JOC The Journal of Organic Chemistry

Article

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Synthesis of Taurine-Containing Peptides, Sulfonopeptides, and *N*- and *O*-Conjugates

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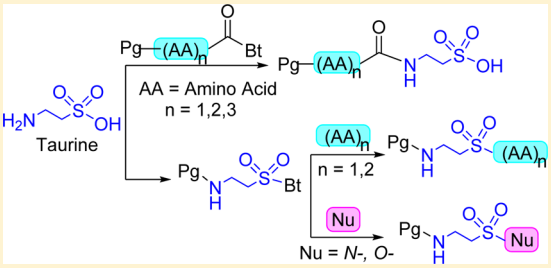
Supporting Information

ABSTRACT: Taurine-containing water-soluble peptidomimetics were designed and synthesized. *N*-terminal taurine acylations allowed synthesis of a number of taurine-containing peptides. *N*-protection of taurine with Cbz and SO_2-activation with benzotriazole followed by coupling with various amino esters, dipeptides and nucleophiles provided taurine *N*- and *O*-conjugates and sulfonopeptides.



INTRODUCTION

Peptides are widely used as drug delivery systems, biopharmaceuticals, prodrugs, and bioactive moieties.[1] However, when they are introduced into living systems, peptides show rapid enzymatic degradation, which significantly limits their utilization in vivo.[2] For decades, various peptidomimetics, including phosphonopeptides,[3] ureidopeptides,[4] and sulfonopeptides,[5,6] have been developed and reported.

Aminoalkanesulfonic acid peptidomimetics are hydrolysis-resistant sulfono analogues of naturally occurring peptides.[7,8] The sulfonamide group increases the polarity and hydrogen-bonding ability of the molecule, since the SO_2-NH_2 group is more acidic (pK_a 11−12) than the amide bond $CO-NH_2$.[9] Accordingly, the conjugate base is weaker than that of the amide bond and therefore is less prone to protonation, the first step in acidic hydrolysis of amides and peptides. Synthesis of α- or β-substituted aminoalkylsulfonates and sulfonamidopeptides has allowed the preparation of a large number of oligomers which structurally mimic native peptides[10] and render extended conformation in contrast to *cis* or *trans* isomers of their native peptide analogues.[11]

Sulfonopeptides can be prepared by the reaction of *N*-protected aminoalkanesulfonyl chlorides with amino acid[12] or peptide esters[8,13] or by condensation of *N*-protected aminoalkanesulfinyl chlorides and amino or peptide esters followed by oxidation.[14] Chlorination of sulfono acids usually requires harsh reaction conditions (e.g., use of thionyl chloride, oxalyl chloride, phosgene, phosphorus pentachloride, and high temperatures), which may cause loss of chirality and affect *N*-protecting groups.[12,15,16] Alternative routes to sulfonopeptides lie in (i) NCS/HCl oxidative chlorination of xanthines and thioacetates into **1** and **2**,[5] (ii) Mannich-type reactions of *N*-protected 2-aminoalkanesulfonamides, aldehydes, and aryldichlorophosphines, followed by aminolysis with amino esters to form **3**,[17] and (iii) reaction of β-aminoalkanesulfone amides with *C*-terminal α-aminoalkylphosphinic acids.[17] Liskamp synthesized α- or β-substituted aminoethane sulfonamide arginine−glycine peptidomimetics **4** and **5**[13] and also the various peptidomimetics **6**−**8**, which contained mono- and disulfonyl moieties.[6] Gennari and colleagues reported the synthesis[7] and conformational study of chiral vinylogous aminosulfonic acids[18] (vs-amino acids) and corresponding oligomers **9** (vs-peptides) (Figure 1).[8]

The synthesis and utility of taurine peptidomimetics and conjugates involving the sulfono group have not yet been

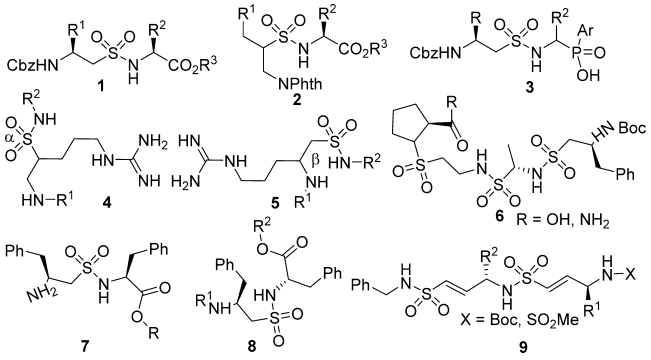


Figure 1. Some sulfonopeptides reported in the literature.

Received: January 24, 2014
Published: February 25, 2014

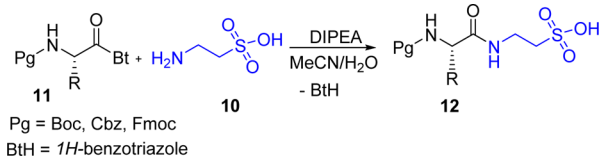
explored in full.[12,19−22] The high hydrophilicity of taurine challenges its synthetic incorporation into peptides; therefore, convenient methods to design β-aminosulfonic acid containing peptides need to be developed. The present work describes general and high-yielding synthetic routes for incorporation of the taurine unit into di-, tri-, and tetrapeptides. The synthetic protocol was explored and utilized for a series of taurine acylations at its *C*-terminus[23] (SO_3H group), which allowed synthesis of sulfonopeptides and taurine *N*- and *O*-conjugates.

RESULTS AND DISCUSSION

Our group has developed an expertise in the synthesis of peptides which contain non-natural amino acid units such as hydrazino-,[24] aza-,[25] aminoxy-,[25] depsi-,[26] and oxyazapeptides.[27] In this work, the replacement of an amide bond by a sulfonamide unit led to the facile synthesis of hybrid sulfonopeptidomimetics and conjugates composed of taurine and natural amino acids, peptides, and bioactive moieties.

