sulfinyl chloride **13** was coupled to H-Pro-N(H)Me **20** (93 mg, 0.73 mmol) according to general procedure A. Column chromatography (15 g silica of eluent: CH_2Cl_2/MeOH, 99/1, v/v) gave the diastereomeric sulfinamides **25** as an oil in 57% yield (ratio by NMR: 1/2): R_f 0.25 (eluent: CH_2Cl_2 /MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H), 1.43 (s, 9H), 1.71–1.99 (m, 4H), 2.00–2.27 (m, 4H), 2.68 (d, 3H, J = 4.9 Hz), 2.82 (d, 3H, J = 4.8 Hz), 2.85 (dd, 1H, A of ABX, J_{AX} = 10.1 Hz, J_{AB} = 14.1 Hz), 2.94–3.08 (m, 4H), 3.18–3.33 (m, 3H), 3.40–3.56 (m, 4H), 3.62 (8 lines, 1H, B of ABXM, J_{BX} = 3.9 Hz, J_{BM} = 7.1 Hz, J_{AB} = 14.7 Hz), 3.70 (6 lines, 1H, B of ABX, J_{BX} = 7.9 Hz, J_{AB} = 9.8 Hz), 4.15 (dd, 1H, A of AXY, J_{AX} = 3.5 Hz, J_{AY} = 8.2 Hz), 4.50 (dd, 1H, A of AXY, J_{AX} = 3.1 Hz, J_{AY} = 8.5 Hz), 4.65 (dd, 1H, A of AXY, J_{AX} = 6.0 Hz, J_{AY} = 6.9 Hz), 5.44 (br, 1H), 6.12 (br, 1H), 7.18–7.40 (m, 10H), 7.42 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 26.1, 26.3, 28.1, 31.0, 31.8, 32.8, 33.2, 38.0, 40.0, 42.3, 52.7, 57.7, 63.8, 64.2, 66.7, 79.3, 79.6, 126.8, 128.7, 129.0, 129.1, 136.8, 137.3, 155.8, 172.1, 173.0.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-benzylhypotauryl]glycine Ethyl Ester (26).** Sulfinyl chloride **13** (0.66 mmol) was coupled to H-Gly-OEt·HCl (119 mg, 0.85 mmol) suspended in DMF/CH_2Cl_2 (1/3, v/v, 4 mL) and Et_3N (118 μL, 0.85 mmol) according to general procedure A. Column chromatography (20 g of silica, eluent: CH_2Cl_2 with gradient to CH_2Cl_2/MeOH, 99/1, v/v) gave the diastereomeric sulfinamides **26** as an oil in 70% yield (ratio by NMR 1.2/1): R_f 0.43 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 1.42 (s, 18H), 2.73–2.91 (m, 2H), 3.05–3.30 (m, 4H), 3.30–3.64 (m, 4H), 3.75, 3.96 (two dd, 2H, AB of ABX, J_{AX} = 5.7 Hz, J_{BX} = 5.5 Hz, J_{AB} = 17.7 Hz), 3.81, 3.97 (two dd, 2H, AB of ABX, J_{AX} = 5.7 Hz, J_{BX} = 5.8 Hz, J_{AB} = 17.8 Hz), 4.23 (q, 2H, J = 7.1 Hz), 4.24 (q, 2H, J = 7.1 Hz), 4.60 (br, 1H), 4.72 (br, 1H), 5.19 (br, 1H), 5.46 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 28.1, 32.0, 38.7, 39.0, 43.1, 43.6, 61.4, 64.3, 64.5, 79.2, 126.6, 128.5, 128.9, 129.0, 129.1, 129.2, 137.0, 137.1, 137.2, 155.7, 170.3.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-benzylhypotauryl]phenylalanine Methyl Ester (27).** Sulfinyl chloride **13** (0.69 mmol) was coupled to H-Phe-OMe·HCl (180 mg, 0.83 mmol) suspended in a mixture of DMF (2 mL), CH_2Cl_2 (5 mL), and NMM (91 μL, 0.83 mmol) according to general procedure A. Column chromatography (20 g of silica, eluent CH_2Cl_2/MeOH, 99/1, v/v) afforded the separated diastereomers **27** as oils in a total yield of 74% (ratio by NMR: R_f 0.38, 0.34 1/2). Higher running diastereomer: R_f 0.38 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H), 2.52–2.70 (m, 1H), 2.91–3.01 (m, 2H), 3.09, 3.16 (two dd, 2H, AB of ABX, J_{AX} = 6.4 Hz, J_{BX} = 5.9 Hz, J_{AB} = 13.7 Hz), 3.34–3.42 (m, 1H), 3.47–3.55 (m, 1H), 3.71 (s, 3H), 4.28 (6 lines, 1H, X of ABX, J_{XA} = J_{XB} = 6.4 Hz, J_{XNH} = 8.9 Hz), 4.60 (d, 1H, J = 8.9 Hz), 5.37 (br, 1H), 7.08–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.2, 32.1, 39.0, 39.8, 52.3, 57.1, 64.6, 79.3, 126.6, 127.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.4, 135.4, 137.0, 154.9, 172.5.

Lower running diastereomer: R_f 0.34 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 2.67 (dd, 1H, A of ABX, J_{AX} = 8.3 Hz, J_{AB} = 15.0 Hz), 2.95-3.05 (m, 2H), 2.90, 3.13 (two dd, 2H, AB of ABX, J_{AX} = 8.6 Hz, J_{BX} = 5.3 Hz, J_{AB} = 13.8 Hz), 3.26–3.45 (m, 2H), 3.76 (s, 3H), 4.15 (6 lines, 1H, X of ABX, J_{XA} = 8.6 Hz, J_{XB} = 5.3 Hz, J_{XNH} = 8.6 Hz), 4.61 (d, 1H, J = 8.6 Hz), 4.92 (br, 1H), 7.10–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.3, 31.5, 39.1, 40.2, 52.6, 59.8, 65.1, 79.6, 126.8, 127.1, 128.6, 128.7, 129.2, 129.4, 136.1, 137.3, 155.7, 172.7.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-methyltauryl]proline Methylamide (28).** The sulfinamide **23** (93 mg, 0.28 mmol) was oxidized to the sulfonamide **28** according to general procedure B. Column chromatography (15 g of silica, eluent: CH_2Cl_2/MeOH, 98/2, v/v) afforded the sulfonamide **28** as an oil in 96% yield: R_f 0.27 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (d, 3H, J = 6.9 Hz), 1.44 (s,

