Preparation of Sugar Amino Acids by Claisen-Johnson Rearrangement: Synthesis and Incorporation into Enkephalin Analogues[‡]

Ana Montero,[a] Enrique Mann,*[a] and Bernardo Herradón*[a]

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We have developed a convenient route for the synthesis of an unsaturated branched sugar bearing a carboxylic acid and an amino group (masked as an azide group) by employing a totally stereoselective Claisen–Johnson rearrangement as the key step. Several Met- and Leu-enkephalin analogues with different substitution patterns at the *N*- and *C*-termini were prepared by incorporating this sugar amino acid (SAA) as a substitute for the central Gly–Gly fragment of the parent pentapeptides.

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Introduction

The design and development of new amino acids and peptidomimetics has attracted considerable attention due to the pharmacological limitations (such as conformational flexibility and in vivo instability) of bioactive peptides.[1] Sugar amino acids (SAAs), carbohydrate derivatives containing a carboxylic acid and amino functionality, have emerged as an attractive option to be used as building blocks for the preparation of new analogues designed in order to circumvent those limitations.[2] The conformationally biased furan or pyran rings of these molecules make them suitable candidates for non-peptide scaffolds in peptidomimetics where they can easily be incorporated using their carboxyl and amino termini. SAAs occur in nature as subunits of oligosasaccharides in cell walls of bacteria (e.g. neuraminic acid[3]) and in some antibiotics as A40926[4] (Figure 1). Furthermore, in recent years, different unnatural SAAs have been prepared by Kessler (**A**),[5] Fleet (**B**),[6] Overhand[7] (**C**) and Hirschman[8] (**D**) among others,[9] and have found broad applications in different topics, for example, in the synthesis of peptidomimetics[10] or in the preparation of linear and cyclic oligomers designed to act as foldamers and host molecules (Figure 1).[11]

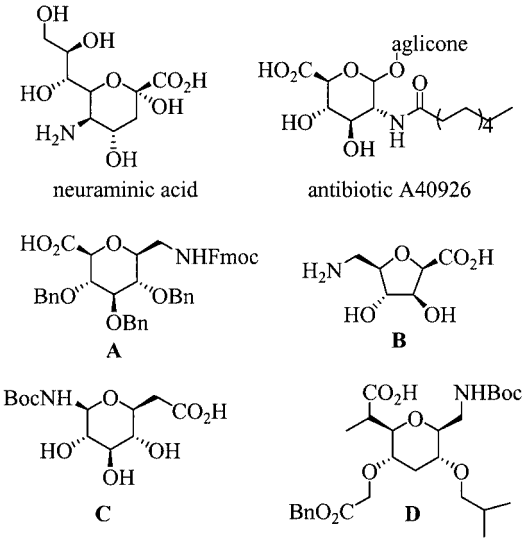

Figure 1. Natural and unnatural sugar amino acids (SAAs)

A review of the different SAAs already reported shows that the carboxylic acid functionality is located, in general, at the contiguous position of the endocyclic oxygen atom present in the sugar framework and is usually obtained by direct oxidation of the primary hydroxyl group attached to that position. Furthermore, the presence of additional functional groups is generally limited to several protected- or free hydroxyl groups that are difficult to manipulate independently. Thus, it would be desirable to develop new synthetic approaches in order to expand the diversity of SAA-like structures.

In connection with ongoing projects on the synthesis, structure and properties of peptidic compounds,[12] we have been interested in the preparation of new peptide derivatives that employ unsaturated carbohydrates as scaffolds (*peptide-carbohydrate hybrids*).[13] Herein we report our re-

[‡] Taken in part from the Ph. D. thesis of E. M. (Universidad Autónoma, Madrid, 2002) and the projected Ph. D. thesis of A. M.
Dedicated to Prof. J. L. Soto (Universidad Complutense, Madrid) on the occasion of his retirement from the chair of Organic Chemistry

[a] Instituto de Química Orgánica General, C.S.I.C.,
Juan de la Cierva 3, 28006 Madrid, Spain
Fax: (internat.) +34-91-5644-853
E-mail: herradon@iqog.csic.es
ictm317@ictp.csic.es

sults on the design and synthesis of a novel SAA with a 3,6-dihydro-2*H*-pyran structure (**E**, Figure 2), using a Claisen−Johnson rearrangement as the key step. Although the application of the Claisen rearrangement in carbohydrate chemistry has proven to be a valuable method for the realization of complex synthetic schemes,[14] it has not been used previously for the preparation of SAAs. Additionally, we have incorporated this SAA into Leu- and Met-enkephalin analogues (**F**). Although the enkephalins (**G**) are potent analgesic natural peptides that act on the opioid receptor,[15] their pharmacological utility is limited, and this is what makes the search for enkephalin analogues an active research field.[16] Most enkephalin analogues have been prepared with the aim to increase their enzymatic stability as well as to restrict their conformational mobility. The non-peptidic fragment of compounds of type **F** replaces the conformationally flexible Gly−Gly sequence in the corresponding enkephalins (**G**) that are known to adopt different conformations depending on the binding environment (Figure 2).[17] The *cis* stereochemistry of the SAA would allow suitable interactions between the amino acid residues that flank the non-peptidic scaffold. Furthermore, the presence of additional functional groups (the endocyclic carbon−carbon double bond and R′) in molecules of type **F** provides sites to generate molecular diversity.

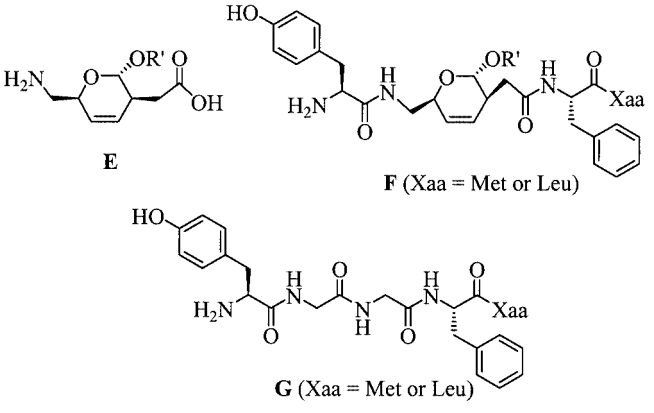

Figure 2. Structures of the SAA (**E**), the target enkephalin analogues (**F**), and natural Met- and Leu-enkephalins (**G**)

Results and Discussion

The preparation of enkephalin analogues of type **F** has been approached through the retrosynthetic correlation summarized in Figure 3. Peptidic chains could be attached to the sugar amino acid template **H** with the use of conventional peptide chemistry. This conveniently functionalized derivative of 3,6-dihydro-2*H*-pyran should be obtainable from commercially available 3,4,6-tri-*O*-triacetyl D-glucal (**1**), by employing Claisen−Johnson and Ferrier rearrangements as key steps.

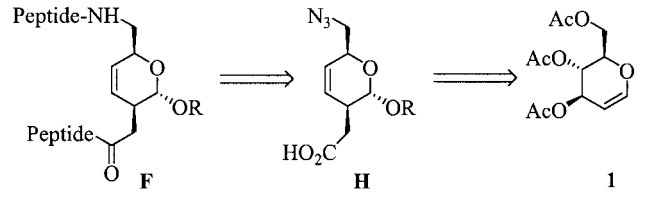

Figure 3. Retrosynthetic analysis of target molecules **F**

The synthesis of the key intermediate **7** started from **1**,[18] which was subjected to a Ferrier rearrangement[19] using allyl alcohol as nucleophile (Scheme 1). Two methods were compared to perform the transformation, employing either I_2[20] or $FeCl_3$[21] as catalysts. Although similar high yields (81% with I_2, 91% with $FeCl_3$) and identical anomeric ratios of the glycosides **2**α and **2**β (α/β ratio = 8:1) were obtained with both methods, it was easier to purify the resulting product when $FeCl_3$ was used. Our choice of the allyloxy group as the substituent at the anomeric position was based on the possibility of providing an additional site for potential chemoselective modifications. Since the two anomers proved difficult to separate chromatographically, the synthetic sequence was carried out with the mixture. Methanolysis of the diacetate **2** gave the diol **3** (98% yield) with *erythro* configuration, which underwent a double Mitsunobu reaction[22] with benzoic acid as the nucleophile to give dibenzoate **4** (95% yield), with *threo* configuration, as a ca 8:1 mixture of anomers. The dibenzoate **4** was treated with sodium methoxide to afford the diol **5**, which was selectively protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl) to give the allylic alcohol **6** (77% yield). At this stage, the minor anomer was separated by chromatography. Claisen−Johnson rearrangement was accomplished by refluxing compound **6** in triethyl orthoacetate in the presence of propanoic acid and hydroquinone,[23] and this gave the corresponding γ,δ-unsaturated ester **7** as the only product in excellent yield. Furthermore, the reaction took place in a completely stereoselective way, as is expected for such suprafacial allyl rearrangements. The stereochemistry in compound **7** was confirmed by ^{1}H NMR spectroscopic analysis, which showed that the anomeric proton (H-2) signal resonated as a singlet.[24] This data is in agreement with the empirical rule reported by Ferrier for similar 3-substituted 3,6-dihydro-2*H*-pyrans, which relates the value of the coupling constant between the protons H-2 and H-3 ($J_{2,3}$) to their relative stereochemistry: a value of $J_{2,3} \approx 0$ Hz is indicative of a *trans*-relationship.[25] The pseudo axial disposition of the free hydroxy group at C-3 in **6** seems to play an important role in the outcome of the rearrangement. Recently, Krohn et al. reported the Claisen−Johnson rearrangement of a related substrate that is epimeric at C-3 (the *erythro* diastereoisomer with *pseudo*-equatorial conformation of the OH);[26] their results show a moderate conversion (55%) after refluxing for two days. The different behavior of **6** and its epimer in the Claisen−Johnson rearrangement reflects the poor tendency of the last compound to adopt a suitable arrangement of the allylic C−C and the intermediate ketene ketal double bonds (structure non-shown).[27]

Having established a convenient route to the ester **7**,[28] the last step for the synthesis of the target SAA was per-

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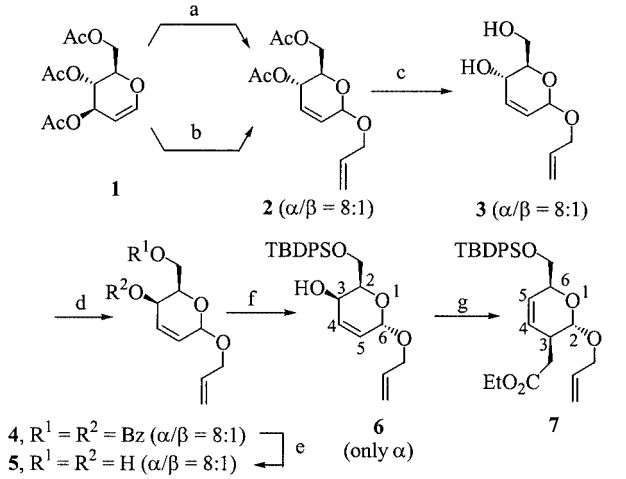
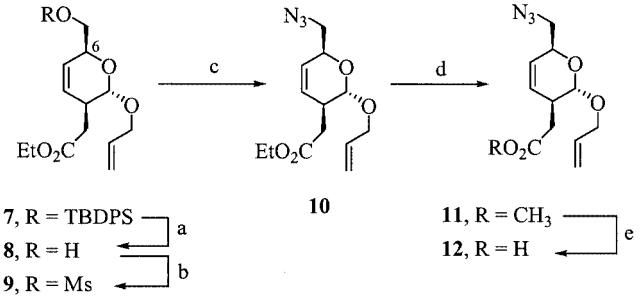


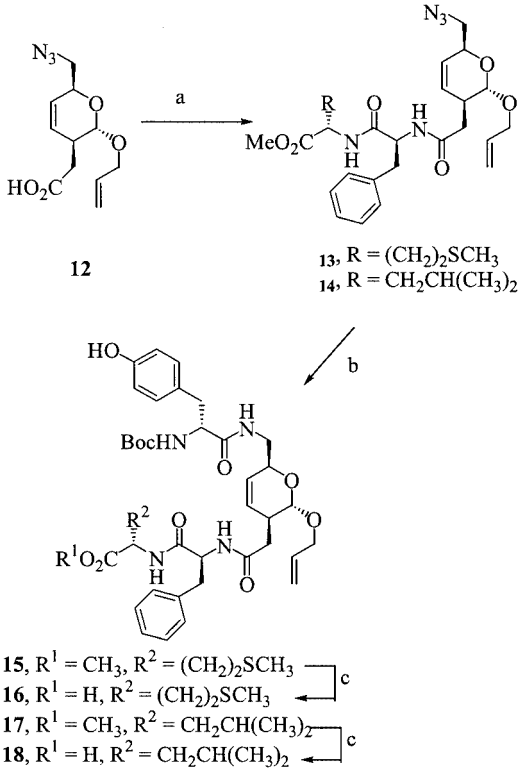
Scheme 1. Reagents and conditions: (a) I_2, $CH{=}CHCH_2OH$, THF, room temp., 81% (b) $FeCl_3$, $CH{=}CHCH_2OH$, CH_3CN, 91%. (c) KOH, MeOH, room temp., 99% (d) PPh_3, benzoic acid, DIAD, THF, room temp., 95% (e) MeONa/MeOH, 99% (f) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temp., 77% (g) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, hydroquinone, 140 °C, 20 h, 85%

formed as follows (Scheme 2). Desilylation of compound **7** with tetrabutylammonium fluoride (TBAF) afforded alcohol **8** (91% yield) that, in turn, was reacted with methanesulfonyl chloride in the presence of triethylamine to give the methanesulfonate **9** in excellent yield (98%). Compound **9** was converted into compound **10** by reaction with sodium azide (76% yield). Since the direct hydrolysis of ethyl ester **10** to the acid **12** with lithium hydroxide was sluggish and gave variable yields and side products, we performed this transformation in a two-step sequence: first the transesterification to the methyl ester **11** by reaction with sodium methoxide in methanol (72% yield), followed by treatment with lithium hydroxide to afford acid **12** (93% yield).