Synthesis of Taurine-Containing Dipeptides. *N*-Acylbenzotriazoles have been advantageous reagents to construct peptides, peptidomimetics, and peptide conjugates.[23−27] Several activated amino acids **11** were prepared following our reported procedures.[24,27] Utilization of our well-developed methodology showed the general applicability and scope of this synthetic protocol to prepare water-soluble taurine dipeptides **12** (Scheme 1). MeCN was employed as the solvent, and a few

Scheme 1. Incorporation of Taurine Unit To Prepare Dipeptides 12



drops of water were used to dissolve taurine **10**, using DIPEA as base. After completion of the reaction, the mixture was evaporated to dryness and diethyl ether was added to the crude product; this mixture was then stirred for 20 min and dried again. During acylations of the taurine *N*-terminus we paid special attention to complete elimination of water from the reaction mixture. Due to the high polarity of reaction products **12**, water would dissolve them, lowering the reaction yields when present even at trace amounts. Acidification of the reaction mixture was provided by dropwise addition of dry 4 N HCl solution in dioxane for *N*-Cbz- and *N*-Fmoc-protected products. For *N*-Boc-protected products HCl was diluted in ether prior to addition to the mixture and the solvent was then evaporated. *C*-Terminus taurine dipeptides **12** were then isolated by flash column chromatography (1/1 EtOAc/hexanes to remove any impurities other than products and then MeOH was passed to isolate products **12**). With this methodology we managed to synthesize taurine−dipeptides in excellent yields (**12**; Scheme 1 and Table 1; 76−90%), and this purification concept has proved to be effective for all of the reaction products.

Almost every coupling reaction was completed within 1−2 h, and in the presence of water/base the benzotriazole intermediates **11** show sufficient stability to afford high yields of the reaction products. The stability of benzotriazole intermediates in water solution has been studied in detail in a number of research papers from our group.[23]

Table 1. Preparation of Taurine-Containing Dipeptides 12

compd	Pg	R	target **12**	yield, %
12a	Cbz	H	Cbz-Gly-Tau-OH	78
12b	Cbz	Me	Cbz-L-Ala-Tau-OH	87
12b,b′	Cbz	Me	Cbz-DL-Ala-Tau-OH	84
12c	Cbz	CH_2CH_2SMe	Cbz-L-Met-Tau-OH	82
12d	Boc	Me	Boc-L-Ala-Tau-OH	88
12e	Boc	CH(OBn)OMe	Boc-L-Thr(OBn)-Tau-OH	86
12f	Boc	H	Boc-Gly-Tau-OH	76
12g	Boc	$CH(Me)_2$	Boc-L-Val-Tau-OH	82
12h	Boc	(3-indolyl)CH_2	Boc-L-Trp-Tau-OH	86
12i	Fmoc	H	Fmoc-Gly-Tau-OH	90
12j	Fmoc	$CH_2CH(Me)_2$	Fmoc-L-Leu-Tau-OH	82
12k	Fmoc	CH_2Ph	Fmoc-L-Phe-Tau-OH	88

Synthesis of Taurine-Containing Tri- and Tetrapeptides. To prepare longer taurine-containing tri- and tetrapeptides, a series of peptidoyl benzotriazoles **13** were synthesized using the benzotriazole methodology.[23] Products **14** were prepared in good to excellent yields by reacting Pg-di- and Pg-tripeptidoyl benzotriazoles **13** with taurine **10**. The synthetic route was applied to various Cbz, Boc, and Fmoc *N*-protected di- and tripeptides **13** (Scheme 2 and Table 2). Products **14** were isolated in good to excellent yields (73−93%), which proved the general applicability and effectiveness of the developed methodology.

Scheme 2. Incorporation of the Taurine Unit into Tri- and Tetrapeptides 14

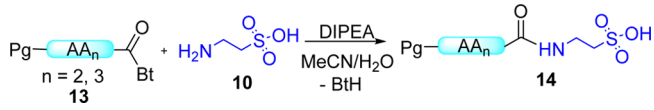


Table 2. Preparation of Taurine-Containing Tri- and Tetrapeptides 14

compd	Pg	AA_1-AA_2	product **14**	yield, %
14a	Cbz	L-Phe-Gly	Cbz-L-Phe-Gly-Tau-OH	89
14b	Cbz	L-Ala-Gly	Cbz-L-Ala-Gly-Tau-OH	91
14c	Cbz	L-Phe-L-Met	Cbz-L-Phe-L-Met-Tau-OH	73
14d	Cbz	L-Val-Gly	Cbz-L-Val-Gly-Tau-OH	93
14e	Cbz	L-Phe-Gly-Gly	Cbz-L-Phe-Gly-Gly-Tau-OH	85
14f	Boc	L-Ala-Gly	Boc-L-Ala-Gly-Tau-OH	75
14g	Boc	L-Pro-L-Ala	Boc-L-Pro-L-Ala-Tau-OH	78
14h	Boc	L-Ala-L-Pro-L-Ala	Boc-L-Ala-L-Pro-L-Ala-Tau-OH	80
14i	Fmoc	L-Val-L-Ala	Fmoc-L-Val-L-Ala-Tau-OH	78
14j	Fmoc	L-Val-Gly	Fmoc-L-Val-Gly-Tau-OH	90
14k	Fmoc	L-Leu-Gly-Gly	Fmoc-L-Leu-Gly-Gly-Tau-OH	84

It was observed that, in some cases, the starting material (especially Fmoc-AA-Bt compounds) did not dissolve completely in the MeCN, but as the reaction proceeded (within 10−20 min) the reaction mixture became clear. The current protocol can also be applied to longer peptide fragments with a hydrophobic sequence. The methodology was very efficient, even when the starting material was not completely soluble.