9H), 1.92–2.06 (m, 2H), 2.12–2.32 (m, 2H), 2.84 (d, 3H, J = 4.8 Hz), 3.27–3.39 (m, 2H), 3.45, 3.62 (six lines (2x), 2H, AB of ABX, J_{AX} = 6.1 Hz, J_{BX} = 7.3 Hz, J_{AB} = 9.8 Hz), 3.59–3.70 (m, 1H), 4.38 (dd, 1H, A of AXY, J_{AX} = 3.9 Hz, J_{AY} = 8.1 Hz), 5.45 (br, 1H), 6.70 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 25.1, 26.3, 28.2, 30.9, 41.3, 49.7, 57.4, 62.1, 79.7, 156.0, 172.2.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-methyltauryl]glycine Ethyl Ester (29).** The sulfonamide **29** was prepared by oxidation of the sulfinamide **24** (49 mg, 0.16 mmol) according to general procedure B. Column chromatography (10 g of silica, eluent: CH_2Cl_2/MeOH, 99/1, v/v) afforded **29** as an oil in 81% yield: R_f 0.41 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, J = 7.2 Hz), 1.39 (d, 3H, J = 7.0 Hz), 1.44 (s, 9H), 3.22–3.32 (10 lines, 1H, A of AXYM, J_{AX} = J_{AM} = 6.9 Hz, J_{AY} = 4.2 Hz), 3.51, 3.65 (six lines (H_x), eight lines (H_y), 2H, XY of AXY, J_{XA} = J_{XNH} = 6.3 Hz, J_{YA} = 4.2 Hz, J_{YNH} = 6.9 Hz, J_{XY} = 14.9 Hz), 3.60–3.69 (m, 1H), 3.95 (d, 2H, J = 5.7 Hz), 4.24 (q, 2H, J = 7.2 Hz), 5.24 (t, 1H, J = 5.7 Hz), 5.33 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.0, 28.2, 41.0, 44.4, 58.3, 61.8, 79.7, 156.1, 169.8.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-benzyltauryl]proline Methylamide (30).** According to general procedure B: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H), 1.91–2.01 (m, 2H), 2.09–2.30 (m, 2H), 2.84 (d, 3H, J = 4.9 Hz), 2.90 (dd, 1H, A of ABX, J_{AX} = 9.9 Hz, J_{AB} = 14.2 Hz), 3.29–3.52 (m, 3H), 3.44, 3.58 (six lines (H_a), six lines (H_b), 2H, AB of ABX, J_{AX} = 6.1 Hz, J_{BX} =7.3 Hz, J_{AB} = 9.6 Hz), 3.53–3.68 (m, 1H), 4.40 (dd, 1H, A of AXY, J_{AX} = 3.8 Hz, J_{AY} = 8.0 Hz), 5.28 (br, 1H), 6.59 (br, 1H), 7.12–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.5, 28.2, 31.0, 33.1, 39.2, 49.6, 62.3, 63.1, 79.6, 127.0, 128.8, 128.9, 136.7, 155.6, 172.2.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-benzyltauryl]glycine Ethyl Ester (31).** The sulfonamide **31** was prepared from the corresponding sulfinamide **26** (58 mg, 0.15 mmol) according to general procedure B. Column chromatography (10 g of silica, eluent: CH_2Cl_2/MeOH, 99/1, v/v) afforded **31** as an oil in 94% yield, which solidified upon standing: R_f 0.42 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 2.89 (dd, 1H, A of ABX, J_{AX} = 10.7 Hz, J_{AB} = 15.0 Hz), 3.35–3.45 (m, 3H), 3.76–3.83 (m, 1H), 3.87, 3.99 (two dd, 2H, AB of ABX, J_{AX} = 5.4 Hz, J_{BX} = 6.4 Hz, J_{AB} = 18.2 Hz), 4.22 (q, 2H, J = 7.1 Hz), 5.12 (br, 1H), 5.59 (br, 1H), 7.20–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 28.2, 32.7, 38.5, 44.4, 61.8, 64.0, 79.9, 127.0, 128.8, 129.0, 136.7, 156.1, 169.8.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*R*)-benzyltauryl]phenylalanine Methyl Ester (32).** The sulfonamide **32** was prepared from the corresponding sulfinamide **27** (69 mg, 0.15 mmol) according to general procedure B. Column chromatography (10 g of silica, eluent CH_2Cl_2/MeOH, 99/1, v/v) gave the sulfonamide **32** as an oil in 91% yield: R_f 0.87 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 2.59 (dd, 1H, A of ABX, J_{AX} = 10.6 Hz, J_{AB} = 13.8 Hz), 3.09–3.20 (m, 2H), 3.04, 3.16 (two dd, 2H, AB of ABX, J_{AX} = 7.3 Hz, J_{BX} = 5.4 Hz, J_{AB} = 13.8 Hz), 3.24 (six lines, 1H, A of ABX, J_{AX} = 6.1 Hz, J_{AB} = 14.8 Hz), 3.54–3.65 (m, 1H), 3.75 (s, 3H), 4.44 (eight lines, 1H, X of ABX, J_{XA} = 7.3 Hz, J_{XB} = 5.4 Hz, J_{XNH} = 9.1 Hz), 5.04 (t, 1H, J = 6.1 Hz), 5.51 (d, 1H, J = 9.1 Hz), 6.95–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.3, 32.4, 38.2, 39.3, 52.6, 57.6, 64.4, 79.8, 127.0, 127.4, 128.7, 129.0, 129.4, 135.5, 136.5, 155.8, 172.1.

***N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-methylhypotauryl]proline Methylamide (33).** Sulfinyl chloride **18** (1.56 mmol) was coupled to H-Pro-N(H)Me **20** (0.218 g, 1.64 mmol) according to general procedure A. Column chromatography (25 g silica, eluent: EtOAc/MeOH, 95/5, v/v) afforded the two separated diastereomers (R_f 0.34, 0.29 ratio 1.1/1) as oils in a total yield of 72%.

Higher running diastereomer: R_f 0.34 (eluent: EtOAc/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, 3H, J = 6.8 Hz), 1.45 (s, 9H), 1.77–2.05 (m, 2H), 2.12–2.20 (m, 2H), 2.76, 2.96 (two dd, 2H, AB of ABX, J_{AX} = 9.1 Hz, J_{BX} = 4.8 Hz, J_{AB} = 13.8 Hz), 2.85 (d, 3H, J = 4.8 Hz), 3.45, 3.50 (six lines (H_a), eight lines (H_b), 2H, AB of ABXY, J_{AX} = 7.0 Hz, J_{BX} = 5.8 Hz, J_{BY} = 7.5 Hz, J_{AB} = 10.5 Hz), 3.98–4.10 (m, 1H), 4.48 (t, 1H, J = 6.1 Hz), 4.82 (d, 1H, J = 8.9 Hz), 7.39 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 25.3, 26.0, 28.2, 32.1, 42.6, 52.6, 56.9, 61.2, 79.7, 155.1, 173.2.

Lower running diastereomer: R_f 0.29 (eluent: EtOAc/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (d, 3H, J = 6.9 Hz), 1.45 (s, 9H), 1.52–2.05 (m, 2H), 2.05–2.26 (m, 2H), 2.73, 3.23 (two dd, 2H, AB of ABX, J_{AX} = 7.2 Hz, J_{BX} = 4.1 Hz, J_{AB} = 13.2 Hz), 2.82 (d, 3H, J = 4.9 Hz), 3.13, 3.75 (eight lines (H_a), six lines (H_b), 2H, AB of ABXY, J_{AX} = 3.9 Hz, J_{AY} = 7.7 Hz, J_{BX} = 8.1 Hz, J_{AB} = 10.1 Hz), 3.84–3.95 (m, 1H), 4.23 (dd, 1H, A of AXY, J_{AX} = 3.4 Hz, J_{AY} = 8.2 Hz), 4.90 (d, 1H, J = 7.3 Hz), 7.37 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 24.7, 26.2, 28.3, 31.4, 40.7, 42.5, 61.3, 67.1, 80.0, 155.2, 172.7.

***N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-benzylhypotauryl]proline Methylamide (34).** Sulfinamide **34** was prepared by coupling of sulfinylchloride **19** (0.73 mmol) to H-Pro-N(H)Me **20** (98 mg, 0.76 mmol) according to general procedure A. Column chromatography (20 g of silica, eluent: EtOAc/MeOH, 95/5, v/v) afforded the separated diastereomers **34** as oils (R_f 0.31, 0.29 ratio 1.2/1) in 75% total yield.