Scheme 2. Reagents and conditions: (a) TBAF·$3H_2O$, THF, room temp., 95% (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 98% (c) NaN_3, DMF, 60 °C, 76% (d) MeONa/MeOH, 72% (e) LiOH, THF/H_2O, 93%

With the key sugar amino acid **12** in hand, we explored the incorporation of this scaffold into longer peptides that have sequences that are similar to those of Leu- and Met-enkephalin. All the peptide bonds were formed by standard solution methods with 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) as coupling reagents, Et_3N as base, DMAP as catalyst, and DMF as solvent.[29] The protocol followed for the synthesis of the enkephalin analogues **16** and **18** is depicted in Scheme 3. Reaction of acid **12** with dipeptides H−Phe−Met−OMe and H−Phe−Leu−OMe gave intermediates **13** (75%) and **14** (72%), respectively. Reduction of the azido group was performed by the Staudinger reaction,[30] with the use of triphenylphosphane and water in refluxing benzene. The resulting amines, which were used without any purification, were coupled to Boc−Tyr−OH with peptide coupling conditions described above to give compounds **15** (72%) and **17** (84%). Final saponification of the methyl esters (LiOH) afforded enkephalin analogues **16** and **18** in quantitative yields.



Scheme 3. Reagents and conditions: (a) CF_3CO_2H·H−Phe−Met−OMe for **13** or CF_3CO_2H·H−Phe−Leu−OMe for **14**, EDC, HOBt, Et_3N, DMAP, DMF, 75% for **13**, 72% for **14** (b) (i) Ph_3P, H_2O, benzene, reflux (ii) Boc−Tyr−OH, EDC, HOBt, Et_3N, DMAP, DMF, 72%for **15**, 84% for **17** (c) LiOH, THF/H_2O, 99% for **16** and **18**

Finally, since the biological activity of many peptides and analogues is dependent of the *C* and *N*-terminal substituents,[31] we have explored the synthesis of peptide-carbohydrate hybrids related to enkephalins with different substitution patterns at these positions. Synthesis of derivatives **20−24**, presenting the *N*-methyl amide functionality at the *C*-termini and the amino group of the tyrosine residue acylated with several groups, was accomplished in a similar fashion as that described for **16** and **18** (Scheme 4). Coupling of acid **12** with dipeptide H−Phe−Met−NHMe (EDC/HOBt/Et_3N/DMAP) gave intermediate **19** in 74% yield. After Staudinger reduction of the azido group, the resulting free amine underwent condensation reactions five different

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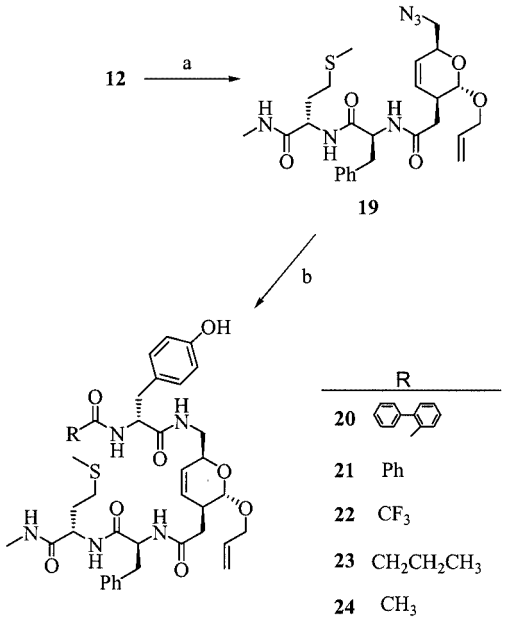
N-acylated tyrosine derivatives to give the corresponding enkephalin analogues **20−24** (49−69%).



Scheme 4. Reagents and conditions: (a) CF_3CO_2H·H−Phe−Met−NHMe, EDC, HOBt, Et_3N, DMAP, DMF, 74% (b) (i) Ph_3P, H_2O, benzene, reflux (ii) 2-BiphCO−Tyr−OH for **20** (67%), Bz−Tyr−OH for **21** (51%), CF_3CO−Tyr−OH for **22** (49%), $CH_3(CH_2)_2CO$−Tyr−OH for **23** (69%), CH_3CO-Tyr−OH for **24** (65%), EDC, HOBt, Et_3N, DMAP, DMF

Conclusion

In summary, we have developed a practical route for the synthesis of a new sugar amino acid derived from 2-alkoxy-3,6-dihydro-2*H*-pyran through a totally stereoselective Claisen−Johnson rearrangement. Compounds **7−12** can be considered as unsaturated branched sugars that are useful synthetic intermediates.[32] In this context, the azido acid **12**, as a masked amino acid, was incorporated in peptidomimetics that resemble the structure of enkephalins. Additionally, further transformations of the endocyclic carbon−carbon double bond by well-established reactions employed in similar substrates[33] might constitute a method to generate molecular diversity[34] by providing compounds with modulated pharmacological properties.

Work is in progress to determine, by solution and computational techniques, the conformational preferences induced by template **12** when introduced into a peptidic chain, as well as the biological activity of the resulting enkephalin analogues.

Experimental Section

General Methods: All the reactions with sensitive materials were carried out using dry solvents under an argon atmosphere. All the solvents and reagents were commercially available and, unless otherwise indicated, were used as received. Anhydrous solvents were purchased from Aldrich or Fluka and kept over molecular sieves under argon. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian UNITY 500, Varian INOVA 400 or Varian INOVA 300 spectrometers; chemical shifts (δ) are reported in parts per million and the coupling constants are indicated in Hz. ^{1}H NMR spectra were referenced to the chemical shift of either TMS (δ = 0.00 ppm) or the residual proton in the deuterated solvent. ^{13}C NMR spectra were referenced to the chemical shift of the deuterated solvent. The IR spectra were measured on a Perkin−Elmer-Spectrum One FT-IR spectrometer; the units in the IR spectra are indicated in cm^{-1}. MS analyses were recorded on a Hewlett Packard 5973 MSD (EI) or on a Hewlett Packard1100 MSD (ESI) spectrometer. Combustion analyses were measured on a Carlo Erba EA 1180-Elemental Analyzer. Optical rotations were determined with a Perkin−Elmer 241 MC polarimeter at room temperature (ca. 295 K). Melting points were measured on a Kofler hot-stage apparatus. All the preparative chromatography was done with silica gel (40−63 nm) using the technique of flash chromatography.

(2*R*,3*S*,6*S*)-6-Allyloxy-2-(acetoxymethyl)-3,6-dihydro-2*H*-pyran-3-yl acetate (2): A 1 M solution of $FeCl_3$ in CH_3CN (6.9 mL, 6.98 mmol) was added to a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal **1** (19.0 g, 69.8 mmol) and allyl alcohol (5.2 mL, 76.8 mmol) in anhydrous CH_3CN (250 mL) under argon. The mixture was stirred for 30 min and saturated solution of $NaHCO_3$ was added. The aqueous phase was thoroughly extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$). Solvent evaporation and purification of the residual product by flash chromatography gave diacetate **2** (17.11 g, 91%) as a mixture of anomers (α/β ratio = 8:1). White solid; m.p. 44−45 °C. $[\alpha]_D^{22}$ = +109 (*c* = 1.0, $CHCl_3$). IR (KBr): ṽ = 2902, 1744, 1371, 1235, 1043 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, $COCH_3$), 2.10 (s, 3 H, $COCH_3$), 4.07 (dd, *J* = 12.7 and *J* = 4.7 Hz, 1 H, CH*H*CH=CH_2), 4.09 (m, 1 H, 2-H), 4.21 (m, 2 H, CH_2OAc), 4.30 (dd, *J* = 12.7 and *J* = 6.9 Hz, 1 H, C*H*HCH=CH_2), 5.07 (s, 1 H, 6-H), 5.20 (m, $J_{cis\text{-}H}$ = 10.3 Hz, 1 H, =CH_2 *cis*), 5.30 (m, $J_{trans\text{-}H}$ = 17.4 Hz, 1 H, =CH_2 *trans*), 5.31 (m, 1 H, 3-H), 5.89 (m, 2 H, 4-H, 5-H), 6.00 (m, 1 H, C*H*=CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7 (q, COCH_3), 21.9 (q, COCH_3), 64.0 (t, CH_2OAc), 66.4 (d, C-3), 68.1 (d, C-2), 70.3 (t, CH_2CH=CH_2), 94.7 (d, C-6), 118.4 (t, CH=CH_2), 128.8 (d, C-5), 130.3 (d, C-4), 135.2 (d, *CH*=CH_2), 171.2 (s, CO), 171.6 (s, CO) ppm. MS (EI): *m*/*z* (%) = 270 (< 1) [M$^+$], 213 (10), 168 (20), 153 (13), 126 (78), 111 (35), 97 (11), 85 (45), 43 (100). $C_{13}H_{18}O_6$ (270.28): calcd. C 57.77, H 6.71; found C 57.69, H 7.07.

(2*R*,3*S*,6*S*)-6-Allyloxy-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol (3): KOH (100 mg) was added to a solution of diacetate **2** (16.50 g, 61.08 mmol) in MeOH (150 mL). The mixture was stirred for 2 h. The solvent was evaporated, and the residual product was purified by flash chromatography using hexane/EtOAc (2:8) as eluent. Diol **3** was obtained (11.30 g, 99%) as a mixture of anomers (α/β ratio = 9.5:1).White solid; m.p. 69−70 °C. $[\alpha]_D^{22}$ = +72 (*c* = 1.2, $CHCl_3$). IR (KBr): ṽ = 3391, 2879, 1396, 1043 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (br. s, 1 H, OH), 3.41 (br. s, 1 H, OH), 3.66 (dt, *J* = 9.1 and *J* = 4.0 Hz, 1 H, 2-H), 3.81 (m, 2 H, CH_2OAc), 4.04 (dd, *J* = 12.7 and *J* = 4.7 Hz, 1 H, CH*H*CH=CH_2), 4.16 (m, 1 H, 3-H), 4.22 (dd, *J* = 12.7 and *J* = 6.9 Hz, 1 H, C*H*HCH=CH_2), 4.99 (s, 1 H, 6-H), 5.17 (m, $J_{cis\text{-}H}$ = 10.4 Hz, 1 H, =CH_2 *cis*), 5.27 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =CH_2 *trans*), 5.72 (ddd, *J* = 10.1, *J* = 2.7 and *J* = 2.1 Hz, 1 H, 5-H), 5.88 (m, 1 H, C*H*=CH_2), 5.94 (dd, *J* = 10.1 and *J* = 1.3 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 62.6 (t, CH_2OAc), 64.1 (d, C-3), 69.2 (t, CH_2CH=CH_2), 71.6 (d, C-2), 93.6 (d, C-6), 117.5 (t, CH=

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CH$_2$), 126.0 (d, C-5), 133.7 (d, C-4), 134.3 (d, *CH*=CH$_2$) ppm. MS (EI): *m*/*z* = 185 (1) [M$^+$ − 1], 129 (23), 126 (48), 97 (27), 85 (100), 83 (22), 69 (23), 57 (48), 55 (27). $C_9H_{14}O_4$ (186.21): calcd. C 58.05, H 7.58; found C 57.87, H 7.71.

(2*R*,3*R*,6*S*)-6-Allyloxy-2-(benzoyloxymethyl)-3,6-dihydro-2*H*-pyran-3-yl benzoate (4): DIAD (18.7 mL, 94.5 mmol) was added dropwise to a well stirred solution of diol **3** (8.0 g, 43.0 mmol), Ph_3P (24.7 g, 94.5 mmol), and benzoic acid (11.5 g, 94.5 mmol) in anhydrous THF (60 mL) under argon. Stirring was continued for 2 h, after which the solvent was evaporated, and the residual product was purified by flash chromatography using hexane/EtOAc (9:1) as eluent. Compound **4** was obtained (16.0 g, 95%) as a mixture of anomers (α/β ratio = 9.5:1). Colorless thick oil. $[\alpha]_D^{22}$ = −189 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2904, 1721, 1451, 1315, 1266, 1097, 1026 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.05 (dd, *J* = 12.7 and *J* = 4.7 Hz, 1 H, CH*H*CH=CH$_2$), 4.29 (dd, *J* = 12.7 and *J* = 6.9 Hz, 1 H, C*H*HCH=CH$_2$), 4.52 (m, 1 H, CH*H*OBz), 4.67 (m, 2 H, 2-H, C*H*HOBz), 5.17 (m, $J_{cis\text{-}H}$ = 10.4 Hz, 1 H, =C*H*$_2$ *cis*), 5.20 (d, *J* = 3.1 Hz, 1 H, H-6), 5.25 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =C*H*$_2$ *trans*), 5.37 (dd, *J* = 5.4 and *J* = 1.6 Hz, 1 H, 3-H), 5.94 (m, 1 H, C*H*=CH$_2$), 6.12 (dd, *J* = 10.0 and *J* = 3.1 Hz, 1 H, 5-H), 6.30 (dd, *J* = 10.0 and *J* = 5.4 Hz, 1 H, 4-H), 7.43 (m, 4 H, Ar-H), 7.56 (m, 2 H, Ar-H), 8.05 (m, 4 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.8 (d, t, 2C, C-3, *CH*$_2$OBz), 67.6 (d, C-2), 69.2 (t, *CH*$_2$CH=CH$_2$), 93.4 (d, C-6), 117.9 (t, CH=*CH*$_2$), 125.6 (d, C-4), 128.6 (d, 2C, C_{Ar}), 128.7 (d, 2C, C_{Ar}), 129.9 (d, 2C, C_{Ar}), 130.0 (s, d, d, 3C, C_{Ar}), 130.4 (s, C_{Ar}), 131.1 (d, C-5), 133.4 (d, C_{Ar}), 133.6 (d, C_{Ar}), 134.3 (d, *CH*=CH$_2$), 166.1 (s, CO), 166.4 (s, CO) ppm. MS (EI): *m*/*z* (%) = 337 (6) [M$^+$ − 57], 230 (37), 215 (18), 105 (100), 77 (53).