Synthesis of Taurine Sulfonopeptides. A library of sulfono di- and tripeptides has been synthesized via the *N*-protection of taurine with Cbz to form **15** followed by SO_2 activation with thionyl chloride to form **16** (Scheme 3 and

dx.doi.org/10.1021/jo500181g | J. Org. Chem. 2014, 79, 2688−2693

Scheme 3. Synthesis of Taurine Sulfonopeptides 18

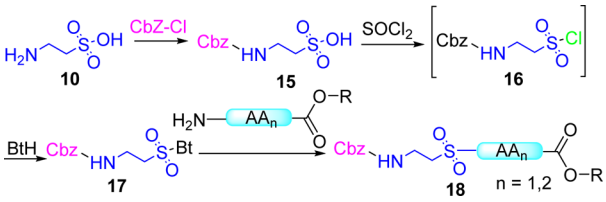


Table 3). *N*-Cbz-protected taurine chloride **16** was an unstable oil that decomposed within 72 h. To stabilize the SO_2-active

Table 3. Preparation of Sulfono Di- and Tripeptides 18

compd	amino ester	sulfono peptide **18**	yield, %
18a	H-Gly-OBn	Cbz-Tau-Gly-OBn	82
18b	H-L-Val-O^{t}Bu	Cbz-Tau-L-Val-O^{t}Bu	80
18c	H-L-Met-OMe	Cbz-Tau-L-Met-OMe	86
18d	H-L-Phe-OBz	Cbz-Tau-L-Phe-OBz	78
18e	H-L-Leu-OMe	Cbz-Tau-L-Leu-OMe	70
18f	H-Gly-Gly-OMe	Cbz-Tau-Gly-Gly-OMe	75

intermediate, we employed benzotriazole and obtained the *N*-Cbz-taurine sulfonyl benzotriazole **17** in good yield (72%). Reaction of **17** with a number of amino esters or dipeptide esters formed *N*-protected taurine sulfonopeptides **18** (Scheme 3) in good to excellent yields (70−86%). Isolation of the final products was achieved by extraction with EtOAc from 3 N HCl followed by either recrystallization (DCM/hexanes) or flash chromatography (EtOAc/hexanes) to give **18**. Synthesis of SO_2 active taurine intermediate **17** via the benzotriazole methodology allowed fast incorporation of the taurine unit as an *N*-terminus amino acid in the peptide chains.

It is important to show that no racemization occurs in our synthetic protocol. In previous studies we confirmed that the chiral integrity of the products was maintained.[26,27] In this work we studied the chiral purity of our products by measuring the optical rotation of all the chiral compounds.

Synthesis of Taurine *N*- and *O*-Conjugates. The synthetic route to **19** employed stable *N*-protected taurine benzotriazole **17** to acylate *N*- and *O*-nucleophilic compounds. Coupling of *N*-Cbz-protected SO_2Bt-activated taurine **17** with *N*-nucleophiles allowed the formation of sulfonoamides **19a−c**. The reactions proceeded at room temperature overnight, forming products **19a−c** (Scheme 4 and Table 4) in good

Scheme 4. Synthesis of Taurine *N*- and *O*-Conjugates 19

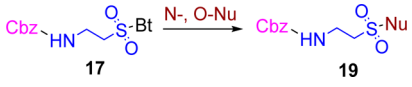


Table 4. Preparation of Taurine *N*- and *O*-Bioconjugates 19

entry	Nu	product **19**	yield, %
1	−NH_2	**19a**	70
2	−NHBn	**19b**	73
3	−$N(CH_2)_2O(CH_2)_2$	**19c**	64
4	−*O*-L-Thr	**19d**	78
5	−*O*-L-menthol	**19e**	62

yields (64−73%). For the *O*-acylation of threonine Cbz-*N*-Tau-Bt (**17**) and Boc-Thr were coupled (1:1, o/n, room temperature) using excess DIPEA as base. The Boc group of the threonine moiety was displaced during the isolation of the *O*-acylated taurine conjugate to afford **19d**, most probably due to the acidic silica column. *O*-Acylation of L-menthol gave **19e** in 62% yield, and the product was isolated via column chromatography.

Generally, isolation of **19** was easily performed by extraction of the final products with EtOAc from 3 N HCl solution followed by recrystallization from DCM/hexanes or flash column chromatography. Thus, the general SO_2-activating methodology proved to be effective for the synthesis of taurine *N*- and *O*-conjugates.

CONCLUSION

In conclusion, a viable synthetic route toward sulfonopeptides, taurine−peptides, and conjugates is reported. Moisture-sensitive taurine peptidomimetics with a series of amino acids and di- and tripeptides have been conveniently synthesized and isolated in high yields. Taurine-containing peptidomimetics and sulfonopeptides mimic natural peptides and therefore represent attractive scaffolds for drug delivery as well as prodrug and tool applications. We believe that our general and straightforward synthetic approach represents a significant development in the peptide field which could further facilitate the synthesis and evaluation of sulfonopeptides and related bioconjugated systems.

EXPERIMENTAL SECTION

All commercial materials were used without further purification. All solvents were reagent grade or HPLC grade. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, CD_3OD, and D_2O using 300 and 500 MHz spectrometers (with TMS as an internal standard). All ^{13}C NMR spectra were recorded with complete proton decoupling. The coupling constants are reported in Hz. Reaction progress was monitored by thin-layer chromatography (TLC) and visualized by UV light. Elemental analyses were performed. DCM was dried and distilled over CaH_2, whereas tetrahydrofuran (THF) was used after distillation over Na−benzophenone. *N*-Pg-(α-aminoacyl)-benzotriazoles **11a−k** and *N*-Pg-(α-di- and α-tripeptidoyl)-benzotriazoles **13a−k** were prepared according to the literature methods.[23]

General Methods for the Preparation of Taurine-Containing Dipeptides 12a−k and Tri- and Tetrapeptides 14a−k. *N*-Pg-(α-peptidoyl)benzotriazoles **11a−k** and **13a−k** (1.0 equiv, 1.0 mmol) and taurine (1.1 equiv, 1.1 mmol, 0.14 g) were dissolved in MeCN (20 mL) and 2 drops of water. DIPEA (0.21 mL, 1.2 equiv) was added to the reaction mixture, which was then stirred for 1 h at room temperature. After the reaction was complete (monitored by TLC), the solvent was evaporated and ether (20.0 mL) was added to the mixture, and it was then acidified with 4 N HCl in dioxane. The solvent was evaporated again, and the residue was dried overnight under vacuum. The crude product was purified by column chromatography (1/1 EtOAc to remove any impurities and then 100% MeOH) to give the corresponding taurine-containing dipeptides **12a−k** and tri- and tetrapeptides **14a−k**.

*(Z)-Gly-Tau-OH (**12a**):* white solid, 0.25 g, 78%, mp 244.5−246.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (br s, 1H), 7.51 (t, J = 5.7 Hz, 1H), 7.40−7.26 (m, 5H), 5.03 (s, 2H), 3.55 (d, J = 6.0 Hz, 2H), 3.35−3.27 (m, 2H), 2.56 (t, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.3, 157.1, 137.7, 129.0, 128.4, 128.3, 66.2, 51.0, 44.4, 36.1; HRMS (ESI−TOF) m/z [M − H]$^-$ calcd for $C_{12}H_{15}N_2O_6S$ 315.0656, found 315.0667.