Higher running diastereomer: R_f 0.31 (eluent: EtOAc/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 1.75–1.94 (m, 2H), 2.11–2.17 (m, 2H), 2.76, 2.93 (two dd, 2H, AB of ABX, J_{AX} = 10.1 Hz, J_{BX} = 4.5 Hz, J_{AB} = 13.9 Hz), 2.77–2.83, 2.87 (m (H_a), dd (H_b), 2H, AB of ABX, J_{BX} = 6.6 Hz, J_{AB} = 13.7 Hz), 2.87 (d, 3H, J = 4.8 Hz), 3.37, 3.43 (six lines (H_a), eight lines (H_b), 2H, AB of ABXY, J_{AX} = 7.2 Hz, J_{BX} = 7.6 Hz, J_{BY} = 5.4 Hz, J_{AB} = 10.6 Hz), 4.19–4.22 (m, 1H), 4.42 (dd, 1H, A of AXY, J_{AX} = 4.7 Hz, J_{AY} = 7.6 Hz), 4.77 (d, 1H, J = 9.3 Hz), 7.12–7.34 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.1, 28.2, 32.2, 41.2, 47.9, 52.1, 57.4, 59.0, 79.9, 127.0, 128.7, 129.2, 136.4, 155.3, 173.0.

Lower running diastereomer R_f 0.29 (eluent: EtOAc/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 1.76–1.86, 1.89–1.97 (two m, 2H), 2.07–2.21 (m, 2H), 2.90, 3.11 (two dd, 2H, AB of ABX, J_{AX} = 5.5 Hz, J_{BX} = 7.7 Hz, J_{AB} = 13.4 Hz), 2.93, 3.07 (two dd, 2H, AB of ABX, J_{AX} = 5.6 Hz, J_{BX} = 7.5 Hz, J_{AB} = 13.5 Hz), 2.81 (d, 3H, J = 4.9 Hz), 3.37, 3.70 (six lines (H_a), six lines (H_b), 2H, AB of ABX, J_{AX} = 7.6 Hz, J_{BX} = 8.0 Hz, J_{AB} = 9.9 Hz), 4.08–4.14 (m, 1H), 4.21 (dd, 1H, A of AXY, J_{AX} = 3.9 Hz, J_{AY} = 8.2 Hz), 5.03 (d, 1H, J = 8.0 Hz), 7.12 (br, 1H), 7.18–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8, 26.1, 28.2, 31.3, 40.6, 41.0, 47.9, 58.3, 66.8, 80.0, 127.0, 128.7, 129.2, 136.7, 155.3, 172.6.

***N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-methyltauryl]proline Methylamide (35).** The sulfinamide **33** (0.282 g, 0.84 mmol) was converted to the corresponding sulfonamide **35** according to general procedure B. Column chromatography (15 g of silica, eluent: EtOAc/MeOH, 96/4, v/v) afforded **35** as an oily substance in 95% yield: R_f 0.59 (eluent: EtOAc/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (d, 3H, J = 6.9 Hz), 1.45 (s, 9H), 1.82–2.05 (m, 2H), 2.13, 2.28–2.37 (15 lines (H_a), m (H_b), 2H, AB of ABXYM, J_{AX} = 8.6 Hz, J_{AY} = 12.7 Hz, J_{AM} = 6.7 Hz, J_{AB} = 10.3 Hz), 2.83 (d, 3H, J = 4.9 Hz), 3.03 (dd, 1H, A of ABX, J_{AX} = 6.5 Hz, J_{AB} = 14.1 Hz), 3.38–3.53 (m, 3H), 4.11 (12 lines, 1H, A of AXY, J_{AX} = 6.9 Hz, J_{AY} = 4.6 Hz), 4.29 (dd, 1H, A of AXY, J_{AX} = 2.8 Hz, J_{AY} = 8.6 Hz), 4.99 (d, 1H, J = 6.9 Hz), 7.03 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 24.5, 26.0, 28.0, 30.6, 42.8, 48.9, 54.2, 61.4, 79.3, 154.9, 171.9; exact mass m/z calcd 350.4594, found 350.1750.

***N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-benzyltauryl]proline Methylamide (36).** The sulfonamide **36** was prepared from the sulfinamide **34** (79 mg, 0.24 mmol) according to general procedure B. Column chromatography (10 g silica, eluent: EtOAc/MeOH, 96/4, v/v) gave **36** as a white solid in 96% yield: R_f 0.67 (eluent: EtOAc/MeOH, 9 /1, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H), 1.85–1.95 (m, 2H), 2.01–2.15, 2.26–2.34 (two m, 2H), 2.80 (d, 3H, J = 4.9 Hz), 3.01, 3.09 (two dd, 2H, AB of ABX, J_{AX} = 7.3 Hz, J_{BX} = 8.6 Hz, J_{AB} = 14.0 Hz), 3.05–3.15, 3.31–3.38 (two m, 2H), 3.33, 3.46 (six lines (H_a), seven lines (H_b), 2H, AB of ABXY, J_{AX} = 7.3 Hz, J_{BX} = 5.3 Hz, J_{BY} = 6.1 Hz, J_{AB} = 10.0 Hz), 4.18–4.34 (m, 2H), 5.15 (d, 1H, J = 8.0 Hz), 6.92 (br, 1H), 7.21-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.7, 26.2, 28.2, 30.6, 39.8, 48.6, 49.1, 51.5, 61.8, 79.9, 126.8, 128.6, 129.2, 137.0, 155.1, 171.8; exact mass m/z calcd 426.5571, found 426.2063.

***N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-benzyltauryl]phenylalanine Methyl Ester (37).** HCl·H-Phe-OMe (0.91 g, 4.2

mmol), treated with NMM (0.46 mL, 4.2 mmol) in a mixture of CH_2Cl_2 (5 mL) and DMF (2 mL), was coupled to sulfinyl chloride **19** (4.0 mmol) dissolved in CH_2Cl_2 (10 mL) according to general procedure A. Column chromatography (100 g of silica, eluent: EtOAc/MeOH, 98/2, v/v) afforded the separated diastereomers as white solids (R_f 0.74, 0.65 ratio 1/1.6) in 66% total yield.

Higher running diastereomer: R_f 0.74 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 2.56, 2.60 (two dd, 2H, AB of ABX, J_{AX} = 4.7 Hz, J_{BX} = 6.7 Hz, J_{AB} = 13.3 Hz), 2.78 (dd, 1H, A of ABX, J_{AX} = 8.0 Hz, J_{AB} = 13.6 Hz), 2.98–3.03 (m, 2H), 3.13 (dd, 1H, B of ABX, J_{BX} = 5.5 Hz, J_{AB} = 13.6 Hz), 3.72 (s, 3H), 4.01–4.06 (m, 1H), 4.23–4.29 (m, 1H), 4.67 (d, 1H, J = 9.1 Hz), 5.10 (d, 1H, J = 8.4 Hz), 7.14–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.2, 39.9, 48.6, 52.3, 55.2, 57.2, 79.2, 126.5, 127.0, 128.4, 129.2, 129.4, 135.8, 137.0, 154.8, 172.6.

Lower running diastereomer: R_f 0.65 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 2.72 (dd, 1H, A of ABX, J_{AX} = 7.3 Hz, Hz, J_{AB} = 13.6 Hz), 2.86–2.95 (m, 3H), 2.99, 3.14 (two dd, 2H, AB of ABX, J_{AX} = 7.4 Hz, J_{BX} = 5.7 Hz, J_{AB} = 13.7 Hz), 3.73 (s, 3H), 4.00–4.08 (m, 1H), 4.23 (seven lines, 1H, X of ABX, J_{XA} = 7.4 Hz, J_{XB} = 5.7 Hz, J_{XNH} = 7.9 Hz), 4.54 (d, 1H, J = 7.9 Hz), 4.63 (d, 1H, J = 7.0 Hz), 7.14–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.3, 40.2, 48.4, 52.5, 58.6, 59.5, 79.2, 126.7, 127.0, 128.5, 129.4, 136.0, 137.0, 154.8, 172.7.