(2*R*,3*R*,6*S*)-6-Allyloxy-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol (5): A solution of dibenzoate **4** (6.0 g, 15.2 mmol) in MeOH (130 mL) was added to a solution of sodium methoxide (16.4 mg, 0.3 mmol) in MeOH (10 mL), and the mixture was stirred for 2 h. The solvent was evaporated, and the residual product was purified by flash chromatography using hexane/EtOAc (4:6). Diol **5** was obtained (2.8 g, 99%) as a mixture of anomers (α/β ratio = 9.5:1). White solid; m.p. 85−87 °C. $[\alpha]_D^{22}$ = −101 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3430, 2905, 1189, 1094, 1064 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.65 (bd, *J* = 8.2 Hz, 1 H, OH), 2.76 (br. s, 1 H, OH), 3.89 (m, 3 H, *CH*$_2$OH, 3-H), 4.04 (m, 1 H, 2-H), 4.05 (dd, *J* = 12.7 and *J* = 4.7 Hz, 1 H, CH*H*CH=CH$_2$), 4.24 (dd, *J* = 12.7 and *J* = 6.9 Hz, 1 H, C*H*HCH=CH$_2$), 5.07 (d, *J* = 3.1 Hz, 1 H, 6-H), 5.18 (m, $J_{cis\text{-}H}$ = 10.3 Hz, 1 H, =C*H*$_2$ *cis*), 5.27 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =C*H*$_2$ *trans*), 5.90 (dd, *J* = 10.0 and *J* = 3.1 Hz, 1 H, 5-H), 5.92 (m, 1 H, C*H*=CH$_2$), 6.12 (dd, *J* = 10.0 and *J* = 5.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.0 (t, *CH*$_2$OH), 63.2 (d, C-3), 69.3 (t, *CH*$_2$CH=CH$_2$), 70.7 (d, C-2), 94.0 (d, C-6), 117.9 (t, CH=*CH*$_2$), 129.8 (d, C-5), 131.4 (d, C-4), 134.7 (d, *CH*=CH$_2$) ppm. MS (EI): *m*/*z* (%) = 186 (< 1) [M$^+$], 126 (37), 85 (100), 69 (14), 55 (27). $C_9H_{14}O_4$ (186.21): calcd. C 58.05, H 7.58; found C 57.91, H 7.76.

(2*R*,3*R*,6*S*)-6-Allyloxy-2-[(*tert*-butyldiphenylsilanyloxy)methyl]-3,6-dihydro-2*H*-pyran-3-ol (6): *tert*-Butyldiphenylsilyl chloride (10 mL, 38.61 mmol), Et_3N (5.86 mL, 42.13 mmol), and DMAP (643 mg, 0.15 mmol) were added to a solution of diol **5** (6.54 g, 35.11 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C under argon. The mixture was stirred overnight and allowed to warm to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography using hexane/EtOAc (6:4) to afford compound **6** (11.48 g, 77%). Colorless oil. $[\alpha]_D^{22}$ = −63 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3446, 2931, 2857, 1427, 1113, 1031 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 [s, 9 H, (*CH*$_3$)$_3$C], 1.92 (d, *J* = 8.5 Hz, 1 H, OH), 3.90 (m, 3 H, 3-H, *CH*$_2$OTBDPS), 4.03 (dd, *J* = 12.7 and *J* = 4.7 Hz, 1 H, CH*H*CH=CH$_2$), 4.13 (dt, *J* = 6.2 and *J* = 2.2 Hz, 1 H, 2-H), 4.24 (dd, *J* = 12.7 and *J* = 6.9 Hz, 1 H, C*H*HCH=CH$_2$), 5.06 (d, *J* = 2.8 Hz, 1 H, 6-H), 5.17 (m, $J_{cis\text{-}H}$ = 10.3 Hz, 1 H, =C*H*$_2$ *cis*), 5.25 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =C*H*$_2$ *trans*), 5.90 (m, 1 H, C*H*=CH$_2$), 5.91 (dd, *J* = 9.9 and *J* = 2.8 Hz, 1 H, 5-H), 6.16 (ddd, *J* = 9.9, *J* = 5.5 and *J* = 0.9 Hz, 1 H, 4-H), 7.38 (m, 6 H, Ar-H), 7.70 (m, 4 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.7 [s, (CH$_3$)$_3$*C*], 27.3 (q, 3C, (*CH*$_3$)$_3$C], 62.4 (t, *CH*$_2$OTBDPS), 64.0 (d, C-3), 69.1 (t, *CH*$_2$CH=CH$_2$), 71.3 (d, C-2), 93.1 (d, C-6), 117.9 (t, CH=*CH*$_2$), 128.2 (d, 4C, C_{Ar}), 129.0 (d, C-5), 130.2 (s, 2C, C_{Ar}; d, C-4), 134.9 (d, *CH*=CH$_2$), 136.1 (d, 4C, C_{Ar}) ppm. MS (EI): *m*/*z* (%) = 309 (18) [M$^+$ − 115], 241 (100), 223 (28), 199 (50), 181 (17), 163 (61), 135 (16). $C_{25}H_{32}SiO_4$ (424.60): calcd. C 70.72, H 7.60; found C 70.47, H 7.42.

Ethyl 2-{(2*S*,3*S*,6*S*)-2-Allyloxy-6-[(*tert*-butyldiphenylsilanyloxy)-methyl]-3,6-dihydro-2*H*-pyran-3-yl}acetate (7): A mixture of alcohol **6** (5.0 g, 11.8 mmol) and triethyl orthoacetate (22.1 mL, 118 mmol) was heated to 100 °C, and then hydroquinone (129 mg, 1.18 mmol) and propionic acid (0.09 mL, 1.18 mmol) were added. The mixture was stirred for 20 h at 140 °C (EtOH formed during the reaction was eliminated periodically with a rotavapor). The solvent was evaporated, and the residual product was purified by flash chromatography using hexane/EtOAc (9:1). Ester **7** was obtained (4.93 g, 85%) as a colorless thick oil. $[\alpha]_D^{22}$ = +41 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2931, 2858, 1735, 1428, 1264, 1113, 1031 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 [s, 9 H, (*CH*$_3$)$_3$C], 1.25 (t, *J* = 7.2 Hz, 3 H, CO$_2$CH$_2$*CH*$_3$), 2.34 (dd, *J* = 16.1 and *J* = 6.0 Hz, 1 H, CH*H*CO$_2$Et), 2.46 (dd, *J* = 16.1 and *J* = 8.7 Hz, 1 H, C*H*HCO$_2$Et), 2.60 (m, 1 H, 3-H), 3.70 (dd, *J* = 10.4 and *J* = 5.3 Hz, 1 H, CH*H*OTBDPS), 3.76 (dd, *J* = 10.4 and *J* = 5.8 Hz, 1 H, C*H*HOTBDPS), 4.06 (dd, *J* = 12.8 and *J* = 4.9 Hz, 1 H, CH*H*CH=CH$_2$), 4.14 (q, *J* = 7.2 Hz, 2 H, CO$_2$*CH*$_2$CH$_3$), 4.22 (dd, *J* = 12.8 and *J* = 6.4 Hz, 1 H, C*H*HCH=CH$_2$), 4.23 (m, 1 H, 6-H), 4.80 (s, 1 H, 2-H), 5.18 (m, $J_{cis\text{-}H}$ = 10.2 Hz, 1 H, =C*H*$_2$ *cis*), 5.28 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =C*H*$_2$ *trans*), 5.79 (m, 2 H, 5-H, 4-H), 5.92 (m, 1 H, C*H*=CH$_2$), 7.40 (m, 6 H, Ar-H), 7.68 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (q, CH$_2$*CH*$_3$), 19.5 [s, *C*(CH$_3$)$_3$], 27.1 (q, 3C, C(*CH*$_3$)$_3$], 35.9 (d, C-3), 38.1 (t, *CH*$_2$CO$_2$Et), 60.7 (t, CO$_2$*CH*$_2$), 66.4 (t, *CH*$_2$OTBDPS), 68.7 (t, *CH*$_2$CH=CH$_2$), 69.6 (d, C-6), 98.4 (d, C-2), 117.5 (t, CH=*CH*$_2$), 126.2 (d, C-4), 127.1 (d, C-5), 127.9 (d, 4C, C_{Ar}), 129.9 (d, 2C, C_{Ar}), 133.7 (s, C_{Ar}), 133.8 (s, C_{Ar}), 134.5 (d, *CH*=CH$_2$), 135.8 (d, 2C, C_{Ar}), 135.9 (d, 2C, C_{Ar}), 172.1(s, CO) ppm. ESI-MS: *m*/*z* (%) = 517 (100) [MNa]$^+$.

Ethyl 2-[(2*S*,3*S*,6*S*)-2-Allyloxy-6-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-yl]acetate (8): Tetrabutylammonium fluoride trihydrate (6.76 g, 21.44 mmol) was added to a solution of ester **7** (8.21 g, 16.49 mmol) in THF (100 mL). The mixture was stirred for 2 h at room temperature. The solvent was evaporated, and the residual product was purified by flash chromatography using hexane/EtOAc (1:1). Alcohol **8** was obtained (4.0 g, 95%) as a colorless thick oil. $[\alpha]_D^{22}$ = +126 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3446, 2929, 1733, 1268, 1182, 1114, 1051 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H, CO$_2$CH$_2$*CH*$_3$), 2.43 (m, 2 H, *CH*$_2$CO$_2$), 2.64 (m, 1 H, 3-H), 3.61 (m, 1 H, CH*H*OH), 3.77 (m, 1 H, C*H*HOH), 4.10 (m, 1 H, CH*H*CH=CH$_2$), 4.14 (q, *J* = 7.2 Hz, 2 H, CO$_2$*CH*$_2$CH$_3$), 4.28 (m, 2 H, 6-H, C*H*HCH=CH$_2$), 4.85 (s, 1 H, 2-H), 5.19 (m, $J_{cis\text{-}H}$ = 10.4 Hz, 1 H, =C*H*$_2$ *cis*), 5.30 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =C*H*$_2$ *trans*), 5.66 (d, *J* = 10.4 Hz, 1 H, 5-H),

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5.86 (m, 1 H, C*H*=CH_2), 5.92 (m, 1 H, 4-H), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (q, CH_2CH_3), 35.8 (d, C-3), 38.0 (t, CH_2CO_2), 60.7 (t, $CO_2CH_2CH_3$), 65.0 (t, CH_2OH), 68.6 (t, $CH_2CH=CH_2$), 69.2 (d, C-6), 98.3 (d, C-2), 117.5 (t, CH=CH_2), 125.8 (d, C-5), 127.1 (d, C-4), 134.2 (d, *C*H=CH_2), 171.8 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 279 (100) $[MNa]^+$.

Ethyl 2-{(2*S*,3*S*,6*S*)-2-Allyloxy-6-[(methylsulfonyloxy)methyl]-3,6-dihydro-2*H*-pyran-3-yl}acetate (9): Et_3N (0.57 mL, 4.10 mmol) was added to a solution of alcohol **8** (450 mg, 1.71 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C under argon. After 5 minutes of stirring, a solution of methylsulfonyl chloride (0.17 mL, 2.22 mmol) in dry CH_2Cl_2 (5 mL) was added. The reaction mixture was allowed to warm up to room temperature for 1 h and quenched by addition of saturated solution of $NaHCO_3$. The organic phase was washed with water, HCl (5%) and brine, dried ($MgSO_4$), and the solvents evaporated. Purification of the residue by flash chromatography using hexane/EtOAc (7:3) afforded compound **9** (512 mg, 98%) as a colorless thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 2.35 (dd, *J* = 16.1 and *J* = 6.7 Hz, 1 H, CH*H*CO_2), 2.45 (dd, *J* = 16.1 and *J* = 8.1 Hz, 1 H, C*H*HCO_2), 2.61 (m, 1 H, 3-H), 3.04 (s, 3 H, OSO_2CH_3), 4.10 (m, 3 H, $CO_2CH_2CH_3$, CH*H*CH=CH_2), 4.27 (m, 3 H, CH_2OSO_2, C*H*HCH=CH_2), 4.45 (m, 1 H, 6-H), 4.83 (s, 1 H, 2-H), 5.19 (m, $J_{cis\text{-}H}$ = 10.4 Hz, 1 H, =CH_2 *cis*), 5.31 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =CH_2 *trans*), 5.66 (d, *J* = 10.4 Hz, 1 H, 5-H), 5.88 (m, 2 H, 4-H, C*H*=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (q, CH_2CH_3), 35.5 (d, C-3), 37.7 (q, OSO_2CH_3), 37.8 (t, CH_2CO_2), 60.7 (t, $CO_2CH_2CH_3$), 66.9 (d, C-6), 68.8 (t, $CH_2CH=CH_2$), 70.7 (t, CH_2OSO_2), 98.3 (d, C-2), 117.7 (t, CH=CH_2), 123.9 (d, C-5), 128.5 (d, C-4), 134.0 (d, *C*H=CH_2), 171.6 (s, CO) ppm.

Ethyl 2-[(2*S*,3*S*,6*S*)-2-Allyloxy-6-(azidomethyl)-3,6-dihydro-2*H*-pyran-3-yl]acetate (10): NaN_3 (8.57 g, 131.90 mmol) was added to a solution of mesylate **9** (4.41 g, 13.19 mmol) in dry DMF (40 mL) under argon, and the mixture was stirred at 60 °C overnight. The solvent was concentrated in vacuo, EtOAc was added to the residue and washed with H_2O (twice). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. Purification of the residual product by flash chromatography using hexane/EtOAc (9:1) afforded azide **10** (3.20 g, 76%) as a colorless oil. $[\alpha]_D^{22}$ = +130 (*c* = 0.25, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2099, 1733, 1267, 1114 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.37 (dd, *J* = 16.1 and *J* = 6.6 Hz, 1 H, CH*H*CO_2), 2.48 (dd, *J* = 16.1 and *J* = 8.0 Hz, 1 H, C*H*HCO_2), 2.60 (m, 1 H, 3-H), 3.26 (dd, *J* = 12.8 and *J* = 3.6 Hz, 1 H, CH*H*N_3), 3.36 (dd, *J* = 12.8 and *J* = 6.3 Hz, 2 H, C*H*HN_3), 4.11 (m, 1 H, CH*H*CH=CH_2), 4.12 (q, *J* = 7.1 Hz, 2 H, CO_2CH_2), 4.23 (m, 1 H, C*H*HCH=CH_2), 4.33 (m, 1 H, 6-H), 4.83 (s, 1 H, 2-H), 5.19 (m, $J_{cis\text{-}H}$ = 10.4 Hz, 1 H, =CH_2 *cis*), 5.31 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =CH_2 *trans*), 5.63 (d, *J* = 10.3 Hz, 1 H, 5-H), 5.86 (m, 1 H, 4-H), 5.89 (m, 1 H, C*H*=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (q, CH_2CH_3), 35.7 (d, C-3), 37.9 (t, CH_2CO_2), 54.3 (t, CH_2N_3), 60.8 (t, CO_2CH_2), 68.1 (d, C-6), 68.8 (t, $CH_2CH=CH_2$), 98.4 (d, C-2), 117.6 (t, CH=CH_2), 125.8 (d, C-5), 127.8 (d, C-4), 134.2 (d, *C*H=CH_2), 171.8 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 198 (100) [MH − N_2 − OAllyl]$^+$. $C_{13}H_{19}N_3O_4$ (281.31): calcd. C 55.50, H 6.81, N 14.94; found C 55.65, H 6.79, N 14.82.

