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A New Method for the Solution and Solid Phase Synthesis of Chiral β-Sulfonopeptides under Mild Conditions

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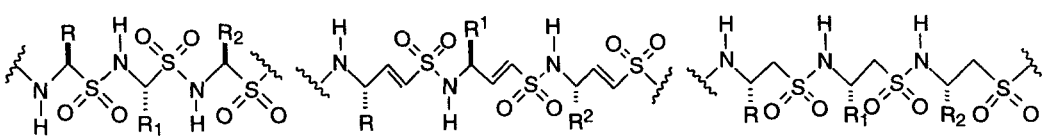
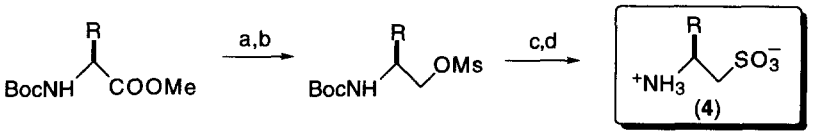
Abstract: Chiral β-sulfonopeptides were synthesized both in solution and in the solid phase using the sulfonyl chlorides derived from enantiomerically pure 2-substituted taurines under mild coupling conditions [cat. 4-dimethylaminopyridine (DMAP) and excess methyl trimethylsilyl dimethylketene acetal (MTDA) as a proton trap]. Copyright © 1996 Elsevier Science Ltd

Peptides are attractive targets for drug discovery because of their affinities and specificities toward biological receptors and the simplicity with which large peptide libraries can be synthesized in a combinatorial format. However, the poor stability and bioavailability of peptides *in vivo* have generally limited their therapeutic application. One approach toward overcoming this obstacle has been the development of non-natural biopolymer scaffolds (carbamates, peptoids, ureas, sulfonamides, etc.) with improved pharmacological properties relative to peptides.[1] The ability to efficiently assemble large synthetic oligomers also provides an opportunity to generate unnatural polymers with defined secondary and tertiary structures. Such structures should provide increased insight into the relationships between monomer structure and polymer conformation and may provide new classes of folded polymers with novel properties.[2] In the field of sulfonamides, the synthesis of α-sulfonopeptides (**1**) has remained an elusive goal.[1i,3] Our group at Milano has recently described the synthesis of vinylogous sulfonopeptides (**2**, vs-peptides) via an iterative process, both in solution[1i,4] and in the solid phase.[1j] In collaboration with Clark Still at Columbia University and Peter Nestler at Cold Spring Harbor Laboratory, we also described the binding of tweezer-like molecular receptors based on vs-peptides to an encoded combinatorial tripeptide library, showing not only that vs-peptide based receptors bind oligopeptides, but also that the binding selectivity is just as high as that of receptors built with α-aminoacids.[1j] β-Sulfonopeptides (**3**) were synthesized by our group via 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated sulfonyl chloride coupling,[1i] and by the Liskamp group in The Netherlands via *N*-methylmorpholine (NMM)-mediated sulfinyl chloride coupling followed by oxidation of the resulting sulfinamides to sulfonamides.[1h,5]



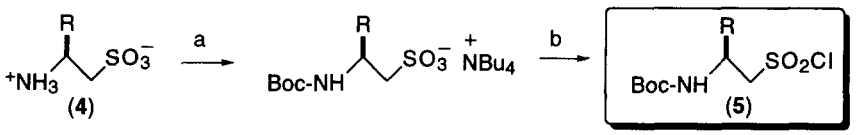
α-sulfonopeptides (**1**) vinylogous sulfonopeptides (**2**) β-sulfonopeptides (**3**)

A recent report by the Liskamp group on the solid phase synthesis of β-sulfonopeptides via NMM-mediated sulfonyl chloride coupling[6] prompted us to disclose our recent results in this field. Here we report on the solution and solid phase synthesis of β-sulfonopeptides under mild, "neutral" conditions. Chiral, enantiomerically pure 2-substituted taurines (**4**) were prepared from natural α-aminoacids following the 1989 route of Ienaga *et al.* (Scheme 1).[7]



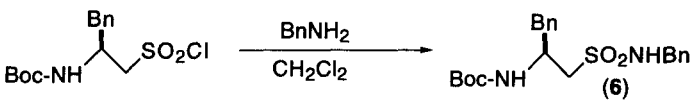
Scheme 1. a) $LiBH_4$, EtOH; b) MsCl, Et_3N, CH_2Cl_2; c) HCl in dioxane; d) Na_2SO_3, H_2O.