The sulfonamide **37** was prepared from the sulfinamides (0.569 g, 1.23 mmol) according to general procedure B. Additional CH_2Cl_2 (3.5 mL) was used to dissolve the sulfinamide completely, and after being stirred for 1.5 h, the mixture was diluted with EtOAc instead of CH_2Cl_2. Column chromatography (20 g of silica, eluent: petroleum ether/ether, 1/2, v/v) afforded **37** in 79% yield: R_f 0.29 (eluent: ether/petroleum ether, 1/1, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 2.81 (dd, 1H, A of ABX, J_{AX} = 6.9 Hz, J_{AB} = 13.8 Hz), 2.86–2.99 (m, 3H), 3.07, 3.15 (two dd, 2H, AB of ABX, J_{AX} = 6.7 Hz, J_{BX} = 5.6 Hz, J_{AB} = 13.8 Hz), 3.70 (s, 3H), 4.42 (six lines, 1H, X of ABX, J_{XA} = 6.2 Hz, J_{XB} = 9.1 Hz, J_{XNH} = 9.1 Hz), 4.48–4.60 (m, 1H), 4.72 (d, 1H, J = 9.2 Hz), 5.85 (d, 1H, J = 9.1 Hz), 7.15–7.61 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.2, 39.2, 40.5, 47.7, 52.4, 56.4, 57.1, 80.0, 126.8, 127.2, 128.5, 128.6, 129.4, 135.4, 136.5, 154.1, 172.0.

***N*-[2(*S*)-Benzyltauryl]phenylalanine (38).** The methyl ester **37** was saponified according to a slightly adapted version of the method described by Corey *et al.*[37] Compound **37** (0.299 g, 0.63 mmol) was dissolved in 0.25 N LiOH (12.5 mL, 3.13 mmol, solution in MeOH/H_2O, 3/1, v/v) and stirred overnight at rt. Subsequently, the reaction mixture was neutralized with 2 N $KHSO_4$, concentrated *in vacuo*, and partitioned between EtOAc and water. The pH of the aqueous layer was adjusted to 2 with 2 N $KHSO_4$. The water layer was extracted with EtOAc (3 × 30 mL). The collected EtOAc layers were washed with brine (1 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford the carboxylic acid in 98% yield: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.76–3.08 (m, 4H), 3.05, 3.19 (two dd, 2H, AB of ABX, J_{AX} = 6.9 Hz, J_{BX} = 5.1 Hz, J_{AB} = 13.9 Hz), 4.32–4.52 (m, 2H), 4.88 (br, 1H), 5.74 (br, 1H), 7.14–7.40 (m, 10H), 8.76 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 38.8, 40.1, 47.7, 56.1, 56.9, 80.2, 126.6, 127.0, 128.4, 128.5, 129.2, 129.5, 135.6, 136.5, 155.9, 174.4.

The Boc group of the thus obtained carboxylic acid (0.149 g, 0.32 mmol) was removed according to general procedure C. The TFA salt was dissolved in a mixture of *t*-BuOH/water (ratio 1/1) and purified by ion exchange column chromatography (Dowex H^+, 100–200 mesh, eluent *t*-BuOH/H_2O (1/1, v/v) with an aqueous ammonia gradient from 0.05 to 0.25 N). After lyophilization **38** was obtained in 93% yield: ^{1}H NMR (0.1 M NaOD, 300 MHz) δ 2.50 (dd, 1H, A of ABX, J_{AX} = 8.3 Hz, J_{AB} = 13.5 Hz), 2.60 (dd, 1H, A of ABX, J_{AX} = 8.7 Hz, J_{AB} = 14.4 Hz), 2.68–2.80 (m, 3H), 3.02 (dd, 1H, B of ABX, J_{BX} = 6.0 Hz, J_{AB} = 13.4 Hz), 3.25-3.34 (m, 1H), 3.79 (dd, 1H, X of ABX, J_{XA} = 8.5 Hz, J_{XB} = 6.0 Hz), 7.21–7.40 (m, 10H); ^{13}C NMR (0.1 M NaOD) δ 41.2, 42.3, 48.6, 57.8, 63.0, 127.0, 127.2, 129.0, 129.2, 130.0, 130.1, 138.6, 139.5, 181.7; FABMS m/z 363 $(M + H)^+$.

***N*-[*N*-(*tert*-Butoxycarbonyl)-1(*RS*)-benzyltauryl]-*N'*-*tert*-butyl-(4a*S*,8a*S*)-decahydro-3(*S*)-isoquinolinecarboxamide (40).** Sulfinyl chloride **5** (1.44 mmol) was coupled to DIQ-NH-*t*-Bu (**39**) (342 mg, 1.44 mmol) according to general procedure A. Purification using column chromatography (20 g of silica, eluent: gradient of ether/petroleum ether, 1/2, v/v to ether/petroleum ether, 1/1, v/v) afforded the sulfinamide as a mixture of four diastereomers in 53% yield. R_f 0.14 (eluent: ether/petroleum ether, 1/1, v/v). These sulfinamides (371 mg, 0.71 mmol) were converted to the sulfonamide **40** according to general procedure B. Column chromatography (20 g silica, eluent ether/petroleum ether, 2/3, v/v) gave **40** as an oil in 85% yield. R_f 0.19 (eluent: ether/petroleum ether, 1/1, v/v). The numbering of the carbon atoms in (4a*S*, 8a*S*)-decahydro-3(*S*)-isoquinolinecarbonyl-*tert*-butylamide **39** is indicated in Scheme 4: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14–1.98 (m, 22H), 1.36, 1.39 (two s, 18H), 1.41, 1.42 (two s, 18H), 2.16–2.26 (m, 2H), 2.81-2.91, 2.87 (m, dd, 2H, A of ABX, J_{AX} = 10.0 Hz, J_{AB} = 14.0 Hz), 3.28–3.60 (m, 12H), 4.15–4.21 (m, 2H), 5.43–5.51 (m, 2H), 5.82, 5.90 (two s, 2H), 7.21–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.6, 25.3, 26.5, 28.1, 28.3, 28.4, 32.5, 32.6, 33.2, 34.5, 34.6, 38.4, 44.3, 44.8, 51.2, 55.5, 63.7, 79.0, 126.7, 128.5, 128.8, 128.9, 136.5, 136.7, 155.3, 170.5, 170.6.

***N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-benzyltauryl]-*N'*-*tert*-butyl-(4a*S*,8a*S*)-decahydro-3(*S*)-isoquinolinecarboxamide (41).** Sulfinyl chloride **19** (1.50 mmol) was coupled to DIQ-NH-*t*-Bu (**39**) (0.365 g, 1.53 mmol) according to general procedure A. By using column chromatography (30 g of silica, eluent: EtOAc/petroleum ether, 1/1, v/v) a mixture of the diastereomeric sulfinamides (ratio by NMR: 1.3/1) was obtained as an oil in 76% yield: R_f 0.30, 0.37 (eluent: EtOAc/petroleum ether, 1/1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.08–2.48 (m, 24H), 1.36, 1.39 (two s, 18H), 1.42 (s, 18H), 2.66–3.38 (m, 12H), 3.61–3.65 (m, 1H), 3.83–3.90 (m, 1H), 4.04–4.20 (m, 2H), 4.86 (d, 1H, J = 8.9 Hz), 5.28 (d, 1H, J = 8.7 Hz), 6.38 (br, 2H), 7.16–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.2, 24.8, 25.8, 26.2, 26.4, 29.0, 29.8, 28.0. 28.2, 28.3, 30.3, 31.8, 33.3, 33.6, 34.0, 34.9, 39.7, 41.3, 42.2, 45.7, 48.3, 50.9, 55.4, 56.8, 63.7, 78.8, 79.1, 126.3, 126.6, 128.2, 128.4, 128.9, 129.2, 136.8, 137.2, 154.7, 169.9, 170.2.