Methyl 2-[(2*S*,3*S*,6*S*)-2-Allyloxy-6-(azidomethyl)-3,6-dihydro-2*H*-pyran-3-yl]acetate (11): A solution of ester **10** (1.00 g, 3.55 mmol) in MeOH (15 mL) was added to a solution of NaOMe (0.21 mmol, generated from 5 mg of Na in 15 mL of MeOH). The reaction mixture was stirred for 3 h at room temperature. The solvent was removed at reduced pressure, and the resulting residue was purified by flash chromatography using hexane/EtOAc (9:1) to afford ester **11** (680 mg, 72%) as a colorless oil. $[\alpha]_D^{22}$ = +40 (*c* = 0.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3382, 2922, 2099, 1736, 1437, 1267, 1168, 1115, 1057, 1021 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (dd, *J* = 16.2 and *J* = 6.6 Hz, 1 H, C*H*HCO_2Me), 2.48 (dd, *J* = 16.2 and *J* = 8.0 Hz, 1 H, C*H*HCO_2Me), 2.58 (m, 1 H, 3-H), 3.25 (dd, *J* = 12.8 and *J* = 3.6 Hz, 1 H, CH*H*N_3), 3.34 (dd, *J* = 12.8 and *J* = 6.3 Hz, 1 H, C*H*HN_3), 3.65 (s, 3 H, CO_2CH_3), 4.07 (dd, *J* = 13.0 and *J* = 4.9 Hz, 1 H, CH*H*CH=CH_2), 4.22 (dd, *J* = 13.0 and *J* = 6.4 Hz, 1 H, C*H*HCH=CH_2), 4.33 (m, 1 H, 6-H), 4.81 (s, 1 H, 2-H), 5.17 (m, $J_{cis\text{-}H}$ = 10.4 Hz, 1 H, =CH_2 *cis*), 5.28 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =CH_2 *trans*), 5.63 (d, *J* = 10.4 Hz, 1 H, 4-H), 5.84 (*m,* 1 H, 5-H), 5.89 (m, 1 H, C*H*=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4 (d, C-3), 37.3 (t, CH_2CO_2Me), 51.6 (q, CO_2CH_3), 54.0 (t, CH_2N_3), 67.8 (t, $CH_2CH=CH_2$), 68.5 (d, C-6), 98.1 (d, C-2), 117.4 (t, CH=CH_2), 125.6 (d, C-4), 127.4 (d, C-5), 133.9 (d, *C*H=CH_2), 172.0 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 507 (86) [2(M − N)H]$^+$, 529 (100) [2(M − N)Na]$^+$, 290 (92) $[MNa]^+$. $C_{12}H_{17}N_3O_4$ (267.28): calcd. C 53.92, H 6.41, N 15.72; found C 53.85, H 6.74, N 15.62.

2-[(2*S*,3*S*,6*S*)-2-Allyloxy-6-(azidomethyl)-3,6-dihydro-2*H*-pyran-3-yl]acetic Acid (12): LiOH (197 mg, 4.68 mmol) was added to a solution of ester **11** (624 mg, 2.34 mmol) in a THF/H_2O (1:1, 10 mL) mixture. After standing for 3.5 h at room temperature, the mixture was treated with 5% aqueous HCl until pH 1−2 was reached. The organic solvent was removed at reduced pressure, and the aqueous phase was thoroughly extracted with EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$). Solvent evaporation afforded pure acid **12** (578 mg, 93%). Colorless thick oil. $[\alpha]_D^{22}$ = +115 (*c* = 0.5, MeOH). IR (neat): $\tilde{\nu}$ = 2926, 2100, 1711, 1412, 1271, 1165, 1114, 1055, 1016 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (m, 2 H, CH_2CO_2H), 2.62 (m, 1 H, 3-H), 5.92 (m, 1 H, C*H*=CH_2), 3.28 (dd, *J* = 12.9 and *J* = 3.6 Hz, 1 H, CH*H*N_3), 3.37 (dd, *J* = 12.9 and *J* = 6.3 Hz, 1 H, C*H*HN_3), 4.10 (dd, *J* = 12.9 and *J* = 4.9 Hz, 1 H, CH*H*CH=CH_2), 4.26 (dd, *J* = 12.9 and *J* = 6.4 Hz, 1 H, C*H*HCH=CH_2), 4.36 (m, 1 H, 6-H), 4.86 (s, 1 H, 2-H), 5.19 (m, $J_{cis\text{-}H}$ = 10.5 Hz, 1 H, =CH_2 *cis*), 5.30 (m, $J_{trans\text{-}H}$ = 17.1 Hz, 1 H, =CH_2 *trans*), 5.66 (d, *J* = 10.5 Hz, 1 H, 4-H), 5.89 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.2 (d, C-3), 37.3 (t, CH_2CO_2H), 54.1 (t, CH_2N_3), 67.9 (t, $CH_2CH=CH_2$), 68.6 (d, C-6), 98.1 (d, C-2), 117.5 (t, CH=CH_2), 125.9 (d, C-4), 127.2 (d, C-5), 133.9 (d, *C*H=CH_2),176.9 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 228 (100) [M − 25], 732 (72) [(3M − N_2)H]$^+$.

Peptidyl Azide 13: HOBT (395 mg, 2.92 mmol), Et_3N (0.9 mL, 6.75 mmol), EDC (560 mg, 2.92 mmol), and DMAP (28 mg, 0.01 mmol) were added to a solution of acid **12** (570 mg, 2.25 mmol) and dipeptide TFA·H−Phe−Met−OMe (1.10 g, 2.92 mmol) in dry DMF (8 mL) under argon. After stirring overnight at room temperature, the reaction mixture was concentrated, and the residue was taken in EtOAc. The organic phase was treated with 5% aqueous solution of HCl, saturated aqueous $NaHCO_3$, brine, and dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography using hexane/EtOAc (1:1) as eluent afforded compound **13** (922 mg, 75%) as a white solid; m.p. 108−109 °C. $[\alpha]_D^{22}$ = +95 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (m, 1 H, CH*H*β_{Met}), 2.05 (s, 3 H, CH_3S), 2.09 (m, 1 H, C*H*Hβ_{Met}), 2.32 (m, 2 H, CH_2CONH_{Phe}), 2.41 (m, 2 H, CH_2S), 2.66 (m, 1 H, 3-H), 3.06 (m, 2 H, $CH_2\beta_{Phe}$), 3.25 (dd, *J* = 12.9 and *J* = 3.4 Hz, 1 H, CH*H*N_3), 3.44 (dd, *J* = 12.9 and *J* = 5.8 Hz, 1 H, C*H*HN_3), 3.72 (s, 3 H, CO_2CH_3), 4.03 (dd, *J* = 12.9 and *J* = 5.3 Hz, 1 H, CH*H*CH=CH_2), 4.21 (dd, *J* = 12.9 and *J* =

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6.0 Hz, 1 H, C*H*HCH=CH_2), 4.37 (m, 1 H, 6-H), 4.61 (m, 1 H, CHα $_{Met}$), 4.66 (s, 1 H, 2-H), 4.67 (m, 1 H, CHα$_{Phe}$), 5.18 (m, $J_{cis\text{-}H}$ = 10.3, 1 H, =CH_2 *cis*), 5.29 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =CH_2 *trans*), 5.64 (d, *J* = 10.4 Hz, 1 H, 5-H), 5.87 (dd, *J* = 10.4 and *J* = 5.9 Hz, 1 H, 4-H), 5.90 (m, C*H*=CH_2), 6.11 (d, *J* = 7.8 Hz, 1 H, NH_{Phe}), 6.41 (d, *J* = 7.9 Hz, 1 H, NH_{Met}), 7.25 (m, 5 H, Ar-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6 (q, CH_3S), 30.0 (t, CH_2β$_{Met}$), 31.6 (t, CH_2S), 35.9 (d, C-3), 38.4 (t, CH_2β$_{Phe}$), 39.9 (t, CH_2CONH$_{Phe}$), 51.8 (d, CHα$_{Met}$), 52.8 (q, CO_2CH_3), 54.2 (t, CH_2N_3), 54.4 (d, CHα$_{Phe}$), 68.2 (t, CH_2CH=CH_2), 68.9 (d, C-6), 98.4 (d, C-2), 117.2 (t, CH=CH_2), 125.9 (d, C-5), 127.3 (d, C_{Ar}), 127.3 (d, C-4), 129.0 (d, 2C, C_{Ar}), 129.5 (d, 2C, C_{Ar}), 134.2 (d, *C*H=CH_2), 136.5 (s, C_{Ar}), 170.8 (CO), 170.9 (CO), 171.9 (CO) ppm. ESI-MS: *m*/*z* (%) = 568 (100) $[MNa]^+$. $C_{26}H_{35}N_5O_6S$ (545.65): calcd. C 57.23, H 6.47, N 12.83; found C 57.44, H 6.39, N 12.80.

Peptidyl Azide 14: Acid **12** (658 mg, 2.59 mmol) was coupled to dipeptide TFA·H−Phe−Leu−OMe (1.32 g, 3.37 mmol) as described for **13**. The crude product was purified by column chromatography using hexane/EtOAc (7:3) as eluent to afford **14** (976 mg, 72%) as a white solid; m.p. 128−129 °C. $[\alpha]_D^{22}$ = +84 (C = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 5.9 Hz, 6 H, CH(*CH*$_3$)$_2$], 1.53 (m, 3 H, CH_2β$_{Leu}$, *CH*(CH_3)$_2$], 2.32 (m, 2 H, CH_2CO), 2.65 (m, 1 H, 3-H), 3.07 (m, 2 H, CH_2β$_{Phe}$), 3.25 (dd, *J* = 12.9 and *J* = 3.4 Hz, 1 H, CH*H*N_3), 4.43 (dd, *J* = 12.9 and *J* = 5.8 Hz, 1 H, C*H*HN_3), 3.71 (s, 3 H, CO_2CH_3), 4.04 (dd, *J* = 12.9 and *J* = 5.3 Hz, 1 H, CH*H*CH=CH_2), 4.21 (dd, *J* = 12.9 and *J* = 6.0 Hz, 1 H, C*H*HCH=CH_2), 4.38 (m, 1 H, 6-H), 4.53 (m, 1 H, CHα$_{Leu}$), 4.67 (s, 1 H, 2-H), 4.68 (m, 1 H, CHα$_{Phe}$), 5.19 (m, $J_{cis\text{-}H}$ = 10.3 Hz, 1 H, =CH_2 *cis*), 5.30 (m, $J_{trans\text{-}H}$ = 17.3 Hz, 1 H, =CH_2 *trans*), 5.63 (d, *J* = 10.5 Hz, 1 H, 5-H), 5.84 (dd, *J* = 10.2 and *J* = 5.9 Hz, 1 H, 4-H), 5.90 (m, 1 H, C*H*=CH_2), 6.16 (m, 2 H, NH_{Leu}, NH_{Phe}), 7.27 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (q, CHCH_3), 22.7 (q, CHCH_3), 24.7 [t, *CH*(CH_3)$_2$], 35.6 (d, C-3), 38.1 (t, CH_2β$_{Phe}$), 39.8 (t, CH_2CO), 41.4 (t, CH_2β$_{Leu}$), 50.8 (d, CHα$_{Leu}$), 52.3 (q, CO_2CH_3), 53.9 (t, CH_2N_3), 54.3 (d, CHα$_{Phe}$), 67.9 (d, C-6), 68.7 (t, CH_2CH=CH_2), 98.2 (d, C-2), 117.4 (t, CH=CH_2), 125.6 (d, C-5), 127.1 (d, 1C, C_{Ar}), 127.7 (d, C-4), 129.7 (d, 2C, C_{Ar}), 129.3 (d, 2C, C_{Ar}), 133.9 (d, *C*H=CH_2), 136.3 (s, C_{Ar}), 170.4 (CO), 170.5 (CO), 172.6 (CO) ppm. ESI-MS: *m*/*z* (%) = 470 (100) $[M - OAllyl]^+$, 550 (94) $[MNa]^+$, 528 (49) $[MH]^+$. $C_{27}H_{37}N_5O_6$ (527.61): calcd. C 61.46, H 7.07, N 13.27; found C 61.27, H 6.89, N 13.10.