In selected cases, the final ion-exchange-resin purification of the betain could be avoided, and the crude betain was purified by evaporating the solvent (H_2O) to a small volume and precipitation (e.g. **4**, R = $PhCH_2$, overall yield 60%). Betains **4** were then transformed into the N-Boc protected tetrabutylammonium salts by treatment with Bu_4NOH-$30H_2O$ and Boc_2O in water : THF (1:3) followed by dichloromethane extraction. The crude salts were then converted into sulfonyl chlorides (**5**) using triphosgene and cat. DMF in dichloromethane at 0° ' RT (Scheme 2).[1i,8] The sulfonyl chlorides were purified by a rapid flash chromatography and can be stored indefinitely without decomposition at +4°C (e.g. **5**, R = $PhCH_2$, overall yield 60%).



Scheme 2. a) Bu_4NOH-$30H_2O$ (1 mol.eq.), Boc_2O (1 mol.eq.), water:THF (1:3), dilution with water and extraction with CH_2Cl_2; b) triphosgene (0.66 mol.eq.), DMF (cat.), dichloromethane, 0° ' RT; flash chromatography.

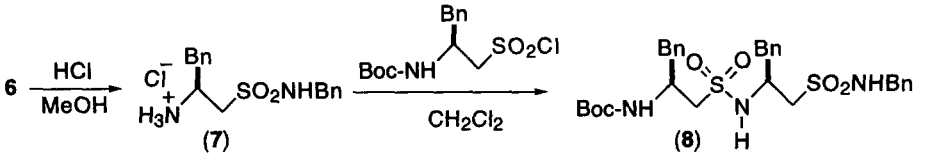
With the activated monomers **5** in our hands, we started the coupling experiments using benzylamine as a model case. Reaction of sulfonyl chloride **5** (R=Bn, 1.5 mol.eq.) with benzylamine (1 mol. eq.) in dichloromethane in the presence of various bases and additives was investigated (Table).



Table

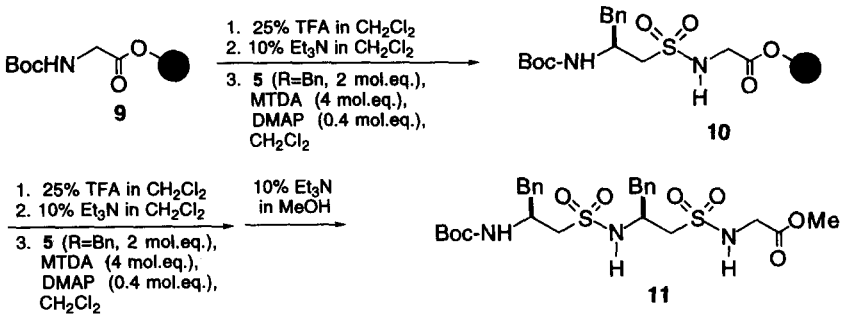
Base or additive	Mol.eq.	% Yield	excess RSO_2Cl decomposes within
DBU	2	80	1 h
DBU + DMAP	1 + 1	88	2 h
DMAP	2	86	5 h
MTDA	2	94	>24 h
MTDA + DMAP	1 + 1	94	24 h

It is worth noting that bases like DMAP or DBU (in particular), although they are known to catalyse the coupling process,[1i,j] are harmful to the sulfonyl chloride (see last column of the Table). Therefore it is important to find coupling conditions which make use of substoichiometric amounts of a mild base or no base at all.[9] A solution to this problem was found using methyl trimethylsilyl dimethylketene acetal (MTDA) as a proton trap. The new coupling procedure was then tested in the synthesis of a real β-sulfono dipeptide (**8**, Scheme 3). In this case, the sulfonyl chloride (**5**, R=Bn, 1.5 mol.eq.) was reacted with the ammonium chloride (**7**, 1 mol.eq.) in the presence of excess (4 mol.eq.) MTDA. The reaction was sluggish (38% yield) in the absence of DMAP, but became fast and clean with increasing amounts of DMAP (3% DMAP: 50% yield; 15% DMAP: 69% yield; 40% DMAP: 78% yield; 150% DMAP: 78% yield).