The sulfinamides (0.566 g, 1.09 mmol) were converted to sulfonamide **41** according to general procedure B. Column chromatography (20 g of silica, eluent: petroleum ether/ether, 1/1, v/v) afforded **41** as an oil in 98% yield: R_f 0.11 (eluent: ether/petroleum ether, 1/1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.08–1.56, 1.60–1.88 (two m, 11H), 1.34 (s, 9H), 1.39 (s, 9H), 2.16-2.30 (m, 1H), 3.01–3.05 (m, 2H), 3.22 (d, 2H, J = 5.7 Hz), 3.34–3.39 (m, 2H), 4.16–4.28 (m, 2H), 5.15 (br, 1H), 6.08 (br, 1H), 7.18–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.1, 25.9, 26.0, 28.1, 28.3, 28.7, 31.6, 33.1, 33.6, 40.0, 42.5, 48.8, 51.0, 54.0, 54.2, 79.3, 126.4, 128.4, 129.2, 137.1, 154.8, 170.1.

***N*-[*N*-[*N*-(*tert*-Butoxycarbonyl)asparaginyl]-[1(*R*)- and 1(*S*)-benzyl]tauryl]-*N'*-*tert*-butyl-(4a*S*,8a*S*)-decahydro-3(*S*)-isoquinolinecarboxamide (42a,b).** The Boc group of sulfonamide **40** (122 mg, 0.23 mmol) was removed according to general procedure C. Upon lyophilization the amine was isolated in 90% yield: R_f 0.26 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$) δ 1.20–2.04 (m, 22H), 1.34, 1.38 (two s, 18H), 2.06–2.28 (m, 2H), 2.74 (dd, 1H, A of ABX, J_{AX} = 11.6 Hz, J_{AB} = 13.6 Hz), 2.84 (dd, 1H, A of ABX, J_{AX} = 11.3 Hz, J_{AB} = 13.9 Hz), 3.29–3.80 (m, 12H), 3.67 (s, 4H), 4.24–4.34 (m, 2H), 6.07, 6.37 (two s, 2H), 7.17–7.38 (m, 10); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.5, 25.5, 25.7, 26.4, 28.3, 28.5, 28.6, 32.7, 33.1, 33.3, 34.6, 38.7, 39.2, 43.9, 44.4, 51.2, 51.3, 54.8, 63.3, 64.6, 126.8, 128.6, 128.8, 128.9, 136.1, 136.4, 170.7, 171.0.

The amine (92 mg, 0.21 mmol) was coevaporated in dioxane (4 × 10 mL) and dissolved in a mixture of THF (2 mL) and DMF (2 mL). Boc-Asn-OH (55 mg, 0.23 mmol) and HOBt (35 mg, 0.23 mmol) were added. The apparent pH was adjusted to 7–8 with NMM, and the mixture was cooled to 0 °C. After addition of DCC (49 mg, 0.24 mmol) the mixture was stirred for 1 h at 0 °C and overnight at rt. The precipitated DCU was filtered and the filtrate diluted with EtOAc (50 mL) and subsequently washed with citric acid 5% (1 × 5 mL), saturated Na_2CO_3 (2 x 5 mL), and brine (5 mL). The organic layer was

(37) Corey, E. J.; Székely, I.; Shiner, C. S. *Tetrahedron Lett.* **1977**, 3529–3532.

dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (75 g silica, eluent: EtOAc) afforded the separated diastereomers **42a** and **42b** (ratio 1/1) as oils in 90% total yield, which solidified upon standing.

Higher running diastereomer **42a**: R_f 0.63 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14−1.67 (m, 8H), 1.35 (s, 9H), 1.45 (s, 9H), 1.76−2.05 (m, 3H), 2.19 (six lines, 1H, B of ABX, J_{BX} = 3.4 Hz, J_{AB} = 14.0 Hz), 2.57, 2.95 (two dd, 2H, AB of ABX, J_{AX} = 5.6 Hz, J_{BX} = 4.1 Hz, J_{AB} = 15.8 Hz), 2.88, 3.31 (two dd, 2H, AB of ABX, J_{AX} = 3.4 Hz, J_{BX} = 11.0 Hz, J_{AB} = 14.0 Hz), 3.38 (dd, 1H, A of ABX, J_{AX} = 4.6 Hz, J_{AB} = 13.5 Hz), 3.41−3.46 (m, 1H), 3.51-3.61 (m, 3H), 4.20 (dd, 1H, A of AXY, J_{AX} = 3.0 Hz, J_{AY} = 6.7 Hz), 4.30−4.44 (m, 1H), 5.53, 6.06 (two s, 2H), 5.97 (s, 1H), 6.00 (d, 1H, J = 8.2 Hz), 7.22−7.33 (m, 5H), 7.54 (br, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.7, 25.6, 26.7, 28.3, 28.5, 28.7, 32.2, 32.7, 33.4, 34.6, 36.7, 36.8, 44.4, 51.1, 51.4, 55.5, 63.2, 80.2, 127.0, 128.8, 129.2, 136.7, 155.5, 170.6, 171.2, 173.4.

Lower running diastereomer **42b**: R_f 0.56 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18−1.69 (m, 8H), 1.38 (s, 9H), 1.46 (s, 9H), 1.77−1.95 (m, 3H), 2.11−2.17 (m, 1H), 2.58, 2.89 (two dd, 2H, AB of ABX, J_{AX} = 5.3 Hz, J_{BX} = 4.6 Hz, J_{AB} = 15.6 Hz), 2.78 (dd, 1H, A of ABX, J_{AX} = 11.0 Hz, J_{AB} = 13.6 Hz), 3.38−3.63 (m, 6H), 4.27 (dd, 1H, A of AXY, J_{AX} = 2.8 Hz, J_{AY} = 6.7 Hz), 4.42−4.48 (m, 1H), 5.90 (s, 1H), 5.49, 6.10 (two s, 2H), 5.99 (d, 1H, J = 7.7 Hz), 7.22−7.33 (m, 5H), 7.59 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 25.7, 26.6, 28.3, 28.6, 28.7, 32.5, 33.1, 33.4, 34.8, 37.0, 44.5, 51.4, 51.5, 55.2, 63.2, 80.2, 127.0, 128.7, 129.2, 136.4, 155.6, 170.8, 171.3, 173.2.

***N*-[*N*-[*N*-(*tert*-Butoxycarbonyl)asparaginyl]-2(*S*)-benzyltauryl]-*N'*-*tert*-butyl-(4a*S*,8a*S*)-decahydro-3(*S*)-isoquinolinecarboxamide (43).** The Boc group of sulfonamide **41** (0.377 g, 0.70 mmol) was removed according to general procedure C. After lyophilization the amine was obtained in 91% yield: R_f 0.19 (eluent: EtOAc/petroleum ether, 1/1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.08-1.88 (m, 13H), 1.35 (s, 9H), 2.26−2.36 (m, 1H), 2.71, 2.81 (two dd, 2H, AB of ABX, J_{AX} = 7.6 Hz, J_{BX} = 5.9 Hz, J_{AB} = 13.1 Hz), 3.02, 3.19 (two dd, 2H, AB of ABX, J_{AX} = 9.1 Hz, J_{BX} = 2.6 Hz, J_{AB} = 14.0 Hz), 3.34−3.48 (m, 2H), 3.59−3.66 (m, 1H), 4.20 (dd, 1H, A of AXY, J_{AX} = 6.6 Hz, J_{AY} = 2.0 Hz), 6.15 (br, 1H), 7.20−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.9, 25.9, 28.2, 28.9, 31.6, 33.0, 33.4, 42.4, 43.2, 48.6, 50.9, 54.0, 58.3, 126.4, 128.3, 129.0, 137.2, 169.9.