Boc−Tyr−SAA−Phe−Met−OMe (15): A mixture of azide **13** (922 mg, 1.69 mmol), Ph_3P (886 mg, 3.78 mmol), and H_2O (0.06 mL) in benzene (20 mL) was refluxed overnight. The solvent was evaporated, and the residue was dissolved in dry DMF (5 mL). Boc−Tyr−OH (618 mg, 2.19 mmol), HOBT (297 mg, 2.19 mmol), Et_3N (0.7 mL, 5.07 mmol), EDC (421.2 mg, 2.19 mmol), and DMAP (21 mg, 0.219 mmol) were added sequentially. The reaction mixture was stirred for 21 h at room temperature. The solvent was removed at reduced pressure, and the residue was purified by silica gel column chromatography using hexane/EtOAc (7:3) as eluent to afford compound **15** (957 mg, 72%) as a white solid; m.p. 183−184 °C. $[\alpha]_D^{22}$ = +26 (*c* = 0.25, $CHCl_3$). IR (KBr): ṽ = 3429, 1739, 1644, 1517, 1445, 1367, 1166 cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 40 °C): δ = 1.29 [s, 9 H, (CH_3)$_3$C], 1.92 (m, 2 H, CH_2β$_{Met}$), 2.03 (s, 3 H, SCH_3), 2.07 (dd, *J* = 14.6 and *J* = 6.9 Hz, 1 H, CH*H*CO), 2.16 (dd, *J* = 14.6 and *J* = 7.7 Hz, 1 H, C*H*HCO), 2.28 (m, 1 H, 3-H), 2.46 (m, 2 H, CH_2S), 2.58 (m, 1 H, CH*H*β$_{Tyr}$), 2.75 (dd, *J* = 13.9 and *J* = 3.9 Hz, 1 H, CH*H*β$_{Phe}$), 2.77 (dd, *J* = 15.3 and *J* = 4.3 Hz, 1 H, C*H*Hβ$_{Tyr}$), 3.00 (dd, *J* = 13.9 and *J* = 4.8 Hz, 1 H, C*H*Hβ$_{Phe}$), 3.17 (m, 2 H, CH_2NH), 3.62 (s, 3 H, CO_2CH_3), 3.85 (dd, *J* = 13.1 and *J* = 5.6 Hz, 1 H, CH*H*CH=CH_2), 4.07 (m, 3 H, 6-H, CHα$_{Tyr}$, C*H*HCH=CH_2), 4.41 (m, 1 H, CHα$_{Met}$), 4.45 (s, 1 H, 2-H), 4.57 (m, 1 H, CHα$_{Phe}$), 5.11 (m, $J_{cis\text{-}H}$ = 10.5 Hz, 1 H, =CH_2 *cis*), 5.21 (m, $J_{trans\text{-}H}$ = 17.3 Hz, 1 H, =CH_2 *trans*), 5.76 (m, 2 H, 4-H, 5-H), 5.84 (m, 1 H, C*H*=CH_2), 6.62 (m, 2 H, Ar-H$_{Tyr}$), 6.86 (d, *J* = 8.5 Hz, 1 H, NH_{Tyr}), 7.03 (m, 2 H, Ar-H$_{Tyr}$), 7.25 (m, 5 H, Ar-H$_{Phe}$), 7.96 (t, *J* = 6.1 Hz, 1 H, CH_2NHCO), 8.17 (d, *J* = 8.3 Hz, 1 H, NH_{Phe}), 8.46 (d, *J* = 7.6 Hz, 1 H, NH_{Met}), 9.17 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, 40 °C, [D_6]DMSO): δ = 14.9 (q, CH_3S), 28.5 (q, 3C, (CH_3)$_3$C], 29.8 (t, CH_2S), 30.9 (t, CH_2β$_{Met}$), 36.0 (d, C-3), 31.1 (t, CH_2β$_{Tyr}$), 37.8 (t, CH_2β$_{Phe}$), 38.8 (t, CH_2CO), 42.6 (t, CH_2NH), 51.3 (d, CHα$_{Met}$), 52.3 (q, CO_2CH_3), 53.9 (d, CHα$_{Phe}$), 56.5 (d, CHα$_{Tyr}$), 66.9 (d, C-6), 67.7 (t, CH_2CH=CH_2), 78.3 [s, *C*(CH_3)$_3$], 98.0 (d, C-2), 115.1 (d, 2C, C_{Ar}), 116.8 (t, CH=CH_2), 126.6 (d, C-5), 126.8 (d, C-4), 128.4 (d, 2C, C_{Ar}), 128.6 (d, C_{Ar}), 129.4 (d, 2C, C_{Ar}), 130.4 (d, 2C, C_{Ar}), 131.2 (s, C_{Ar}), 135.1 (d, *C*H=CH_2), 138.2 (s, C_{Ar}), 155.6 (s, C_{Ar}), 156.0 (s, CO), 170.5 (s, CO), 171.9 (s, CO), 172.4 (s, 2C, CO) ppm. ESI-MS: *m*/*z* (%) = 783 (100) $[MH]^+$. $C_{40}H_{54}N_4O_{10}S$ (782.94): calcd. C 61.36, H 6.71, N 7.16, S 4.10; found C 61.18, H 7.02, N 7.17, S 3.95.

Boc−Tyr−SAA−Phe−Met−OH (16): LiOH (10.7 mg, 0.250 mmol) was added to a solution of ester **15** (100 mg, 0.127 mmol) in a THF/H_2O (1:1, 2 mL) mixture. After standing for 1 h at room temperature, the mixture was treated with 5% aqueous HCl. The organic solvent was removed at reduced pressure, and the aqueous phase was thoroughly extracted with EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$). Solvent evaporation afforded pure acid **16** (97 mg, 99%) as a white solid; m.p. 146−147 °C. $[\alpha]_D^{22}$ = +25 (*c* = 0.21, MeOH). IR (KBr): ṽ = 3429, 2928, 1647, 1516, 1368, 1249, 1166, 1052 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 40 °C): δ = 1.38 [s, 9 H, (CH_3)$_3$C]), 2.03 (s, 3 H, SCH_3), 1.98 (m, 1 H, CH*H*β$_{Met}$), 2.15 (m, 2 H, CH*H*CO, C*H*Hβ$_{Met}$), 2.22 (d, *J* = 14.7 Hz, 1 H, C*H*HCO), 2.42 (m, 2 H, CH_2S), 2.49 (m, 1 H, 3-H), 2.96 (m, 3 H, CH_2β$_{Tyr}$, CH*H*β$_{Phe}$), 3.10 (dd, *J* = 14.1 and *J* = 4.8 Hz, 1 H, C*H*Hβ$_{Phe}$), 3.32 (m, 2 H, CH_2NH), 3.95 (dd, *J* = 12.9 and *J* = 5.3 Hz, 1 H, CH*H*CH=CH_2), 4.12 (dd, *J* = 12.9 and *J* = 5.6 Hz, 1 H, C*H*HCH=CH_2), 4.19 (m, 1 H, 6-H), 4.36 (m, 1 H, CHα$_{Tyr}$), 4.48 (m, 1 H, CHα$_{Met}$), 4.59 (s, 1 H, 2-H), 4.81 (m, 1 H, CHα$_{Phe}$), 5.11 (m, $J_{cis\text{-}H}$ = 11.6 Hz, 1 H, =CH_2 *cis*), 5.23 (m, $J_{trans\text{-}H}$ = 17.3 Hz, 1 H, =CH_2 *trans*), 5.28 (bd, 1 H, NH_{Tyr}), 5.45 (d, *J* = 10.4 Hz, 1 H, 5-H), 5.69 (dd, *J* = 10.4 and *J* = 4.9 Hz, 1 H, 4-H), 5.85 (m, 1 H, C*H*=CH_2), 6.39 (bt, CH_2NH), 6.72 (d, *J* = 8.5 Hz, 2 H, Ar-H$_{Tyr}$), 7.01 (d, *J* = 8.3 Hz, 2 H, Ar-H$_{Tyr}$), 7.14 (bd, NH_{Phe}), 7.19 (m, 5 H, Ar-H$_{Phe}$; 1 H, NH_{Met}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (q, SCH_3), 28.4 (*q*, 3C, (CH_3)$_3$C], 30.0 (t, CH_2S), 30.7 (t, CH_2β$_{Met}$), 35.7 (d, C-3), 38.1 (t, t, 2C, CH_2β$_{Phe}$, CH_2β$_{Tyr}$), 39.4 (t, CH_2CO), 42.6 (t, CH_2NH), 51.9 (d, CHα$_{Met}$), 54.5 (d, CHα$_{Phe}$), 56.2 (d, CHα$_{Tyr}$), 66.5 (d, C-6), 68.6 (t, CH_2CH=CH_2), 80.6 [s, *C*(CH_3)$_3$], 98.4 (d, C-2), 115.8 (d, 2C, C_{Ar}), 117.5 (t, CH=CH_2), 126.2 (d, C-4), 127.1 (s, C_{Ar}), 127.2 (d, C-5), 127.9 (d, 1C, C_{Ar}), 128.7 (d, 2C, C_{Ar}), 129.3 (d, 2C, C_{Ar}), 130.6 (d, 2C, C_{Ar}), 134.1 (d, *C*H=CH_2), 136.4 (s, C_{Ar}), 155.4 (s, C_{Ar}), 156.1 (s, CO), 171.8 (s, CO), 172.3 (s, CO), 172.7 (s, CO), 174.1 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 769 (100) $[MH]^+$. $C_{39}H_{52}N_4O_{10}S$ (768.92): calcd. C 60.92, H 6.82, N 7.29, S 4.17; found C 60.73, H 7.02, N 6.99, S 3.98.

Boc−Tyr−SAA−Phe−Leu−OMe (17): The azide **14** (954 mg, 1.81 mmol) was reduced and coupled to Boc−Tyr−OH (662 mg, 2.35 mmol) as described for **15**. The crude product was purified by column chromatography using hexane/EtOAc (7:3) as eluent to af-

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ford **17** (762 mg, 84%) as a white solid; m.p. 107−110 °C. $[\alpha]_D^{22}$ = +20 (*c* = 0.25, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3420, 2959, 1652, 1516, 1442, 1367, 1250, 1167, 1052, 1019, 700 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 0.84 (d, *J* = 6.6 Hz, 3 H, CH*CH*$_3$), 0.89 (d, *J* = 6.3 Hz, 3 H, CH*CH*$_3$), 1.29 (m, 1 H, CH*H*β_{Leu}), 1.29 [s, 9 H, C(*CH*$_3$)$_3$], 1.54 [m, 2 H, *CH*(CH$_3$)$_2$, C*H*Hβ_{Leu}), 2.12 (m, 2 H, *CH*$_2$CO), 2.28 (m, 1 H, 3-H), 2.59 (m, 1 H, CH*H*β_{Tyr}), 2.75 (dd, *J* = 13.7 and *J* = 10.1 Hz, 1 H, CH*H*β_{Phe}), 2.77 (m, 1 H, C*H*Hβ_{Tyr}), 3.03 (dd, *J* = 13.7 and *J* = 4.2 Hz, 1 H, C*H*Hβ_{Phe}), 3.19 (m, 1 H, CH*H*N$_3$), 3.61 (s, 3 H, CO$_2$*CH*$_3$), 3.87 (dd, *J* = 13.0 and *J* = 5.3 Hz, 1 H, CH*H*CH=CH$_2$), 4.07 (m, 4 H, 6-H, CHα_{Tyr}, C*H*HCH=CH$_2$, C*H*HN$_3$), 4.30 (m, 1 H, CHα_{Leu}), 4.49 (s, 1 H, 2-H), 4.60 (m, 1 H, CHα_{Phe}), 5.10 (m, $J_{cis\text{-}H}$ = 10.5 Hz, 1 H, =C*H*$_2$ *cis*), 5.20 (m, $J_{trans\text{-}H}$ = 18.7 Hz, 1 H, =C*H*$_2$ *trans*), 5.74 (m, 2 H, 4-H, 5-H), 5.85 (m, 1 H, C*H*=CH$_2$), 6.62 (m, 2 H, Ar-H$_{Tyr}$), 6.69 (d, *J* = 6.5 Hz, 1 H, NH$_{Tyr}$), 7.03 (m, 2 H, Ar-H$_{Tyr}$), 7.25 (m, 5 H, Ar-H$_{Phe}$), 7.98 (t, *J* = 6.1 Hz, 1 H, CH$_2$*NH*), 8.16 (d, *J* = 8.6 Hz, 1 H, NH$_{Phe}$), 8.42 (d, *J* = 7.5 Hz, 1 H, NH$_{Leu}$), 9.16 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 40 °C): δ = 22.0 (q, CH*CH*$_3$), 23.5 (q, CH*CH*$_3$), 24.9 [d, *CH*(CH$_3$)$_2$], 29.8 (q, 3C, *(CH*$_3$*)*$_3$C], 36.4 (d, C-3), 37.5 (d, CH$_2\beta_{Tyr}$), 38.0 (t, CH$_2\beta_{Phe}$), 38.3 (t, *CH*$_2$CO), 38.5 (t, CH$_2\beta_{Leu}$), 43.2 (t, *CH*$_2$NH), 51.0 (d, CHα_{Leu}), 52.6 (q, CO$_2$*CH*$_3$), 54.1 (d, CHα_{Phe}), 55.7 (d, CHα_{Tyr}), 67.3 (d, C-6), 68.1 (t, *CH*$_2$CH=CH$_2$), 78.6 [s, *C*(CH$_3$)$_3$], 98.4 (d, C-2), 115.5 (d, 2C, C$_{Ar}$), 117.2 (t, CH=*CH*$_2$), 126.9 (d, d, 2C, C$_{Ar}$, C-5), 128.2 (d, C-4), 128.7 (d, 2C, C$_{Ar}$), 129.8 (d, 2C, C$_{Ar}$), 129.0 (s, C$_{Ar}$), 130.9 (s, C$_{Ar}$), 135.5 (d, *CH*=CH$_2$), 138.6 (s, C$_{Ar}$), 155.7 (s, C$_{Ar}$), 156.4 (s, CO), 170.8 (s, CO), 172.3 (s, CO), 172.8 (s, CO), 173.5 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 765 (100) $[MH]^+$. $C_{41}H_{56}N_4O_{10}$ (764.90): calcd. C 64.38, H 7.38, N 7.32; found C 64.17, H 7.68, N 7.02.