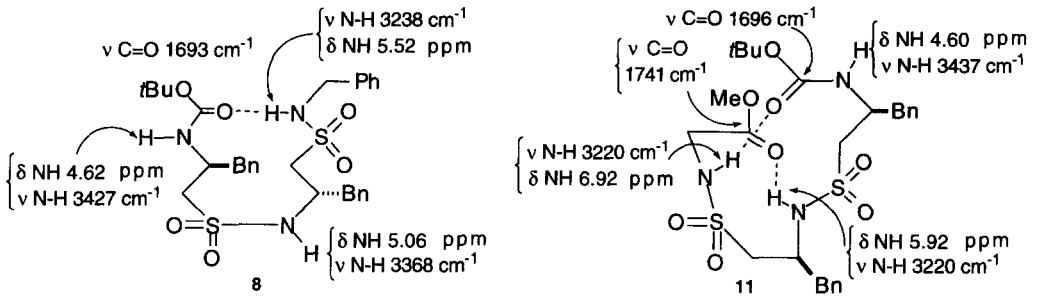
Scheme 3

Synthesis of a β-sulfonopeptide on solid support was initiated by removal of the Boc group from Boc-glycine PEG-resin **9**[1j] [PEG = poly(ethylene glycol)] by treatment of the resin with 25% TFA (TFA = trifluoroacetic acid) in CH_2Cl_2 for 30 min (3 cycles), followed by washings with CH_2Cl_2, 10% Et_3N in CH_2Cl_2, and again CH_2Cl_2. The first monomer (**5**, R=Bn, 2 mol.eq.) was then coupled to the free glycine amine in CH_2Cl_2 (1 mol.eq., 0.028 M) in the presence of cat. DMAP (0.4 mol.eq.) and excess MTDA (4 mol.eq.). One coupling was enough to achieve essentially complete conversion of the amines on the support (≥ 95%).[10a] Two more coupling cycles were routinely run to obtain a "combinatorial grade" conversion (>99%). The sequence was repeated (Boc removal, coupling with **5**, R=Bn), and finally the β-sulfonopeptide was cleaved by treatment of the resin with 10% Et_3N in MeOH (24 h) to give the corresponding methyl ester (**11**, Scheme 4) in 70% yield[10b] as a single compound, whose identity was proved by IR, NMR, and MS analysis, and by comparison with an authentic sample synthesized in solution.



Scheme 4

We have investigated the conformational preferences of β-sulfonopeptides **8** and **11** in chloroform solution by variable-temperature ^{1}H-NMR spectroscopy, FT-IR spectroscopy, and N.O.E. (N.O.E. = nuclear Overhauser effect) experiments.[11] The experimental results are complemented by computer modeling,[11] and show a strong tendency for β-sulfonopeptides to form well defined folded structures via intramolecular hydrogen-bonding (dotted lines, Scheme 5).



Scheme 5. IR and NMR data shown here were obtained from chloroform solutions (0.002 M) at 297 K. Chemical shifts are independent of concentration at or below 0.005 M.

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REFERENCES AND NOTES

1. (a) For a recent review, see: Liskamp, R.M.J. *Angew.Chem., Int.Ed.Engl.* **1994**, *33*, 633; (b) Kim, J.-M.; Bi, Y.; Paikoff, S.J.; Schultz, P.G. *Tetrahedron Lett.* **1996**, *37*, 5305; (c) Kim, J.-M.; Wilson, T.E.; Norman, T.C.; Schultz, P.G. *Tetrahedron Lett.* **1996**, *37*, 5309; (d) Zuckermann, R.N.; Kerr, J.M.; Kent, S.B.H.; Moos, W.H. *J. Am. Chem. Soc.* **1992**, *114*, 10646; (e) 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; (f) Burgess, K.; Linthicum, D.S.; Shin, H. *Angew.Chem., Int.Ed.Engl.* **1995**, *34*, 907; (g) Han, H.; Janda, K.D. *J. Am. Chem. Soc.* **1996**, *118*, 2539; (h) Moree, W.J.; van der Marel, G.A.; Liskamp, R.M.J. *J. Org. Chem.* **1995**, *60*, 5157; (i) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew.Chem., Int.Ed.Engl.* **1994**, *33*, 2067; (j) Gennari, C.; Nestler, H.P.; Salom, B.; Still, W.C. *Angew.Chem., Int.Ed.Engl.* **1995**, *34*, 1763 and 1765.