The amine (0.275 g, 0.63 mmol) was coevaported in dioxane (4 × 10 mL) and dissolved in a mixture of CH_2Cl_2 (5 mL) and DMF (3 mL). Boc-Asn-OH (0.161 g, 0.69 mmol) and HOBt (0.106 g, 0.69 mmol) were added. The apparent pH was adjusted to 7−8, and the mixture was cooled to 0 °C. After addition of DCC (0.142 g, 0.69 mmol) the mixture was stirred for 1 h at 0 °C and overnight at rt. The precipitated DCU was filtered and the filtrate diluted with CH_2Cl_2 (50 mL) and subsequently washed with citric acid 5% (2 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and brine (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (20 g of silica, eluent: gradient of CH_2Cl_2 to CH_2Cl_2/MeOH, 98/2, v/v) afforded **43** as an oil in 84% yield: R_f 0.52 (eluent: CH_2Cl_2/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.08−1.92 (m, 11H), 1.33 (s, 9H), 1.44 (s, 9H), 2.18−2.25 (m, 1H), 2.61, 2.84 (two dd, 2H, AB of ABX, J_{AX} = 6.6 Hz, J_{BX} = 3.6 Hz, J_{AB} = 15.6 Hz), 2.91, 3.05 (two dd, 2H, AB of ABX, J_{AX} = 7.1 Hz, J_{BX} = 8.5 Hz, J_{AB} = 14.5 Hz), 3.12−3.40 (m, 4H), 4.18 (dd, 1H, A of AXY, J_{AX} = 5.7 Hz, J_{AY} = 1.2 Hz), 4.36−4.60 (m, 2H), 5.46, 6.00 (two s, 2H), 5.99−6.06 (m, 2H), 7.19−7.32 (m, 5H), 7.56 (d, 1H, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$/MeOD) δ 21.1, 26.0, 28.1, 28.3, 28.8, 31.8, 33.1, 33.6, 37.2, 39.9, 42.5, 47.3, 51.1, 53.3, 54.3, 80.0, 126.8, 128.5, 129.3, 136.7, 155.5, 170.6, 171.0, 173.5.

***N*-[*N*-[*N*-(Quinoline-2-carbonyl)asparaginyl]-[1(*R*)- and 1(*S*)-benzyl]tauryl]-*N'*-*tert*-butyl-(4a*S*,8a*S*)-decahydro-3(*S*)-isoquinolinecarboxamide (44, 45).** The Boc group of **42a** (115 mg, 0.177 mmol) was removed according to general procedure C, and the amine was isolated in 98% yield: ^{1}H NMR ($CDCl_3$) δ 1.27−2.04 (m, 13H), 1.36 (s, 9H), 2.16−2.24 (m, 1H), 2.51, 2.65 (two dd, 2H, AB of ABX, J_{AX} = 7.1 Hz, J_{BX} = 4.2 Hz, J_{AB} = 15.1 Hz), 2.85 (dd, 1H, A of ABX, J_{AX} = 10.6 Hz, J_{AB} = 14.0 Hz), 3.32−3.62 (m, 7H), 4.23 (dd, 1H, A of AXY, J_{AX} = 2.2 Hz, J_{AY} = 5.9 Hz), 5.60, 6.35 (two s, 2H), 6.03 (br, 1H), 7.22−7.36 (m, 5H), 8.05 (br, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.6, 25.5, 26.5, 28.4, 28.5, 32.7, 33.3 (C^4), 33.3, 34.5, 37.1, 39.9, 44.4, 51.3, 52.3, 55.4, 63.4, 126.8, 128.7, 129.0, 136.8, 170.7, 173.6, 174.0.

The amine (88 mg, 0.16 mmol) was coupled to quinaldic acid (31 mg, 0.176 mmol) in DMF (2 mL) using the DCC/HOBt method described above. Column chromatography (15 g of silica, eluent: CH_2Cl_2/MeOH, 96/4, v/v) afforded **44** as an oil in 98% yield: R_f 0.22 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11−1.67 (m, 8H), 1.32 (s, 9H), 1.72−1.98 (m, 3H), 2.19 (6 lines, 1H, B of ABX, J_{BX} = 3.3 Hz, J_{AB} = 14.0 Hz), 2.81, 3.06 (two dd, 2H, AB of ABX, J_{AX} = 6.4 Hz, J_{BX} = 4.6 Hz, J_{AB} = 15.9 Hz), 2.88, 3.32 (two dd, 2H, AB of ABX, J_{AX} = 10.5 Hz, J_{BX} = 3.3 Hz, J_{AB} = 14.1 Hz), 3.38−3.56 (m, 4H), 3.67−3.73 (m, 1H), 4.22 (dd, 1H, X of ABX, J_{XA} = 6.7 Hz, J_{XB} = 3.3 Hz), 4.99 (eight lines, 1H, X of ABX, J_{XA} = 6.4 Hz, J_{XB} = 4.6 Hz, J_{XNH} = 8.1 Hz), 5.59, 6.18 (two s, 2H), 6.02 (br, 1H), 7.16−7.30 (m, 5H), 7.59−7.65 (m, 1H), 7.70−7.79 (m, 2H), 7.85−7.88 (m, 1H), 8.16−8.31 (m, 3H), 9.37 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 25.6, 26.6, 28.4, 28.5, 32.5, 32.7, 33.3, 34.5, 37.0, 37.3, 44.2, 50.0, 51.3, 55.3, 63.0, 118.6, 127.4, 127.9, 129.2, 130.0, 137.3, 146.5, 148.8, 126.8, 128.7, 129.0, 136.5, 164.8, 170.6, 170.8, 173.2.

The Boc group of **42b** (104 mg, 0.16 mmol) was removed according to general procedure C to give the amine in quantitative yield:

^{1}H NMR ($CDCl_3$) δ 1.20−2.00 (m, 13H), 1.38 (s, 9H), 2.06−2.21 (m, 1H), 2.45, 2.66 (two dd, 2H, AB of ABX, J_{AX} = 8.0 Hz, J_{BX} = 3.7 Hz, J_{AB} = 15.2 Hz), 2.75 (dd, 1H, A of ABX, J_{AX} = 11.8 Hz, J_{AB} = 14.4 Hz), 3.41−3.69 (m, 7H), 4.27 (dd, 1H, A of AXY, J_{AX} = 2.5 Hz, J_{AY} = 7.9 Hz), 5.63, 6.51 (two s, 2H), 5.98 (br, 1H), 7.21−7.36 (m, 5H), 8.01 (br, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.6, 25.5, 26.5, 28.5, 28.6, 32.8, 33.3, 33.3, 34.8, 37.2, 40.1, 44.6, 51.3, 52.3, 55.0, 63.1, 126.9, 128.6, 129.0, 136.6, 170.9, 173.7, 174.1.