Boc−Tyr−SAA−Phe−Leu−OH (18): Compound **17** was hydrolyzed as described for **16** to afford acid **18** (99%) as a white solid; m.p. 142−145 °C (previous softening). $[\alpha]_D^{22}$ = +18 (*c* = 0.1, MeOH). IR (KBr): $\tilde{\nu}$ = 3416, 2958, 1649, 1516, 1439, 1367, 1248, 1168, 1121, 1051 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 0.86 (d, *J* = 6.2 Hz, 3 H, *CH*$_3$CH), 0.88 (d, *J* = 6.2 Hz, 3 H, *CH*$_3$CH), 1.30 [s, 9 H, (*CH*$_3$*)*$_3$C], 1.45 (m, 1 H, CH*H*β_{Leu}), 1.56 (m, 1 H, C*H*Hβ_{Leu}), 1.66 [m, 1 H, *CH*(CH$_3$)$_2$], 2.07 (dd, *J* = 14.4 and *J* = 6.8 Hz, 1 H, CH*H*CO), 2.17 (dd, *J* = 14.4 and *J* = 7.7 Hz, 1 H, C*H*HCO), 2.30 (m, 1 H, 3-H), 2.64 (m, 1 H, CH*H*β_{Tyr}), 2.77 (m, 2 H, CH*H*β_{Phe}, C*H*Hβ_{Tyr}), 3.07 (dd, *J* = 13.9 and *J* = 10.1 Hz, 1 H, C*H*Hβ_{Phe}), 3.19 (m, 2 H, *CH*$_2$NH), 3.87 (dd, *J* = 12.8 and *J* = 5.3 Hz, 1 H, CH*H*CH=CH$_2$), 4.07 (m, 4 H, C*H*HCH=CH$_2$, CHα_{Tyr}, 6-H, CHα_{Leu}), 4.48 (s, 1 H, 2-H), 4.53 (m, 1 H, CHα_{Phe}), 5.11 (m, $J_{cis\text{-}H}$ = 10.2 Hz, 1 H, =C*H*$_2$ *cis*), 5.22 (m, $J_{trans\text{-}H}$ = 17.2 Hz, 1 H, =C*H*$_2$ *trans*), 5.55 (m, 2 H, 4-H, 5-H), 5.85 (m, 1 H, C*H*=CH$_2$), 6.64 (d, *J* = 8.3 Hz, 2 H, Ar-H$_{Tyr}$), 6.84 (d, *J* = 7.9 Hz, 1 H, NH$_{Tyr}$), 7.01 (d, *J* = 8.3 Hz, 2 H, Ar-H$_{Tyr}$), 7.16 (m, 2 H, Ar-H$_{Phe}$), 7.24 (m, 3 H, Ar-H$_{Phe}$), 7.60 (bd, 1 H, NH$_{Leu}$), 8.00 (bt, 1 H, CH$_2$*NH*), 8.17 (d, *J* = 8.7 Hz, 1 H, NH$_{Phe}$), 9.16 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 40 °C): δ = 22.1 (q, CH*CH*$_3$), 23.3 (q, CH*CH*$_3$), 24.8 [d, *CH*(CH$_3$)$_2$], 29.9 (q, 3C, *(CH*$_3$*)*$_3$C], 36.3 (d, C-3), 37.5 (t, *CH*$_2\beta_{Tyr}$), 37.9 (t, *CH*$_2\beta_{Phe}$), 39.7 (t, *CH*$_2$CO), 42.0 (t, *CH*$_2\beta_{Leu}$), 42.7 (t, *CH*$_2$NH), 53.0 (d, CHα_{Leu}), 54.0 (d, CHα_{Phe}), 56.2 (d, CHα_{Tyr}), 67.5 (d, C-6), 67.9 (t, *CH*$_2$CH=CH$_2$), 78.5 [s, *C*(CH$_3$)$_3$], 98.6 (d, C-2), 115.7 (d, 2C, C$_{Ar}$), 117.1 (t, CH=*CH*$_2$), 126.9 (d, d, 2C, C$_{Ar}$, C-5), 128.2 (d, C-4), 128.7 (d, 2C, C$_{Ar}$), 129.0 (d, C$_{Ar}$), 129.1 (d, 2C, C$_{Ar}$), 130.9 (s, C$_{Ar}$), 135.4 (d, *CH*=CH$_2$), 138.0 (s, C$_{Ar}$), 155.3 (s, C$_{Ar}$), 155.6 (s, CO), 171.1 (s, CO), 171.2 (s, CO), 171.5 (s, CO), 171.7 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 751 (100) $[MH]^+$, 773 (31) $[MNa]^+$. $C_{40}H_{54}N_4O_{10}$ (750.88): calcd. C 63.98, H 7.25, N 7.46; found C 63.71, H 7.45, N 7.56.

Methyl Amide 19: The acid **12** (790 mg, 3.12 mmol) was coupled to dipeptide TFA·H−Phe−Met−NHCH$_3$ (1.72 g, 4.05 mmol) as described for **13**. The crude product was purified by column chromatography using hexane/EtOAc (1:1) as eluent to afford **19** (1.25 g, 74%) as a white solid; m.p. 138−141 °C. $[\alpha]_D^{22}$ = +37 (*c* = 0.25, MeOH). IR (KBr): $\tilde{\nu}$ = 3429, 3288, 2922, 2100, 1632, 1537, 1415, 1271, 1123, 1065, 1017, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.92 (m, 1 H, CH*H*β_{Met}), 2.05 (m, 1 H, C*H*Hβ_{Met}), 2.04 (s, 3 H, *CH*$_3$S), 2.32 (m, 2 H, *CH*$_2$CO), 2.45 (m, 2 H, *CH*$_2$S), 2.62 (m, 1 H, 3-H), 2.73 (d, *J* = 4.9 Hz, 3 H, NH*CH*$_3$), 3.06 (m, 2 H, *CH*$_2\beta_{Phe}$), 3.24 (dd, *J* = 12.9 and *J* = 3.5 Hz, 1 H, CH*H*N$_3$), 3.42 (dd, *J* = 12.9 and *J* = 5.7 Hz, 1 H, C*H*HN$_3$), 4.05 (dd, *J* = 12.9 and *J* = 4.9 Hz, 1 H, CH*H*CH=CH$_2$), 4.20 (dd, *J* = 12.9 and *J* = 6.4 Hz, 1 H, C*H*HCH=CH$_2$), 4.36 (m, 1 H, 6-H), 4.48 (m, 1 H, CHα_{Met}), 4.63 (m, 1 H, CHα_{Phe}), 4.68 (s, 1 H, 2-H), 5.17 (m, $J_{cis\text{-}H}$ = 10.5 Hz, 1 H, =C*H*$_2$ *cis*), 5.28 (m, $J_{trans\text{-}H}$ = 17.1 Hz, 1 H, =C*H*$_2$ *trans*), 5.63 (d, *J* = 10.5 Hz, 1 H, 5-H), 5.81 (m, 1 H, 4-H), 5.89 (m, 1 H, C*H*=CH$_2$), 6.07 (q, *J* = 4.9 Hz, 1 H, *NH*CH$_3$), 6.13 (d, *J* = 8.0 Hz, 1 H, NH$_{Phe}$), 6.66 (d, *J* = 8.0 Hz, 1 H, NH$_{Met}$), 7.16 (m, 2 H, Ar-H$_{Phe}$), 7.26 (m, 3 H, Ar-H$_{Phe}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (q, S*CH*$_3$), 26.3 (q, NH*CH*$_3$), 30.1 (t, *CH*$_2$S), 30.3 (t, *CH*$_2\beta_{Met}$), 35.6 (d, C-3), 38.0 (t, *CH*$_2\beta_{Phe}$), 39.6 (t, *CH*$_2$CO), 52.4 (t, CHα_{Met}), 53.9 (t, *CH*$_2$N$_3$), 54.8 (d, CHα_{Phe}), 68.0 (d, C-6), 68.7 (t, *CH*$_2$CH=CH$_2$), 98.2 (d, C-2), 117.5 (t, CH=*CH*$_2$), 125.8 (d, C-5), 127.3 (d, C$_{Ar}$), 127.6 (d, C-4), 128.8 (d, 2C, C$_{Ar}$), 129.2 (d, 2C, C$_{Ar}$), 133.9 (d, *CH*=CH$_2$), 136.0 (s, C$_{Ar}$), 170.7 (s, CO), 170.8 (s, CO), 171.0 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 487 (100) $[M - OAllyl]^+$, 545 (13) $[MH]^+$, 567 (40) $[MNa]^+$. $C_{26}H_{36}N_6O_5S$ (544.67): calcd. C 57.33, H 6.66, N 15.43, S 5.89; found C 57.50, H 6.97, N 15.61, S 6.04.

General Procedure for the Synthesis of Compounds 20−24: A mixture of azide **19** (200 mg, 0.37 mmol), Ph_3P (198 mg, 0.73 mmol), and H_2O (0.02 mL) in benzene (4 mL) was refluxed for 1 h. The solvent was evaporated and the residue was dissolved in dry DMF (3 mL). The corresponding *N*-acylated-Tyr−OH derivative (0.48 mmol), HOBT (64.4 mg, 0.48 mmol), Et_3N (0.15 mL, 1.1 mmol), EDC (91 mg, 0.48 mmol), and DMAP (4.5 mg, 0.037 mmol) were added sequentially. The reaction mixture was stirred for 20 h at room temperature. The solvent was removed at reduced pressure, and the residue was purified by silica gel column chromatography to afford the desired compounds **20−24**.

2-(Biph)−Tyr−SAA−Phe−Met−NHMe (20): Azide **19** was coupled to 2-(Biph)−Tyr−OH according to the general procedure described above to afford, after purification by flash chromatography, compound **20** (67%) as a white solid; m.p. 118−120 °C. $[\alpha]_D^{22}$ = +63 (*c* = 0.55, MeOH). IR (KBr): $\tilde{\nu}$ = 3412, 3062, 2920, 1646, 1516, 1449, 1231, 1192, 1111, 1008, 747, 700 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO, 40 °C): δ = 1.59 (m, 2 H, CH$_2\beta_{Met}$), 1.87 (m, 1 H, CH*H*S), 2.01 (m, 1 H, C*H*HS), 1.95 (s, 3 H, S*CH*$_3$), 2.13 (m, 1 H, CH*H*CO), 2.24 (m, 1 H, C*H*HCO), 2.34 (m, 1 H, 3-H), 2.55 (d, *J* = 4.5 Hz, 3 H, NH*CH*$_3$), 2.72 (m, 3 H, CH*H*β_{Phe}, CH$_2\beta_{Tyr}$), 2.84 (m, 1 H, C*H*Hβ_{Phe}), 3.24 (m, 2 H, *CH*$_2$NH), 3.88 (m, 1 H, CH*H*CH=CH$_2$), 4.02 (m, 2 H, 6-H, C*H*HCH=CH$_2$), 4.13 (m, 1 H, CHα_{Met}), 4.40 (m, 1 H, CHα_{Phe}), 4.48 (m, 1 H, CHα_{Tyr}), 4.57 (s, 1 H, 2-H), 5.08 (m, $J_{cis\text{-}H}$ = 10.4 Hz, 1 H, =C*H*$_2$ *cis*), 5.19 (m, $J_{trans\text{-}H}$ = 17.1 Hz, 1 H, =C*H*$_2$ *trans*), 5.59 (m, 2 H, 4-H, 5-H), 5.83 (m, 1 H, C*H*=CH$_2$), 6.68 (d, *J* = 8.3 Hz, 2 H, Ar-H$_{Tyr}$), 7.08 (d, *J* = 8.4 Hz, 2 H, Ar-H$_{Tyr}$), 7.29 (m, 8 H, Ar-H), 7.34 (m, 4 H, Ar-H), 7.47 (m, 2 H, Ar-H), 7.79 (bq, *J* = 4.5 Hz, 1 H, *NH*CH$_3$), 7.90 (t, *J* = 6.1 Hz, 1 H, CH$_2$*NH*), 8.25 (d, *J* = 8.3 Hz, 1 H, NH$_{Met}$), 8.30 (d, *J* = 8.3 Hz, 1 H, NH$_{Phe}$), 8.52 (d, *J* = 8.7 Hz, 1 H, NH$_{Tyr}$), 9.19 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz,

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[D$_6$]DMSO, 40 °C): δ = 14.8 (q, *CH$_3$*S), 25.9 (q, NH*CH$_3$*), 29.8 (t, *CH$_2$*S), 31.3 (t, *CH$_2$*β$_{Met}$), 36.0 (t, *CH$_2$*β$_{Tyr}$), 36.8 (t, *CH$_2$*β$_{Phe}$), 37.6 (t, *CH$_2$*CO), 38.6 (d, C-3), 42.3 (t, *CH$_2$*NH), 52.1 (d, CHα$_{Met}$), 55.3 (d, CHα$_{Tyr}$; d, CHα$_{Phe}$), 67.2 (d, C-6), 67.8 (t, *CH$_2$*CH=CH$_2$), 98.1 (d, C-2), 115.2 (d, 2C, C$_{Ar}$), 116.8 (t, CH=*CH$_2$*), 126.7 (d, C-4; d, C-5), 127.0 (d, C$_{Ar}$), 127.1 (d, C$_{Ar}$), 127.2 (d, C$_{Ar}$), 127.3 (d, C$_{Ar}$), 127.4 (d, C$_{Ar}$), 127.6 (d, C$_{Ar}$), 128.2 (d, 2C, C$_{Ar}$), 128.4 (d, 2C, C$_{Ar}$), 128.6 (d, C$_{Ar}$), 128.7 (d, C$_{Ar}$), 129.5 (d, 2C, C$_{Ar}$), 129.9 (d, C$_{Ar}$), 130.2 (d, C$_{Ar}$), 130.5 (d, 2C, C$_{Ar}$), 135.1 (d, *CH*=CH$_2$), 135.2 (s, C$_{Ar}$), 136.8 (s, C$_{Ar}$), 137.6 (s, C$_{Ar}$), 139.6 (s, C$_{Ar}$), 140.3 (s, C$_{Ar}$), 156.2 (s, C$_{Ar}$), 169.3 (s, CO), 171.3 (s, CO), 171.6 (s, CO), 171.7 (s, CO), 171.8 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 699 (33) [(M − Biph)NH$_4$]$^+$, 862 (100) [MH]$^+$, 884 (26) [MNa]$^+$. $C_{48}H_{55}N_5O_8S$ (861.38): calcd. C 66.88, H 6.43, N 8.12, S 3.72; found C 66.88, H 6.50, N 8.21, S 3.58.