2. (a) Gennari, C.; Salom, B.; Potenza, D.; Longari, C.; Fioravanzo, E.; Carugo, O.; Sardone, N. *Chem.Eur.J.* **1996**, *2*, 644; (b) Moree, W.J.; Schouten, A.; Kroon, J.; Liskamp, R.M.J. *Int.J.Peptide Protein Res.* **1995**, *45*, 501; (c) Calcagni, A.; Gavuzzo, E.; Mazza, F.; Pinnen, F.; Pochetti, G.; Rossi, D. *Gazz.Chim.It.* **1992**, *122*, 17.

3. Dujols, F.J.M.; Mulliez, M.E. *J. Org. Chem.* **1996**, *61*, 5648.

4. C. Gennari, B. Salom, D. Potenza (Università di Milano) IT Pat. Appl. MI94 A 000989 (17 May **1994**); (Pharmacia &Upjohn) Intern. Appl. **PCT/EP 95/01788** (11 May 1995).

5. (a) Moree, W.J.; van der Marel, G.A.; Liskamp, R.M.J.*Tetrahedron Lett.* **1992**, *33*, 6389; (b) Moree, W.J.; van der Marel, G.A.; Liskamp, R.M.J. *ibid.* **1991**,*32*, 409; (c) Moree, W.J.; van Gent, L.C.; van der Marel, G.A.; Liskamp, R.M.J. *Tetrahedron* **1993**, *49*, 1133; (d) de Bont, D.B.A.; Moree, W.J.; Liskamp, R.M.J. *Biorganic&Medicinal Chemistry* **1996**, *4*, 667.

6. 11th International Conference on Organic Synthesis (ICOS-11), June 30-July 4, 1996, Amsterdam, The Netherlands, Book of Abstracts, (a) Loewik, D.W.P.M.; Mulders, S.J.E.; Cheng, Y.; Still, W.C.; Liskamp, R.M.J. PO-033, page 169, (b) de Bont, D.B.A.; Moree, W.J.; Liskamp, R.M.J. PO-303, page 443.

7. Higashiura, K.; Morino, H.; Matsuura, H.; Toyomaki, Y.; Ienaga, K. *J.Chem.Soc. Perkin Trans I* **1989**, 1479. This synthetic route was recently "rediscovered" by Di Bella *et al.* : (a) Braghiroli, D.; Di Bella, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2145; (b) Braghiroli, D.; Mussati, E.; Di Bella, M.; Saladini, M. *Tetrahedron: Asymmetry* **1996**, *7*, 831.

8. Reynolds, R.C.; Crooks, P.A.; Maddry, J.A.; Akhtar, M.S.; Montgomery, J.A.; Secrist III, J.A. *J.Org.Chem.* **1992**, *57*, 2983-2985.

9. For a solution to this problem using TMS-silylated amines and no extra base, see : (a) Paik, S.; White, E.H. *Tetrahedron* **1996**, *52*, 5303; (b) Paik, S.; White, E.H. *Tetrahedron Lett.* **1996**, *37*, 4663.

10a. The progress of the coupling reaction to give **10** was monitored using bromophenol blue as a simple acid-base indicator to test for the presence of free amines on the support, see: Krchňák, V.; Vágner, J.; Šafár, P.; Lebl, M. *Collect. Czech. Chem. Comm.* **1988**, *53*, 2542-2548. Alternatively, the residual free amines were capped with Ac_2O, the compound cleaved from the resin (MeOH, Et_3N), and the crude cleavage mixture analysed by ^{1}H-NMR spectroscopy for the presence of the CH_3CON signal.

10b. The yield of **11** was calculated based on the loading of resin **9**, which was determined by the picric acid method (Stewart, J.F.; Young, J.D. *Solid Phase Peptide Synthesis*, Pierce Chemical: Rockford, Illinois, **1984**).

11. See references 1i and 2a for conformational studies on vinylogous sulfonopeptides **2**.

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