The amine (80 mg, 0.146 mmol) derived from **42b** was coupled to quinaldic acid (28 mg, 0.161 mmol) using the DCC/HOBt coupling method described above. Column chromatography (15 g of silica, eluent: CH_2Cl_2/MeOH, 96/4, v/v) afforded **45** as an oil in 98% yield, which solidified upon standing: R_f 0.46 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11−1.67 (m, 8H), 1.29 (s, 9H), 1.59−1.98 (m, 3H), 2.19 (six lines, 1H, B of ABX, J_{BX} = 3.0 Hz, J_{AB} = 14.0 Hz), 2.81, 3.03 (two dd, 2H, AB of ABX, J_{AX} = 6.0 Hz, J_{BX} = 5.1 Hz, J_{AB} = 15.8 Hz), 2.79 (dd, 2H, A of ABX, J_{AX} = 10.4 Hz, J_{AB} = 13.7 Hz), 3.34−3.55 (m, 5H), 3.65−3.73 (m, 1H), 4.22 (dd, 1H, X of ABX, J_{XA} = 6.5 Hz, J_{XB} = 3.0 Hz), 5.02 (six lines, 1H, X of AX, J_{XA} = 5.5 Hz, J_{XNH} = 8.3 Hz), 5.57, 6.26 (two s, 2H), 5.90 (br, 1H), 7.17−7.32 (m, 5H), 7.59−7.65 (m, 1H), 7.73−7.79 (m, 2H), 7.85−7.88 (m, 1H), 8.15−8.31 (m, 3H), 9.33 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.5, 25.6, 26.5, 28.4, 28.6, 32.9, 33.3, 34.6, 37.2, 37.4, 44.2, 50.1, 51.3, 55.0, 63.1, 118.6, 127.5, 128.0, 129.2, 130.0, 137.2, 146.4, 148.9, 126.9, 128.7, 129.1, 136.4, 164.7, 170.6, 170.8, 173.0.

***N*-[*N*-[*N*-(Quinoline-2-carbonyl)asparaginyl]-2(*S*)-benzyltauryl]-*N'*-*tert*-butyl-(4a*S*,8a*S*)-decahydro-3(*S*)-isoquinolinecarboxamide (46).** The Boc group of sulfonamide **43** (0.274 g, 0.42 mmol) was removed according to general procedure C. Upon lyophilization the amine was obtained in 92% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12−1.96 (m, 13H), 1.34 (s, 9H), 2.16−2.28 (m, 1H), 2.46, 2.63 (two dd, 2H, AB of ABX, J_{AX} = 7.5 Hz, J_{BX} = 4.5 Hz, J_{AB} = 15.2 Hz), 3.01 (d, 2H, J = 6.9 Hz), 3.24 (d, 2H, J = 6.2 Hz), 3.24−3.44 (m, 2H), 3.63−3.69 (m, 1H), 4.18 (dd, 1H, A of AXY, J_{AX} = 1.8 Hz, J_{AY} = 5.1 Hz), 4.48−4.64 (m, 1H), 5.52, 6.26 (two s, 2H), 6.09 (s, 1H), 7.21−7.38 (m, 5H), 7.87 (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 25.9, 28.3, 28.7, 32.0, 33.1, 33.6, 40.0, 42.5, 46.8, 51.0, 52.3, 53.5, 54.1, 126.6, 127.5, 128.1, 128.3, 129.3, 136.8, 170.4, 173.7, 173.9.

The potential protease inhibitor **46** was synthesized from the amine (0.22 g, 0.40 mmol) and quinaldic acid (73 mg, 0.42 mmol) using the DCC/HOBt coupling method described for the synthesis of **43**, with DMF (5 mL) as reaction solvent. Column chromatography (15 g silica, eluent: gradient of CH_2Cl_2/MeOH, 99/1 to 96/4, v/v) afforded **46** as a white solid in 86% yield: R_f 0.38 (eluent: EtOAc/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10−1.52, 1.60−1.72 (two m, 9H), 1.32

(s, 9H), 1.60–1.72 (m, 1H), 1.80–1.90 (m, 1H), 2.25 (six lines, 1H, B of ABX, J_{BX} = 2.4 Hz, J_{AB} = 14.1 Hz), 2.87, 2.94–3.03 (dd (H_a), m (H_b), 2H, AB of ABX, J_{AX} = 7.1 Hz, J_{AB} = 15.8 Hz), 2.95, 3.04 (two dd, 2H, AB of ABX, J_{AX} = 7.3 Hz, J_{BX} = 6.1 Hz, J_{AB} = 13.5 Hz), 3.19, 3.26 (two dd, 2H, AB of ABX, J_{AX} = 4.7 Hz, J_{BX} = 7.7 Hz, J_{AB} = 12.5 Hz), 3.21–3.26, 3.37 (m (H_a), t (H_b), 2H, J = 13.0 Hz), 4.22 (dd, 1H, A of AXY, J_{AX} = 1.8 Hz, J_{AY} = 7.0 Hz), 4.58–4.76 (m, 1H), 4.99 (six lines, 1H, X of ABX, J_{XA} = 7.1 Hz, J_{XB} = 4.2 Hz), 5.77, 6.42 (two s, 2H), 6.21 (s, 1H), 7.10–7.26 (m, 5H), 7.58–7.62, 7.73–7.77, 7.83–7.85, 8.16–8.26 (four m, 7H), 9.40 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0, 25.9, 28.3, 28.7, 31.7, 33.0, 33.4, 37.2, 40.0, 42.5, 47.1, 49.9, 50.9, 53.5, 54.2, 118.3, 126.6, 127.3, 127.8, 128.3, 128.9, 129.2, 129.8, 136.6, 137.0, 164.4, 170.1, 170.4, 173.5; FABMS m/z 705 $(M + H)^+$.

***N*-[*N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-methyltauryl]tauryl]proline Methylamide (50).** The Boc group of Boc-Tau-Pro-N(H)Me[8] (**49**) (0.980 g, 2.92 mmol) was removed according to general procedure C. After lyophilization, Tau-Pro-N(H)-Me was obtained in quantitative yield: R_f 0.34 (eluent: CH_2Cl_2/MeOH/Et_3N, 9/1/0, 1 v/v); ^{1}H NMR ($CDCl_3$) δ 1.92 (br, 2H), 1.80–2.08 (m, 2H), 1.96–2.40 (m, 2H), 2.82 (d, 3H, J = 4.9 Hz), 3.08–3.28 (m, 5H), 3.43–3.53 (m, 1H), 4.30 (dd, 1H, A of AXY, J_{AX} = 3.3 Hz, J_{AY} = 8.2 Hz), 7.10 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.9, 30.7, 36.1, 48.8, 51.4, 61.6, 172.0.

Tau-Pro-N(H)Me (0.334 g, 1.42 mmol), dissolved in dry DMF (5 mL), was coupled to sulfinyl chloride **18** (1.56 mmol) in dry CH_2Cl_2 (5 mL) according to general procedure A. Purification by column chromatography (25 g silica, eluent: CH_2Cl_2/MeOH, 98/2, v/v) gave the separated sulfinamide diastereomers as oils in 70% total yield in a ratio of approximately 1/1.