Bz−Tyr−SAA−Phe−Met−NHMe (21): Azide **19** was coupled to Bz−Tyr−OH according to the general procedure described above to afford, after purification by flash chromatography, compound **21** (51%) as a white solid; m.p. 107−110 °C. $[\alpha]_D^{22}$ = +46 (*c* = 0.8, MeOH). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 40 °C): δ = 1.62 (m, 1 H, CH*H*β$_{Met}$), 1.88 (m, 1 H, C*H*Hβ$_{Met}$), 1.97 (s, 3 H, S*CH$_3$*), 2.13 (m, 3 H, CH*H*CO, *CH$_2$*S), 2.26 (m, 1 H, C*H*HCO), 2.34 (m, 1 H, 3-H), 2.56 (d, *J* = 4.5 Hz, 3 H, NH*CH$_3$*), 2.81 (d, *J* = 13.5 Hz, 1 H, CH*H*β$_{Tyr}$), 2.91 (m, 2 H, CH*H*β$_{Phe}$, C*H*Hβ$_{Tyr}$), 2.98 (dd, *J* = 13.9 and *J* = 4.8 Hz, 1 H, C*H*Hβ$_{Phe}$), 3.35 (m, 2 H, *CH$_2$*NH), 3.88 (dd, *J* = 13.1 and *J* = 4.9 Hz, 1 H, CH*H*CH=CH$_2$), 4.10 (m, 2 H, 6-H, C*H*HCH=CH$_2$), 4.18 (m, 1 H, CHα$_{Met}$), 4.45 (m, 1 H, CHα$_{Tyr}$), 4.58 (s, 1 H, 2-H), 4.63 (m, 1 H, CHα$_{Phe}$), 5.08 (m, *J$_{cis}$*-H = 10.4 Hz, 1 H, =C*H$_2$ cis*), 5.19 (m, *J$_{trans}$*-H = 17.2 Hz, 1 H, =C*H$_2$ trans*), 5.61 (m, 2 H, 4-H, 5-H), 5.82 (m, 1 H, C*H*=CH$_2$), 6.62 (d, *J* = 8.4 Hz, 2 H, Ar-H$_{Tyr}$), 7.11 (d, *J* = 8.4 Hz, 2 H, Ar-H$_{Tyr}$), 7.20 (m, 5 H, Ar-H$_{Phe}$), 7.43 (t, *J* = 7.8 Hz, 2 H, Ar-H$_{Bz}$), 7.50 (t, *J* = 7.4 Hz, 1 H, Ar-H$_{Bz}$), 7.74 (bq, *J* = 4.5 Hz, 1 H, *NH*Me), 7.79 (d, *J* = 7.1 Hz, 2 H, Ar-H$_{Bz}$), 8.02 (t, *J* = 5.8 Hz, 1 H, CH$_2$*NH*), 8.19 (d, *J* = 8.4 Hz, 1 H, NH$_{Met}$), 8.25 (d, *J* = 6.8 Hz, 1 H, NH$_{Tyr}$), 8.43 (d, *J* = 8.4 Hz, 1 H, NH$_{Phe}$), 9.06 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 40 °C): δ = 15.2 (q, *CH$_3$*S), 26.3 (q, NH*CH$_3$*), 30.2 (t, *CH$_2$*S), 31.8 (t, *CH$_2$*β$_{Met}$), 36.5 (t, *CH$_2$*β$_{Phe}$), 37.1 (t, *CH$_2$*β$_{Tyr}$), 38.0 (t, *CH$_2$*CO), 39.0 (d, C-3), 43.0 (t, *CH$_2$*NH), 52.5 (d, CHα$_{Met}$), 55.5 (d, CHα$_{Tyr}$), 56.0 (d, CHα$_{Phe}$), 67.5 (d, C-6), 68.1 (t, *CH$_2$*CH=CH$_2$), 98.5 (d, C-2), 115.6 (d, 2C, C$_{Ar}$), 117.1 (t, CH=*CH$_2$*), 127.0 (d, C-4; d, C-5), 127.2 (d, C$_{Ar}$), 128.1 (d, 2C, C$_{Ar}$), 128.7 (d, 2C, C$_{Ar}$), 128.8 (d, 2C, C$_{Ar}$), 129.1 (s, C$_{Ar}$), 129.8 (d, 2C, C$_{Ar}$), 130.7 (d, 2C, C$_{Ar}$), 131.9 (d, C$_{Ar}$), 134.8 (s, C$_{Ar}$), 135.5 (d, *CH*=CH$_2$), 138.0 (s, C$_{Ar}$), 156.4 (s, C$_{Ar}$), 167.0 (s, CO$_{Bz}$), 171.6 (s, CO), 171.9 (s, CO), 172.0 (s, CO), 172.3 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 786 (100) [MH]$^+$, 808 (48) [MNa]$^+$. $C_{42}H_{51}N_5O_8S$ (785.35): calcd. C 64.18, H 6.54, N 8.91, S 4.08; found C 63.85, H 6.80, N 8.69, S 3.73.

CF$_3$CO−Tyr−SAA−Phe−Met−NHMe (22): Azide **19** was coupled to CF$_3$CO−Tyr−OH according to the general procedure described above to afford, after purification by flash chromatography, compound **22** (49%) as a white solid; m.p. 116−118 °C. $[\alpha]_D^{22}$ = +31 (*c* = 0.2, MeOH), ^{1}H NMR (400 MHz, [D$_6$]DMSO, 40 °C): δ = 1.59 (m, 2 H, CH$_2$β$_{Met}$) 1.59 (m, 2 H, CH$_2$β$_{Met}$), 1.87 (m, 1 H, CH*H*S), 2.05 (s, 3 H, CH$_3$S), 2.09 (m, 1 H, C*H*HS), 2.14 (m, 1 H, CH*H*CO), 2.21 (m, 1 H, C*H*HCO), 2.32 (m, 1 H, H-3), 2.53 (d, *J* = 4.5 Hz, 3 H, NH*CH$_3$*), 2.78 (m, 3 H, CH*H*β$_{Phe}$, CH*H*β$_{Tyr}$), 2.90 (m, 2 H, C*H*Hβ$_{Phe}$, C*H*Hβ$_{Tyr}$), 3.22 (m, 2 H, *CH$_2$*NH), 3.88 (m, 1 H, CH*H*CH=CH$_2$), 4.05 (m, 2 H, 6-H, C*H*HCH=CH$_2$), 4.12 (m, 1 H, CHα$_{Met}$), 4.24 (m, 1 H, CHα$_{Tyr}$), 4.47 (m, 1 H, CHα$_{Phe}$), 4.58 (s, 1 H, 2-H), 5.07 (m, *J$_{cis}$*-H = 10.4, 1 H, =C*H$_2$ cis*), 5.18 (m, *J$_{trans}$*-H = 17.1, 1 H, =C*H$_2$ trans*), 5.56 (m, 2 H, 4-H, 5-H), 5.83 (m, 1 H, C*H*=CH$_2$), 6.60 (d, *J* = 8.4 Hz, 2 H, Ar-H$_{Tyr}$), 7.02 (d, *J* = 8.3 Hz, 2 H, Ar-H$_{Tyr}$), 7.21 (m, 5 H, Ar-H$_{Phe}$), 7.69 (bq, 1 H, *NH*Me), 8.03 (d, *J* = 8.1 Hz, 1 H, NH$_{Met}$), 8.13 (d, *J* = 8.3 Hz, 1 H, NH$_{Tyr}$), 8.22 (bt, 1 H, CH$_2$*NH*), 9.06 (s, 1 H, OH), 9.44 (d, *J* = 8.4 Hz, 1 H, NH$_{Phe}$) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 40 °C): δ = 14.5 (q, *CH$_3$*S), 25.5 (q, NH*CH$_3$*), 29.5 (t, *CH$_2$*CO), 31.7 (t, *CH$_2$*β$_{Met}$), 35.6 (t, C-3), 37.1 (t, *CH$_2$*β$_{Tyr}$), 38.4 (t, *CH$_2$*β$_{Phe}$), 38.4 (t, *CH$_2$*S), 42.2 (t, *CH$_2$*NH), 51.7 (d, CHα$_{Met}$), 51.8 (d, CHα$_{Tyr}$), 53.9 (d, CHα$_{Phe}$), 66.5 (d, C-6), 67.3 (t, *CH$_2$*CH=CH$_2$), 97.7 (d, C-2), 114.7 (d, 2C, C$_{Ar}$), 116.3 (t, CH=*CH$_2$*), 125.9 (d, C-5), 126.1 (d, C$_{Ar}$), 126.6 (d, C-4), 127.9 (d, 2C, C$_{Ar}$), 128.9 (d, 2C, C$_{Ar}$), 129.9 (d, 2C, C$_{Ar}$), 131.8 (s, C$_{Ar}$), 134.6 (d, *CH*=CH$_2$), 137.8 (s, C$_{Ar}$), 155.7 (s, C$_{Ar}$), 169.8 (s, *CO*CF$_3$), 170.0 (s, CO), 170.4 (s, CO), 171.0 (s, CO), 171.1 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 720 (20) [M − OAllyl]$^+$, 778 (100) [MH]$^+$, 800 (67) [MNa]$^+$. $C_{37}H_{46}F_3N_5O_8S$ (777.30): calcd. C 57.13, H 5.96, N 9.00, S 4.12; found C 57.21, H 6.20, N 8.94, S 3.95.

CH$_3$(CH$_2$)$_2$CO−Tyr−SAA−Phe−Met−NHMe (23): Azide **19** was coupled to CH$_3$(CH$_2$)$_2$CO−Tyr−OH according to the general procedure described above to afford, after purification by flash chromatography, compound **23** (69%) as a white solid; m.p. 101−103 °C. $[\alpha]_D^{22}$ = +58 (*c* = 0.1, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 40 °C): δ = 0.73 (t, *J* = 7.3 Hz, 3 H, *CH$_3$*CH$_2$), 1.40 (m, 2 H, *CH$_2$*CH$_2$CO), 1.76 (m, 1 H, CH*H*β$_{Met}$), 1.90 (m, 1 H, C*H*Hβ$_{Met}$), 2.01 (m, 2 H, *CH$_2$*CONH$_{Tyr}$), 2.02 (s, 3 H, S*CH$_3$*), 2.10 (m, 1 H, CH*H*S), 2.19 (m, 1 H, C*H*HS), 2.39 (m, 3 H, 3-H, *CH$_2$*CONH$_{Phe}$), 2.56 (d, *J* = 4.6 Hz, 3 H, NH*CH$_3$*), 2.63 (m, 1 H, CH*H*β$_{Tyr}$), 2.77 (dd, *J* = 13.9 and *J* = 3.9 Hz, 1 H, CH*H*β$_{Phe}$), 2.84 (d, *J* = 14.1 Hz, 1 H, C*H*Hβ$_{Tyr}$), 3.02 (dd, *J* = 13.9 and *J* = 4.8 Hz, 1 H, C*H*Hβ$_{Phe}$), 3.19 (m, 2 H, *CH$_2$*NH), 3.88 (dd, *J* = 12.9 and *J* = 5.6 Hz, 1 H, CH*H*CH=CH$_2$), 4.07 (m, 1 H, 6-H), 4.08 (dd, *J* = 13.1 and *J* = 6.0 Hz, 1 H, C*H*HCH=CH$_2$), 4.27 (m, 1 H, CHα$_{Met}$), 4.44 (m, 1 H, CHα$_{Tyr}$), 4.51 (s, 1 H, 2-H), 4.55 (m, 1 H, CHα$_{Phe}$), 5.12 (m, *J$_{cis}$*-H = 10.2 Hz, 1 H, =C*H$_2$ cis*), 5.22 (m, *J$_{trans}$*-H = 17.3 Hz, 1 H, =C*H$_2$ trans*), 5.56 (m, 2 H, 4-H, 5-H), 5.86 (m, 1 H, C*H*=CH$_2$), 6.62 (d, *J* = 8.3 Hz, 2 H, Ar-H$_{Tyr}$), 7.01 (d, *J* = 8.5 Hz, 2 H, Ar-H$_{Tyr}$), 7.22 (m, 5 H, Ar-H$_{Phe}$), 7.49 (q, *J* = 4.6 Hz, 1 H, *NH*Me), 7.84 (t, *J* = 5.8 Hz, 1 H, CH$_2$NH), 7.87 (d, *J* = 8.3 Hz, 1 H, NHTyr), 7.98 (d, *J* = 8.0 Hz, 1 H, NH$_{Met}$), 8.11 (d, *J* = 7.8 Hz, 1 H, NH$_{Phe}$), 9.04 (s, 1 H, OH), ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 40 °C): δ = 13.3 (q, *CH$_3$*CH$_2$), 14.5 (q, *CH$_3$*S), 18.4 (t, *CH$_2$*CH$_2$CO), 25.4 (q, NH*CH$_3$*), 29.5 (t, *CH$_2$*CONH$_{Phe}$), 31.7 (t, *CH$_2$*β$_{Met}$), 35.5 (d, C-3), 36.7 (t, *CH$_2$*β$_{Tyr}$), 37.0 (t, *CH$_2$*β$_{Phe}$; t, CH$_2$*CH$_2$*CO), 38.4 (t, *CH$_2$*S), 42.1 (t, *CH$_2$*NH), 51.8 (d, CHα$_{Met}$), 53.8 (d, CHα$_{Phe}$), 54.1 (d, CHα$_{Tyr}$), 66.5 (d, C-6), 67.3 (t, *CH$_2$*CH=CH$_2$), 97.7 (d, C-2), 114.6 (d, 2C, C$_{Ar}$), 116.2 (t, CH=*CH$_2$*), 126.1 (d, C-4; d, C-5), 126.4 (d, C$_{Ar}$), 127.8 (d, 2C, C$_{Ar}$), 127.9 (s, C$_{Ar}$), 128.9 (d, 2C, C$_{Ar}$), 129.8 (d, 2C, C$_{Ar}$), 134.7 (d, *CH*=CH$_2$), 137.7 (s, C$_{Ar}$), 155.5 (s, C$_{Ar}$), 170.3 (s, CO), 170.9 (s, CO), 171.0 (s, CO), 171.5 (s, CO), 171.8 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 752 (100) [MH]$^+$, 774 (43) [MNa]$^+$ $C_{39}H_{53}N_5O_8S$ (751.36): calcd. C 62.30, H 7.10, N 9.31, S 4.26; found C 62.12, H 7.37, N 9.22, S 3.98.