*(Z)-L-Ala-Tau-OH (**12b**):* white solid, 0.29 g, 87%, mp 162.2−163.8 °C; $[\alpha]_D^{20}$ = −16.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (t, J = 5.4 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.42−7.24 (m, 5H), 5.01 (s, 2H), 4.03−3.86 (m, 1H), 3.37−3.24 (m, 2H), 2.59 (t, J =

dx.doi.org/10.1021/jo500181g | J. Org. Chem. 2014, 79, 2688−2693

7.0 Hz, 2H), 1.20 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 155.7, 137.0, 128.3, 127.8, 127.7, 65.4, 50.4, 50.3, 35.5, 18.1; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{13}H_{17}N_2O_6S$ 329.0813, found 329.0820.

(Z)-DL-Ala-Tau-OH (**12b,b′**)*:* white solid, 0.28 g, 84%, mp 224.0−246.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80 (t, J = 5.4 Hz, 1H), 7.43−7.25 (m, 6H), 5.03 (s, 2H), 4.08−3.88 (m, 1H), 3.44−3.29 (m, 1H), 2.61 (t, J = 6.9 Hz, 2H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 155.8, 137.1, 128.8, 127.9, 126.8, 65.5, 50.5, 50.4, 35.6, 18.2; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{13}H_{17}N_2O_6S$ 329.0813, found 329.0829.

(Z)-L-Met-Tau-OH (**12c**)*:* white solid, 0.32 g, 82%, mp 148.6−150.6 °C; $[\alpha]_D^{20}$ = −17.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (t, J = 5.4 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.45−7.23 (m, 5H), 5.01 (s, 2H), 4.11−3.92 (m, 1H), 3.40−3.23 (m, 2H), 2.59 (t, J = 7.0 Hz, 2H), 2.50−2.35 (m, 2H), 2.01 (s, 3H), 1.94−1.67 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.1, 156.0, 137.0, 128.3, 127.7, 127.6, 65.5, 54.0, 50.3, 35.5, 31.4, 29.8, 14.6; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{15}H_{21}N_2O_6S_2$ 389.0847, found 389.0865.

Boc-L-Ala-Tau-OH (**12d**)*:* white solid, 0.26 g, 88%, mp 187.9−189.2 °C; $[\alpha]_D^{20}$ = −12.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, D_2O) δ 4.00−3.82 (m, 1H), 3.60−3.41 (m, 2H), 2.99 (t, J = 7.8 Hz, 2H), 1.33 (s, 9H), 1.24 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 176.0, 157.3, 81.5, 50.8, 49.6, 35.0, 27.6, 16.8; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{10}H_{19}N_2O_6S$ 295.0969, found 295.0978.

Boc-L-Thr(OBn)-Tau-OH (**12e**)*:* white solid, 0.35 g, 86%, mp 180−182.5 °C; $[\alpha]_D^{20}$ = −21.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, D_2O) δ 7.41−7.11 (m, 5H), 4.44 (d, J = 12.0 Hz, 1H), 4.30 (d, J = 12.0 Hz, 1H), 4.07−3.80 (m, 2H), 3.53−3.34 (m, 2H), 2.91 (t, J = 6.9 Hz, 2H), 1.32 (s, 9H), 1.09 (d, J = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 172.3, 157.4, 137.6, 128.6, 128.2, 128.1, 81.5, 74.3, 70.9, 59.3, 49.6, 35.2, 27.6, 16.0; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{18}H_{27}N_2O_7S$ 415.1544, found 415.1558.

Boc-Gly-Tau-OH (**12f**)*:* white solid, 0.21 g, 76%, mp 212.0−213.0 °C; ^{1}H NMR (300 MHz, D_2O) δ 3.64 (br s, 2H), 3.58−3.42 (m, 2H), 3.08−2.88 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, D_2O) δ 164.4, 158.1, 81.7, 49.5, 48.2, 34.9, 27.5; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_9H_{17}N_2O_6S$ 281.0813, found 281.0823.

Boc-L-Val-Tau-OH (**12g**)*:* white solid, 0.27 g, 82%, mp 150.3−152.5 °C; $[\alpha]_D^{20}$ = −15.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (br s, 1H), 6.66 (d, J = 7.8 Hz, 1H), 3.77−3.60 (m, 1H), 3.42−3.21 (m, 2H), 2.59 (t, J = 7.2 Hz, 2H), 1.99−1.83 (m, 1H), 1.38 (s, 9H), 0.82 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.0, 155.5, 78.0, 56.1, 50.5, 35.4, 30.2, 28.2, 19.2, 18.1; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{12}H_{23}N_2O_6S$ 323.1282, found 323.1289.

Boc-L-Trp-Tau-OH (**12h**)*:* white solid, 0.35 g, 86%, mp 182.0−184.0 °C; $[\alpha]_D^{20}$ = −11.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, D_2O) δ 7.42 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.12−6.84 (m, 3H), 4.29−3.98 (m, 1H), 3.50−3.17 (m, 4H), 2.68−2.53 (m, 2H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, D_2O) δ 172.1, 155.5, 136.5, 127.6, 125.8, 123.8, 121.6, 119.1, 111.7, 109.7, 79.8, 65.9, 50.2, 35.7, 28.8, 28.3; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{18}H_{24}N_3O_6S$ 410.1391, found 410.1390.

Fmoc-Gly-Tau-OH (**12i**)*:* white solid, 0.36 g, 90%, mp 177.0−179.0 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.39 (d, J = 6.6 Hz, 2H), 7.29 (d, J = 7.2 Hz, 2H), 7.25−7.05 (m, 4H), 4.81−4.69 (m, 3H), 4.14 (d, J = 8.1 Hz, 2H), 3.66−3.53 (m, 2H), 3.09 (t, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, D_2O) δ 171.6, 164.3, 143.5, 140.6, 127.5, 127.0, 124.9, 119.7, 66.6, 54.0, 49.5, 46.4, 34.9; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{19}H_{19}N_2O_6S$ 403.0969, found 403.0973.