Higher running diastereomer: R_f 0.18 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (d, 3H, J = 6.8 Hz), 1.42 (s, 9H), 1.92–2.08 (m, 2H), 2.10–2.27 (m, 2H), 2.83 (d, 3H, J = 4.8 Hz), 3.05–3.13, 3.22 (m (H_a), eight lines (H_b), 2H, AB of ABXY, J_{BX} = 4.5 Hz, J_{BY} = 6.1 Hz, J_{AB} = 14.1 Hz), 3.42, 3.57 (six lines (H_a), eight lines (H_b), 2H, AB of ABXY, J_{AX} = 7.2 Hz, J_{BX} = 5.3 Hz, J_{BY} = 6.5 Hz, J_{AB} = 9.8 Hz), 3.44–3.73 (m, 4H), 3.98–4.07 (m, 1H), 4.29 (dd, 1H, A of AXY, J_{AX} = 4.3 Hz, J_{AY} = 7.9 Hz), 5.19 (d, 1H, J = 6.8 Hz), 5.57 (dd, 1H, A of AXY, J_{AX} = 5.4 Hz, J_{AY} = 7.7 Hz), 6.63 (q, 1H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.5, 25.0, 26.3, 28.3, 31.0, 38.1, 43.0, 49.0, 50.6, 60.2, 61.5, 79.4, 155.0, 172.3.

Lower running diastereomer: R_f 0.14 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3H, J = 6.7 Hz), 1.44 (s, 9H), 1.88–2.36 (m, 4H), 2.84 (d, 3H, J = 4.9 Hz), 3.20–3.76 (m, 8H), 3.92–4.12 (m, 1H), 4.27 (dd, 1H, A of AXY, J_{AX} = 3.7 Hz, J_{AY} = 8.1 Hz), 4.82 (d, 1H, J = 8.0 Hz), 5.27 (t, 1H, J = 5.9 Hz), 6.58 (q, 1H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 25.0, 26.4, 28.3, 30.8, 38.5, 42.9, 49.3, 50.2, 61.6, 61.8, 79.7, 154.9, 171.9.

The sulfinamides (0.208 g, 0.47 mmol) were converted to the sulfonamide **50** according to general procedure B. The sulfonamide **50** was isolated after column chromatography (10 g silica, eluent: CH_2Cl_2/MeOH, 98/2, v/v) in 91% yield and was crystallized from CH_2Cl_2: mp 147–148 °C; R_f 0.45 (eluent: CH_2Cl_2/MeOH, 95/5, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (d, 3H, J = 6.9 Hz), 1.44 (s, 9H), 1.92–2.05 (m, 2H), 2.04–2.25 (m, 2H), 2.85 (d, 3H, J = 4.8 Hz), 3.17–3.25 (m, 2H), 3.30 (dd, 1H, B of ABX, J_{BX} = 6.2 Hz, J_{AB} = 14.5 Hz), 3.38–3.59 (m, 5H), 4.13 (seven lines, 1H, J = 6.9 Hz), 4.33 (dd, 1H, A of AXY, J_{AX} = 4.7 Hz, J_{AY} = 8.1 Hz), 5.30 (d, 1H, J = 6.9 Hz), 6.56 (q, 1H, J = 4.8 Hz), 6.85 (dd, 1H, A of AXY, J_{AX} = 5.3 Hz, J_{AY} = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.1, 25.0, 26.3, 28.1, 31.1, 37.4, 43.1, 48.9, 50.5, 56.6, 61.4, 79.6, 155.2, 172.8; exact mass m/z calcd 457.5906, found 457.1791.

***N*-[*N*-[*N*-[*N*-(*tert*-Butoxycarbonyl)-2(*S*)-benzyltauryl]-2(*S*)-methyltauryl]tauryl]proline Methylamide (51).** The Boc group of sulfonamide **50** (0.141 g, 0.31 mmol) was removed according to general procedure C. The amine was obtained in quantitative yield: R_f 0.37 (eluent: CH_2Cl_2/MeOH/Et_3N, 9/1/0.1, v/v); ^{1}H NMR (MeOD) δ 1.29 (d, 3H, J = 6.7 Hz), 1.93–2.05 (m, 3H), 2.18–2.33 (m, 1H), 2.76 (s, 3H), 3.09–3.56 (m, 9H), 4.29 (dd, 1H, A of AXY, J_{AX} = 3.6 Hz, J_{AY}= 8.2 Hz); ^{13}C NMR (MeOD) δ 21.5, 25.8, 26.3, 32.4, 38.3, 44.3, 49.9, 50.7, 58.8, 62.7, 175.0.

Sulfinyl chloride **19** (0.36 mmol) was coupled to this amine (96 mg, 0.27 mmol) according to general procedure A. Column chromatography (15 g silica, eluent: CH_2Cl_2/MeOH, 97/3, v/v) afforded the diastereomers in 64% total yield. The diastereomers (ratio 2.5/1 by NMR) could only be separated with difficulty; therefore, samples containing an excess of one of the diastereomers were used to interpret the NMR data. The chemical shifts of the diastereomer with the highest R_f value are indicated with an asterisk: R_f 0.40, 0.43 (eluent: CH_2Cl_2/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 18H), 1.41*, 1.42 (two d, 6H, J* = 7.2 Hz, J = 6.8 Hz), 1.88–2.10, 2.05–2.28 (two m, 8H), 2.80, 2.83* (two d, 6H, J = 4.7 Hz, J* = 4.8 Hz), 2.85–3.68 (m, 24H), 3.86–4.02 (m, 2H), 4.14–4.30 (m, 2H), 4.30*, 4.27-4.36 (t, m, 2H, J* = 6.2 Hz), 4.88, 5.23* (two d, 2H, J = 7.8 Hz, J* = 6.8 Hz), 6.50, 7.20 (br (2x), 2H), 7.04 (br, 2H), 7.12-5.35 (m, 10H), 7.70 (br, 2H); ^{13}C NMR ($CDCl_3$) δ 22.3, 25.0*, 25.1, 26.5, 28.3, 31.1*, 31.2, 37.5*, 37.6, 40.2, 40.7*, 47.7, 48.0*, 48.2, 48.4*, 49.0, 49.1*, 49.8*, 50.1, 58.3*, 58.5, 59.9*, 61.6, 61.8*, 79.8, 126.8, 128.5, 129.4, 136.7, 137.0, 155.0*, 155.1, 172.4*, 172.6.

The peptidosulfonamide **51** was prepared from the corresponding sulfinamide (48 mg, 76 μmol) according to general procedure B. Purification by column chromatography (10 g silica, eluent: CH_2Cl_2/MeOH, 98/2, v/v) afforded **12** as a white solid in 90% yield: R_f 0.69 (eluent: CH_2Cl_2/MeOH, 9/1, v/v); ^{1}H NMR ($CDCl_3$/MeOD, 400 MHz) δ 1.41 (s, 9H), 1.45 (d, 3H, J = 6.7 Hz), 2.01–2.11 (m, 3H), 2.28–2.37 (m, 1H), 2.83 (s, 3H), 2.90, 3.04 (two dd, 2H, AB of ABX, J_{AX} = 8.6 Hz, J_{BX} = 5.7 Hz, J_{AB} = 13.6 Hz), 3.24 (dd, 1H, A of ABX, J_{AX} = 6.0 Hz, J_{AB} = 14.5 Hz), 3.29 (dd, 1H, A of ABX, J_{AX} = 4.5 Hz, J_{AB} = 14.5 Hz), 3.33–3.48 (m, 4H), 3.49–3.63 (m, 4H), 3.97–4.02 (m, 1H), 4.26–4.34 (m, 1H), 4.36 (dd, 1H, A of AXY, J_{AX} = 3.9 Hz, J_{AY} = 8.5 Hz), 7.26–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$/MeOD, 100.6 MHz) δ 22.3, 25.7, 26.5, 28.7, 32.2, 38.2, 41.2, 47.0, 49.3, 49.8, 51.0, 57.0, 58.6, 62.5, 80.2, 127.3, 129.1, 130.2, 138.4, 157.0, 174.7; exact mass m/z calcd 654.8474, found 654.2301.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and spectral data for **2–4**, **8–11**, **14–19**, **21–38**, **40–46**, **50**, and **51** (104 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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