Ac−Tyr−SAA−Phe−Met−NHMe (24): Azide **19** was coupled to Ac−Tyr−OH according to the general procedure described above to afford, after purification by flash chromatography, compound **24** (65%) as a white solid. m.p. 106−109 °C. $[\alpha]_D^{22}$ = +61 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 40 °C): δ = 1.75 (s, 3 H, CO*CH$_3$*), 1.76 (m, 1 H, CH*H*β$_{Met}$), 1.89 (m, 1 H, C*H*Hβ$_{Met}$), 2.02 (s, 3 H, S*CH$_3$*), 2.11 (m, 3 H, CH*H*S, *CH$_2$*CO), 2.38 (m, 2 H, 3-H, C*H*HS), 2.56 (d, *J* = 4.6 Hz, 3 H, NH*CH$_3$*), 2.63 (m, 1 H,

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CH*H*β_{Tyr}), 2.82 (m, $CH_2\beta_{Phe}$, 3 H, C*H*Hβ_{Tyr}), 3.19 (m, 2 H, *CH_2*NH), 3.89 (m, 1 H, CH*H*CH=CH_2), 4.07 (m, 1 H, 6-H), 4.14 (m, 1 H, C*H*HCH=CH_2), 4.28 (m, 1 H, CHα_{Met}), 4.42 (m, 1 H, CHα_{Tyr}), 4.51 (s, 1 H, 2-H), 4.55 (m, 1 H, CHα_{Phe}), 5.12 (m, $J_{cis\text{-}H}$ = 10.2 Hz, 1 H, =C*H_2 cis*), 5.22 (m, $J_{trans\text{-}H}$ = 17.3 Hz, 1 H, =C*H_2 trans*), 5.56 (m, 2 H, 4-H, 5-H), 5.87 (m, 1 H, C*H*=CH_2), 6.62 (d, *J* = 8.5 Hz, 2 H, Ar-H_{Tyr}), 7.00 (d, *J* = 8.3 Hz, 2 H, Ar-H_{Tyr}), 7.23 (m, 5 H, Ar-H), 7.49 (bq, *J* = 4.6, 1 H, *NH*Me), 7.87 (t, *J* = 5.6 Hz, 1 H, CH_2*NH*), 7.98 (d, *J* = 8.3 Hz, 1 H, NH_{Tyr}; d, *J* = 8.3 Hz, 1 H, NH_{Met}), 8.11 (d, *J* = 7.8 Hz, 1 H, NH_{Phe}), 9.08 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 40 °C): δ = 14.6 (q, CH_3S), 22.5 (q, CO*CH_3*), 25.6 (q, NHCH_3), 29.5 (t, *CH_2*S), 31.8 (t, $CH_2\beta_{Met}$), 35.6 (t, $CH_2\beta_{Tyr}$), 35.7 (t, $CH_2\beta_{Phe}$), 36.9 (t, *CH_2*CO), 38.4 (d, C-3), 42.1 (t, *CH_2*NH), 51.8 (d, CHα_{Met}), 53.9 (d, CHα_{Phe}), 55.5 (d, CHα_{Tyr}), 66.6 (d, C-6), 67.4 (t, *CH_2*CH=CH_2), 97.7 (d, C-2), 114.8 (d, 2C, C_{Ar}), 116.5 (t, CH=*CH_2*), 126.2 (d, C-5), 126.3 (d, C-4), 126.6 (d, C_{Ar}), 128.1 (d, 2C, C_{Ar}), 129.1 (d, 2C, C_{Ar}), 129.2 (d, C_{Ar}), 130.0 (d, 2C, C_{Ar}), 134.8 (d, *CH*=CH_2), 137.2 (s, C_{Ar}), 137.9 (s, C_{Ar}), 155.7 (s, C_{Ar}), 169.1 (s, CO), 170.4 (s, CO), 171.2 (s, CO), 171.3 (s, CO), 171.7 (s, CO) ppm. ESI-MS: *m*/*z* (%) = 724 (100) $[MH]^+$, 746 (96) $[MNa]^+$. $C_{37}H_{49}N_5O_8S$ (723.33): calcd. C 61.39, H 6.82, N 9.67, S 4.43; found C 61.21, H 6.97, N 9.70, S 4.35.

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[1] [1a] A. Giannis, F. Rübsam, *Adv. Drug Res.* **1997**, *29*, 1−77. [1b] J. Gante, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699−1720. [1c] V. J. Hruby, G. Li, C. Haskell-Luevano, M. Shenderovich, *Biopolymers* **1997**, *43*, 219−248. [1d] S. Lien, H. B. Lowman, *Trends Biotechnol.* **2003**, *21*, 556−562.

[2] For reviews on SAAs, see: [2a] S. A. W. Gruner, E. Locardi, E. Lohof, H. Kessler, *Chem. Rev.* **2002**, *102*, 491−514. [2b] T. K. Chakraborty, S. Ghosh, S. Jayaprakash, *Curr. Med. Chem.* **2002**, *9*, 421−435.

[3] G. Baschang, *Tetrahedron* **1989**, *45*, 6331−6360.

[4] J. P. Waltho, D. H. Williams, E. Selva, P. Ferrari, *J. Chem. Soc., Perkin Trans. 1* **1987**, *9*, 2103−2107.

[5] M. Stöeckle, G. Voll, R. Günther, E. Lohof, E. Locardi, S. Gruner, H. Kessler, *Org. Lett.* **2002**, *4*, 2501−2504.

[6] M. D. Smith, D. D. Long, D. G. Marquess, T. D. W. Claridge, G. W. J. Fleet, *Chem. Commun.* **1998**, 2039−2040.

[7] R. M. van Well, H. S. Overkleeft, J. H. van Boom, A. Coop, J. B. Wang, H. Wang, G. A. van der Marel, M. Overhand, *Eur. J. Org. Chem.* **2003**, 1704−1710.

[8] A. B. Smith III, S. Sasho, A. B. Bari, P. Sprengeler, J. Barbosa, R. Hirschmann, B. S. Cooperman, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3133−3136.

[9] For some references, see: [9a] H. P. Wessel, C. M. Mitchell, C. M. Lobato, G. Schmid, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2712−2713. [9b] J. P. McDevitt, P. T. Lansbury Jr, *J. Am. Chem. Soc.* **1996**, *118*, 3818−3828. [9c] O. Lockhoff, *Angew. Chem. Int. Ed.* **1998**, *37*, 3436−3439. [9d] T. K. Chakraborty, S. Jayaprakash, P. V. Diwan, R. Nagaraj, S. R. B. Jampani, A. C. Kunwar, *J. Am. Chem. Soc.* **1998**, *120*, 12962−12963. [9e] A. Schrey, F. Osterkamp, A. Straudi, C. Rickert, H. Wagner, U. Koert, B. Herrschaft, K. Harms, *Eur. J. Org. Chem.* **1999**, 2977−2990. [9f] J. Xie, *Carbohydr. Res.* **2003**, *338*, 399−406.

[10] [10a] E. Graf von Roedern, E. Lohof, G. Hessler, M. Hoffmann, H. Kessler, *J. Am. Chem. Soc.* **1996**, *118*, 10156−10167. [10b] T. K. Chakraborty, S. Ghosh, S. Jayaprakash, J. A. R. P. Sharma, V. Ravikanth, P. V. Diwan, R. Nagaraj, A. C. Kunwar, *J. Org. Chem.* **2000**, *65*, 6441−6457. [10c] B. Aguilera, G. Siegal, H. S. Overkleeft, N. J. Meeuwenoord, F. P. J. T. Rutjes, J. C. M. Van Hest, H. E. Schoemaker, G. A. Van der Marel, J. H. Van Boom, M. Overhand, *Eur. J. Org. Chem.* **2001**, 1541−1547. [10d] R. M. van Well, H. S. Overkleeft, G. A. van der Marel, D. Bruss, G. Thibault, P. G. de Groot, J. H. van Boom, M. Overhand, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 331−334.

[11] [11a] D. E. A. Brittain, P. P. Watterson, T. D. W. Claridge, M. D. Smith, G. W. J. Fleet, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3655−3665. [11b] E. Locardi, M. Stöckle, S. Gruner, H. Kessler, *J. Am. Chem. Soc.* **2001**, *123*, 8189−8196. [11c] S. A. W. Gruner, V. Truffault, G. Voll, E. Locardi, M. Stöckle, H. Kessler, *Chem. Eur. J.* **2002**, *8*, 4366−4376. [11d] R. M. van Well, L. Marinelli, K. Erkelens, G. A. van der Marel, A. Lavecchia, H. S. Overkleeft, J. H. van Boom, H. Kessler, M. Overhand, *Eur. J. Org. Chem.* **2003**, 2303−2313. [11e] T. K. Chakraborty, P. Srinivasu, E. Bikshapathy, R. Nagaraj, M. Vairamani, S. K. Kumar, A. C. Kunwar, *J. Org. Chem.* **2003**, *68*, 6257−6263.

[12] [12a] E. Mann, A. Chana, F. Sánchez-Sancho, C. Puerta, A. García-Merino, B. Herradón, *Adv. Synth. Catal.* **2002**, *344*, 855−867. [12b] E. Mann, A. Montero, M. A. Maestro, B. Herradón, *Helv. Chim. Acta* **2002**, *85*, 3624−3638. [12c] A. Salgado, E. Mann, F. Sánchez-Sancho, B. Herradón, *Heterocycles* **2003**, *60*, 57−71.

[13] E. Mann, PhD Dissertation, University Autónoma (Madrid), 2002.

[14] B. Werschkun, J. Thiem, *Topics Curr. Chem.* **2001**, *215*, 293−325.

[15] M. Eguchi, *Med. Res. Rev.* **2004**, *24*, 182−212.

[16] [16a] C. T. Dooley, R. A. Houghton, *Biopolymers (Peptide Science)* **1999**, *51*, 379−390. [16b] S. F. Martin, M. P. Dwyer, B. Hartmann, K. S. Knight, *J. Org. Chem.* **2000**, *65*, 1305−1318. [16c] M. Eguchi, R. Y. W. Shen, J. P. Shea, M. S. Lee, M. Kahn, *J. Med. Chem.* **2002**, *45*, 1395−1398.

[17] [17a] V. J. Aldrich in *Burger's Medicinal Chemistry and Drug Discovery* (Ed.: M. E. Wolff), John Wiley & Sons, New York, **1996**, vol. 3, pp. 321−441. [17b] S. Rudolph-Böhner, D. Quarzago, M. Czisch, U. Ragnarsson, L. Moroder, *Biopolymers* **1997**, *41*, 591−606.

[18] For reviews on the chemistry of glycals, see: [18a] S. Czernicki in *Carbohydrates-Synthetic Methods and Applications in Medicinal Chemistry* (Eds.: H. Ogur, A. Hasewaga, T. Suami), VCH, New York, **1991**, pp. 28−48. [18b] A. G. Tolstikov, G. A. Tolstikov, *Russ. Chem. Rev.* **1993**, *62*, 579−601.

[19] [19a] R. J. Ferrier, *Topics Curr. Chem.* **2001**, *215*, 153−175. [19b] R. J. Ferrier, O. A. Zubkov, *Org. React.* **2003**, *62*, 569−736.

[20] M. Koreeda, T. A. Houston, B. K. Shull, E. Klemke, R. J. Tuinman, *Synlett* **1995**, 90−92.

[21] C. Masson, J. Soto, M. Bessodes, *Synlett* **2000**, 1281−1282.

[22] [22a] O. Mitsunobu, *Synthesis* **1981**, 1−28. [22b] S. Valverde, B. Herradón, R. M. Rabanal, M. Martín-Lomas, *Can. J. Chem.* **1987**, *65*, 339−342.

[23] R. Bao, S. Valverde, B. Herradón, *Synlett* **1992**, 217−219.

[24] All the compounds have been named as derivatives of 3,6-dihydro-2*H*-pyrans following IUPAC rules; this implies that the anomeric position is C-6 in compounds **1**−**6** and C-2 in **7**−**24**.

[25] [25a] R. J. Ferrier, N. Vethaviyasar, *J. Chem. Soc., C* **1971**, 1907−1913. [25b] R. J. Ferrier, N. Vethaviyasar, *J. Chem. Soc., Perkin Trans. 1* **1973**, 1791−1793.

[26] K. Krohn, U. Flörke, D. Gehle, *J. Carbohydrate Chem.* **2002**, *21*, 431−443.

[27] For a similar reasoning applied to the related Overman rearrangement, see: T. Nishikawa, M. Asai, N. Ohyabu, M. Isobe, *J. Org. Chem.* **1998**, *63*, 188−192.

[28] The overall sequence can be carried out in multigram scale with reproducible results.

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[29] [29a] P. Lloyd-Williams, F. Albericio, E. Giralt, *Chemical Approaches to the Synthesis of Peptides and Proteins*, CRC Press, Boca Raton, **1997**. [29b] M. Goodman, A. Felix, L. Moroder, C. Toniolo (Eds.), *Synthesis of Peptides and Peptidomimetics*, Georg Thieme Verlag, Stuttgart, **2002**.
[30] [30a] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635−646. [30b] Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, *48*, 1353−1406.
[31] [31a] H.-H. Otto, T. Schirmeister, *Chem. Rev.* **1997**, *97*, 133−171. [31b] C. Adessi, C. Soto, *Current Med. Chem.* **2002**, *9*, 963−978.
[32] [32a] B. Herradón, E. Fenude, R. Bao, S. Valverde, *J. Org. Chem.* **1996**, *61*, 1143−1147. [32b] T. Kodama, S. Shuto, M. Nomura, A. Matsuda, *Chem. Eur. J.* **2001**, *7*, 2332−2340. [32c] K. Sato, D. Miyama, S. Akai, *Tetrahedron Lett.* **2004**, *45*, 1523−1525.
[33] T. J. Donohoe, K. Blades, P. R. Moore, M. J. Waring, J. J. G. Winter, M. Helliwell, N. J. Newcombe, G. Stemp, *J. Org. Chem.* **2002**, *67*, 7946−7956.
[34] [34a] M. J. Sofia, *Molecular Diversity* **1997**, *3*, 75−94. [34b] G. T. Le, G. Abbenante, B. Becker, M. Grathwohl, J. Halliday, G. Tometzki, J. Zuegg, W. Meutermans, *Drug Discovery Today* **2003**, *8*, 701−709.

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