Fmoc-L-Leu-Tau-OH (**12j**)*:* white solid, 0.38 g, 82%, mp 180.0−182.0 °C; $[\alpha]_D^{20}$ = −22.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.64 (m, 3H), 7.60−7.49 (m, 2H), 7.37−7.29 (m, 3H), 7.29−7.20 (m, 2H), 4.50−4.00 (m, 4H), 3.64−3.39 (m, 2H), 3.15−2.85 (m, 2H), 1.80−1.50 (m, 3H), 0.91 (d, J = 4.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 156.4, 143.9, 141.3, 127.8, 127.2, 125.40, 120.0, 67.1, 58.1, 50.6, 47.3, 42.7, 35.8, 24.9, 23.2, 21.9; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{23}H_{27}N_2O_6S$ 459.1595, found 459.1607.

Fmoc-L-Phe-Tau-OH (**12k**)*:* white solid, 0.44 g, 88%, mp 203.0−204.5 °C; $[\alpha]_D^{20}$ = −14.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (t, J = 5.7 Hz, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.73−7.58 (m, 3H), 7.40 (t, J = 7.4 Hz, 2H), 7.33−7.13 (m, 7H), 4.27−4.05 (m, 4H), 3.40−3.20 (m, 2H), 3.03 (dd, J = 13.8, 4.5 Hz, 1H), 2.79 (dd, J = 13.6, 10.2 Hz, 1H), 2.57 (t, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.9, 155.8, 143.8, 143.7, 140.6, 138.3, 129.2, 128.0, 127.6, 127.1, 126.2, 125.4, 125.3, 120.0, 65.7, 56.5, 50.4, 46.6, 37.5, 35.6; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{26}H_{25}N_2O_6S$ 493.1439, found 493.1450.

(Z)-L-Phe-Gly-Tau-OH (**14a**)*:* white solid, 0.41 g, 89%, mp 172.5−174.1 °C; $[\alpha]_D^{20}$ = −13.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (t, J = 5.4 Hz, 1H), 7.87 (t, J = 5.4 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.37−7.17 (m, 10H), 4.97 (d, J = 12.9 Hz, 1H), 4.91 (d, J = 13.5 Hz, 1H), 4.37−4.21 (m, 1H), 3.68 (d, J = 5.4 Hz, 2H), 3.40−3.30 (m, 2H), 3.17−3.00 (m, 1H), 2.78 (dd, J = 13.6, 10.6 Hz, 1H), 2.63 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.0, 168.4, 156.0, 138.3, 137.0, 129.3, 128.3, 128.1, 127.7, 127.5, 126.2, 65.3, 56.3, 50.4, 42.3, 37.3, 35.5; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{21}H_{24}N_3O_7S$ 462.1340, found 462.1353.

(Z)-L-Ala-Gly-Tau-OH (**14b**)*:* white solid, 0.35 g, 91%, mp 216.0−218.0 °C; $[\alpha]_D^{20}$ = −17.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.71 (s, 1H), 7.58−6.95 (m, 6H), 4.92 (s, 2H), 4.14−3.81 (m, 1H), 3.68−3.43 (m, 2H), 3.43−3.02 (m, 4H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 168.5, 155.9, 137.0, 128.4, 127.9, 65.6, 50.4, 50.3, 42.3, 35.5, 18.0; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{15}H_{20}N_3O_7S$ 386.1027, found 386.1036.

(Z)-L-Phe-L-Met-Tau-OH (**14c**)*:* white solid, 0.39 g, 73%, mp 230.0−232.0 °C; $[\alpha]_D^{20}$ = +4.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.42−7.11 (m, 10H), 5.26−4.96 (m, 2H), 4.52−4.20 (m, 2H), 3.69−3.44 (m, 2H), 3.05−2.88 (m, 3H), 2.62−2.33 (m, 1H), 2.16−1.79 (m, 5H); ^{13}C NMR (75 MHz, D_2O) δ 174.5, 173.5, 158.6, 138.6, 138.2, 130.5, 129.8, 129.6, 129.6, 129.1, 129.0, 128.9, 128.9, 127.9, 68.0, 58.9, 54.0, 51.3, 38.6, 36.8, 31.3, 31.1, 15.4; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{24}H_{30}N_3O_7S_2$ 536.1531, found 536.1528.

(Z)-L-Val-Gly-Tau-OH (**14d**)*:* white solid, 0.42 g, 93%, mp 176.4−178.8 °C; $[\alpha]_D^{20}$ = −15.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (d, J = 4.6 Hz, 1H), 7.87−7.78 (m, 1H), 7.51−7.23 (m, 6H), 5.03 (d, J = 5.4 Hz, 2H), 3.98−3.82 (m, 1H), 3.66 (d, J = 6.0 Hz, 2H), 3.42−3.27 (m, 2H), 2.62 (t, J = 6.9 Hz, 2H) 2.10−1.87 (m, 1H), 0.86 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7, 168.5, 156.4, 137.0, 128.4, 127.9, 127.8, 65.6, 60.4, 50.5, 42.2, 35.6, 30.1, 19.3, 18.2; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{17}H_{24}N_3O_7S$ 414.1340, found 414.1348.

(Z)-L-Phe-Gly-Gly-Tau-OH (**14e**)*:* white solid, 0.44 g, 85%, mp 232.0−234.0 °C; $[\alpha]_D^{20}$ = −26.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (t, J = 5.4 Hz, 1H), 8.18 (t, J = 5.6 Hz, 1H), 7.91 (t, J = 4.9 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.43−7.07 (m, 10H), 4.96 (d, J = 13.1 Hz, 1H), 4.91 (d, J = 13.1 Hz, 1H), 4.39−4.17 (m, 1H), 3.78 (d, J = 5.4 Hz, 2H), 3.65 (d, J = 5.7 Hz, 2H), 3.37−3.28 (m, 2H), 3.06 (dd, J = 13.7, 3.8 Hz, 1H), 2.86−2.68 (m, 1H), 2.58 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.9, 169.1, 168.2, 155.9, 138.2, 137.0, 129.2, 128.3, 128.0, 127.6, 127.4, 126.2, 65.2, 56.3, 50.3, 42.2, 42.1, 37.3, 35.4; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{23}H_{27}N_4O_8S$ 519.1555, found 519.1548.

Boc-L-Ala-Gly-Tau-OH (**14f**)*:* white solid, 0.27 g, 75%, mp 163.0−164.5 °C; $[\alpha]_D^{20}$ = −18.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, D_2O) δ 3.98 (q, J = 7.2 Hz, 1H), 3.82 (s, 2H), 3.51 (t, J = 6.8 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H), 1.34 (s, 9H), 1.26 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 164.6, 164.3, 157.6, 81.6, 49.5, 48.6, 42.5, 35.1, 27.6, 16.7; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{12}H_{22}N_3O_7S$ 352.1184, found 352.1189.

Boc-L-Pro-L-Ala-Tau-OH (**14g**)*:* white solid, 0.31 g, 78%, mp 130.0−132.0 °C; $[\alpha]_D^{20}$ = −43.0° (c 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (d, J = 7.4 Hz, 1H), 7.95−7.85 (m, 1H), 4.24−3.98 (m, 2H), 3.38−3.15 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.19−1.63 (m, 4H), 1.30 (s, 9H), 1.19 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 171.6, 153.2, 78.3, 59.3, 50.2, 48.2, 46.5, 35.5,

dx.doi.org/10.1021/jo500181g | J. Org. Chem. 2014, 79, 2688−2693

30.8, 28.0, 23.2, 18.3; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{15}H_{26}N_3O_7S$ 392.1497, found 392.1497.

*Boc-L-Ala-L-Pro-L-Ala-Tau-OH (**14h**):* white solid, 0.37 g, 80%, mp 130.0−132.0 °C; $[\alpha]_D^{20}$ = −59.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.08−7.86 (m, 1H), 7.75 (s, 1H), 6.97 (s, 1H), 4.43−3.91 (m, 3H), 3.56 (s, 2H), 3.33 (s, 2H), 3.12−2.95 (m, 1H), 2.59 (s, 2H), 2.10−1.80 (m, 4H), 1.37 (s, 9H), 1.25 (d, *J* = 4.8 Hz, 3H), 1.25 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7, 171.3, 161.6, 155.1, 78.0, 59.5, 53.0, 50.3, 48.4, 47.7, 35.5, 28.9, 28.2, 24.6, 18.0, 16.8; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{18}H_{31}N_4O_8S$ 463.1868, found 463.1874.

*Fmoc-L-Val-L-Ala-Tau-OH (**14i**):* white solid, 0.52 g, 78%, mp 202.0−203.2 °C; $[\alpha]_D^{20}$ = −26.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (d, *J* = 7.5 Hz, 1H), 7.96−7.56 (m, 5H), 7.55−7.14 (m, 5H), 4.35−4.08 (m, 3H), 4.07−3.94 (m, 1H), 3.93−3.67 (m, 1H), 3.45−3.02 (m, 2H), 2.67−2.39 (m, 2H), 2.10−1.75 (m, 1H), 1.34−0.98 (m, 3H), 0.95−0.65 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.6, 170.8, 156.1, 143.9, 143.8, 140.7, 127.6, 127.1, 125.4, 120.1, 65.7, 60.2, 50.5, 48.3, 46.7, 35.6, 30.4, 19.2, 18.2, 18.1; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{25}H_{30}N_3O_7S$ 516.1810, found 516.1804.

*Fmoc-L-Val-Gly-Tau-OH (**14j**):* white solid, 0.45 g, 90%, mp 195.7−197.4 °C; $[\alpha]_D^{20}$ = −11.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.28 (t, *J* = 4.5 Hz 1H), 7.90−7.60 (m, 5H), 7.51 (t, *J* = 9.0 Hz, 1H), 7.45−7.23 (m, 4H), 4.35−4.15 (m 3H), 3.95−3.82 (m, 1H), 3.76−3.64 (m, 2H), 3.43−3.23 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.10−1.92 (m, 1H), 0.86 (d, *J* = 5.4 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.6, 168.4, 156.2, 143.9, 140.7, 127.7, 127.1, 125.4, 120.1, 65.7, 60.4, 50.5, 46.7, 42.1, 35.6, 30.3, 19.3, 18.3; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{24}H_{28}N_3O_7S$ 502.1653, found 502.1649.

*Fmoc-L-Leu-Gly-Gly-Tau-OH (**14k**):* white solid, 0.48 g, 84%, mp 171.0−173.0 °C; $[\alpha]_D^{20}$ = −22.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.48−8.07 (m, 2H), 8.02−7.81 (m, 3H), 7.83−7.52 (m, 3H), 7.52−7.19 (m, 4H), 4.45−3.90 (m, 4H), 3.83−3.47 (m, 6H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.75−1.22 (m, 3H), 0.85 (d, *J* = 5.7 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 169.1, 168.3, 156.1, 143.9, 140.7, 127.6, 127.1, 125.3, 120.1, 65.6, 53.2, 50.3, 46.7, 42.2, 42.1, 35.4, 24.2, 23.1, 21.4; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{27}H_{33}N_4O_8S$ 573.2025, found 573.2028.

General Methods for the Preparation of Sulfono Peptides 18a−f and *N*- and *O*-Acylated Taurine Conjugates 19a−e. Cbz-Tau-Bt (0.36 g, 1 mmol, 1 equiv) and the amino ester (1.1 mmol, 1.1 equiv) were dissolved in dry MeCN (20 mL). DIPEA (0.44 mL, 2.5 equiv) was added dropwise, and the mixture was stirred overnight at room temperature. Evaporation of the solvent followed by column chromatography (EtOAc/hexanes 1/2) gave *N*- and *O*-acylated taurine conjugates **18a−f**. To prepare **19a−e**, a similar protocol was used with various *N*- and *O*-nucleophiles.

*Cbz-Tau-Gly-OBn (**18a**):* white solid, 0.33 g, 82%, mp 90.6−92.7 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.28 (m, 10H), 5.53 (t, *J* = 6.0 Hz, 1H), 5.41 (t, *J* = 6.3 Hz, 1H), 5.18 (s, 2H), 5.11 (s, 2H), 3.97 (s, 2H), 3.73−3.65 (m, 2H), 3.25 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 156.7, 136.4, 134.9, 129.0, 128.9, 128.7, 128.4, 128.3, 67.9, 67.2, 53.4, 44.4, 36.2. Anal. Calcd for $C_{19}H_{22}N_2O_6S$: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.12; H, 5.71; N, 6.93.

*Cbz-Tau-L-Val-O^{t}Bu (**18b**):* white solid, 0.33 g, 80%, mp 81.9−82.6 °C; $[\alpha]_D^{20}$ = −3.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 7.41−7.42 (m, 5H), 5.07 (s, 2H), 3.74 (d, *J* = 5.4 Hz, 1H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.23−2.90 (m, 2H), 2.15−1.95 (m, 1H), 1.47 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.7, 158.6, 138.2, 129.5, 129.1, 128.9, 83.3, 67.6, 63.4, 53.8, 37.0, 36.9, 32.4, 28.4, 19.8, 18.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{30}N_2O_6SNa$ 437.1717, found 437.1715.

*Cbz-Tau-L-Met-OMe (**18c**):* white solid 0.35 g, 86%, mp 68.5−69.5 °C; $[\alpha]_D^{20}$ = +8.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.12 (m, 5H), 6.20 (d, *J* = 9.0 Hz, 1H), 6.04−5.57 (m, 1H), 5.03 (d, *J* = 5.7 Hz, 2H), 4.43−4.16 (m, 1H), 3.85−3.53 (m, 5H), 3.24 (s, 2H), 2.55 (s, 2H), 2.19−1.81 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 156.9, 136.3, 128.7, 128.4, 128.2, 67.2, 55.0, 53.4, 53.2, 36.2, 32.1, 30.0, 15.4; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{16}H_{23}N_2O_6S_2$ 403.1003, found 403.1000.

*Cbz-Tau-L-Phe-OBz (**18d**):* 0.39 g, 78%, colorless oil; $[\alpha]_D^{20}$ = −19.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−6.97 (m, 16H), 5.87−5.67 (m, 1H), 5.21−4.94 (m, 4H), 4.53−4.22 (m, 1H), 3.45−3.25 (m, 2H), 3.18−3.04 (m, 1H), 3.03−2.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.8, 136.4, 135.8, 135.0, 129.7, 129.2, 128.9, 128.8, 128.7, 128.4, 128.2, 127.8, 127.5, 68.0, 67.2, 57.8, 53.4, 39.3, 36.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{26}H_{28}N_2O_6SNa$ 519.1560, found 519.1577.

*Cbz-Tau-L-Leu-OMe (**18e**):* 0.27 g, 70%, colorless oil; $[\alpha]_D^{20}$ = −30.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 6.51 (d, *J* = 9.2 Hz, 1H), 6.23−6.02 (m, 1H), 5.03 (s, 2H), 4.19−3.99 (m, 1H), 3.72 (q, *J* = 6.8 Hz, 2H), 3.64 (s, 3H), 3.33−3.16 (m, 2H), 1.84−1.47 (m, 3H), 0.92−0.67 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 157.1, 136.3, 128.7, 128.3, 128.1, 67.2, 54.9, 53.5, 52.9, 41.9, 36.2, 24.6, 22.9, 21.5; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{26}N_2O_6SNa$ 409.1404, found 409.1417.

*Cbz-Tau-Gly-Gly-OMe (**18f**):* white solid, 0.29 g, 75%, mp 66.2−67.8 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.08 (m, 5H), 6.71−6.47 (m, 1H), 6.25−6.01 (m, 1H), 5.04 (d, *J* = 3.9 Hz, 2H), 3.92 (t, *J* = 5.2 Hz, 2H), 3.85−3.68 (m, 2H), 3.60 (d, *J* = 4.0 Hz, 3H), 3.47−3.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 170.9, 157.2, 136.3, 128.7, 128.3, 128.1, 67.3, 62.5, 53.3, 52.8, 44.3, 36.3. Anal. Calcd for $C_{15}H_{21}N_3O_7S$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.18; H, 5.31; N 11.14.

*Cbz-Tau-NH$_2$ (**19a**):* white solid, 0.18 g, 70%, mp 161.2−163.3 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 7.42−7.26 (m, 5H), 6.91 (s, 2H), 5.03 (s, 2H), 3.50−3.24 (m, 2H), 3.13 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 137.0, 128.4, 127.8, 127.8, 65.5, 53.9, 35.8. Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.47; H, 5.71; N, 10.75.

*Cbz-Tau-NH-Bn (**19b**):* white solid, 0.25 g, 73%, mp 107.6−109.2 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.12 (m, 10H), 5.48 (s, 1H), 5.22 (s, 1H), 5.07 (s, 2H), 4.25 (s, 2H), 3.65−3.43 (m, 2H), 3.08 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 136.8, 136.3, 129.1, 128.7, 128.4, 128.3, 128.3, 128.2, 67.2, 52.7, 47.3, 36.1. Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04. Found: C, 58.27; H, 5.91; N, 8.11.

*Cbz-Tau-NH-morph (**19c**):* white solid, 0.23 g, 64%, mp 92.8−94.2 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.28 (m, 5H), 5.55 (t, *J* = 6.3 Hz, 1H), 5.11 (s, 2H), 3.77 (t, *J* = 7.8 Hz, 4H), 3.65 (t, *J* = 6.2 Hz, 2H), 3.27−3.14 (m, 4H), 3.10 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 136.3, 128.7, 128.4, 128.2, 67.1, 66.5, 48.4, 45.7, 35.6. Anal. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.36; H, 6.41; N, 8.14.

*Cbz-Tau-O-L-Thr (**19d**).* Cbz-*N*-Tau-Bt (**17**; 0.36 g, 1 mmol, 1 equiv) and Boc-Thr-OH (0.24 g, 1.1 mmol, 1.1 equiv) were dissolved in dry MeCN (20 mL), DIPEA (0.44 mL, 2.5 equiv) was added dropwise, and the mixture was stirred overnight at room temperature. Evaporation of the solvent followed by column chromatography (EtOAc/hexanes 1/2) gave *O*-acylated taurine conjugate **19d**. The Boc group of the threonine moiety was displaced due to the acidic silica column during the isolation of the product: white solid, 0.33 g, 78%, mp 156.0−157.0 °C; $[\alpha]_D^{20}$ = −10.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ 7.42−7.13 (m, 5H), 7.06 (t, *J* = 5.1 Hz, 1H), 4.94 (s, 2H), 4.11−3.84 (m, 1H), 3.34−3.07 (m, 2H), 3.05−2.95 (m, 1H), 2.57 (t, *J* = 6.9 Hz, 2H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 163.8, 156.5, 137.7, 129.0, 128.4, 128.3, 65.9, 53.6, 51.3, 42.0, 37.9, 18.2. Anal. Calcd for $C_{14}H_{20}N_2O_7S$: C, 46.66; H, 5.59; N, 7.77. Found: C, 46.78; H, 5.83; N, 7.42.

*Cbz-Tau-O-L-menthol (**19e**):* white solid, 0.25 g, 62%, mp 67.1−67.9 °C; $[\alpha]_D^{20}$ = −39.0° (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.19 (m, 5H), 5.58 (s, 1H), 5.10 (s, 2H), 4.71−4.43 (m, 1H), 4.23−3.93 (m, 1H), 3.81−3.50 (m, 2H), 3.36−3.12 (m, 2H), 2.34−2.13 (m, 1H), 2.10−1.93 (m, 2H), 1.8−1.58 (m, 2H), 1.55−1.30 (m, 2H), 1.33−1.14 (m, 2H), 0.97−0.87 (m, 6H), 0.81 (d, *J* = 4.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 136.3, 128.6, 128.2, 128.1, 83.7, 67.0, 51.8, 47.5, 42.2, 35.9, 33.7, 31.7, 25.8, 23.1, 21.9, 20.9, 15.6;

dx.doi.org/10.1021/jo500181g | J. Org. Chem. 2014, 79, 2688−2693

HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{31}NO_5SNa$ 420.1815, found 420.1829.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and/or ^{13}C spectra of all compounds given in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ACKNOWLEDGMENTS

We thank the University of Florida and the Kenan Foundation for financial support. This paper was also funded in part by generous support from King Abdulaziz University, under Grant No. D-006/431. The authors, therefore, acknowledge the technical and financial support of KAU. The authors are grateful to Mr. G. G. Pillai, Dr. A. Oliferenko, Dr. C. D. Hall, Mrs. Galyna Vakulenko, and Mr. Z. Wang for helpful discussions and to Dr. M. C. A. Dancel (University of Florida, Mass Spectrometry Services) for HRMS analysis.

■ REFERENCES

(1) Danquah, M. K.; Agyei, D. *OA Biotechnol.* **2012**, *1*, 5−12.

(2) Ghale, G.; Kuhnert, N.; Nau, W. M. *Nat. Prod. Commun.* **2012**, *7*, 343−348.

(3) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56−58.

(4) Rincón, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **2001**, *123*, 3493−3498.

(5) Kakaei, S.; Xu, J. *Tetrahedron* **2013**, *69*, 9068−9075.

(6) Moree, W. J.; van der Marel, G. A.; Liskamp, R. J. *J. Org. Chem.* **1995**, *60*, 5157−5169.

(7) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem., Int. Ed.* **1994**, *33*, 2067−2069.

(8) Gennari, C.; Salom, B.; Potenza, D.; Longari, C.; Fioravanzo, E.; Carugo, O.; Sardone, N. *Chem. Eur. J.* **1996**, *2*, 644−655.

(9) Palakurthy, N. B.; Dev, D.; Rana, S.; Nadimpally, K. C.; Mandal, B. *Eur. J. Org. Chem.* **2013**, 2627−2633.

(10) Obreza, A.; Gobec, S. *Curr. Med. Chem.* **2004**, *11*, 3263−3278.

(11) Moree, W. J.; Schouten, A.; Kroon, J.; Liskamp, R. M. J. *Int. J. Pept. Protein Res.* **2009**, *45*, 501−507.

(12) Humljan, J.; Kotnik, M.; Boniface, A.; Šolmajer, T.; Urleb, U.; Blanot, D.; Gobec, S. *Tetrahedron* **2006**, *62*, 10980−10988.

(13) Lowik, D. W. P. M.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 1219−1228.

(14) Xu, J.; Xu, S. *Synthesis* **2004**, *2004*, 276−282.

(15) Humljan, J.; Gobec, S. *Tetrahedron Lett.* **2005**, *46*, 4069−4072.

(16) Karimi Zarchi, M. A.; Tayefi, M.; Tirgir, F.; Sabzalian, M. R. *J. Appl. Polym. Sci.* **2011**, *121*, 2573−2583.

(17) Meng, F.; He, F.; Song, X.; Zhang, L.; Hu, W.; Liu, G.; Xu, J. *Amino Acids* **2012**, *43*, 423−429.

(18) Patch, J. A.; Barron, A. E. *Curr. Opin. Chem. Biol.* **2002**, *6*, 872−877.

(19) Hara, T.; Durell, S. R.; Myers, M. C.; Appella, D. H. *J. Am. Chem. Soc.* **2006**, *128*, 1995−2004.

(20) Sapronov, N. S.; Khnychenko, L. K.; Polevshchikov, A. V. *Bull. Exp. Biol. Med.* **2001**, *131*, 142−144.

(21) Brouwer, A. J.; Ceylan, T.; van der Linden, T.; Liskamp, R. M. J. *Tetrahedron Lett.* **2009**, *50*, 3391−3393.

(22) Kothandam, H.; Biradugadda, P.; Maganti, B.; Keerthi, T.; Vegunta, B.; Kopparapu, V.; Venkatesh Palaniyapan, V. *Asian J. Biomed. Pharm. Sci.* **2012**, *2*, 21−27.

(23) Panda, S. S.; Hall, C. D.; Scriven, E.; Katritzky, A. R. *Aldrichim. Acta* **2013**, *46*, 43.

(24) Panda, S. S.; El-Nachef, C.; Bajaj, K.; Katritzky, A. R. *Eur. J. Org. Chem.* **2013**, 4156−4162.

(25) Abo-Dya, N. E.; Biswas, S.; Basak, A.; Avan, I.; Alamry, K. A.; Katritzky, A. R. *J. Org. Chem.* **2013**, *78*, 3541−3552.

(26) Avan, I.; Tala, S. R.; Steel, P. J.; Katritzky, A. R. *J. Org. Chem.* **2011**, *76*, 4884−4893.

(27) Biswas, S.; Abo-Dya, N. E.; Oliferenko, A.; Khiabani, A.; Steel, P. J.; Alamry, K. A.; Katritzky, A. R. *J. Org. Chem.* **2013**, *78*, 8502−8509.