Studies on the *C*-alkylation and *C*-allylation of small peptides employing glycyl radical intermediates

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A series of dipeptides and one tripeptide possessing a glycyl xanthate unit has been employed as an alternative method for the introduction of side chains directly onto a peptide chain. Two non-metal-based radical reactions are examined, involving either the addition of the glycyl xanthate unit onto an alkene or an allylation procedure employing allyl alkyl sulfones. These procedures are advantageous as they avoid the use of the toxic but more common tinhydride-based compounds. Variable yields for the side-chain introduction are observed with best results for the dipeptides. Attempts are also made to adapt the allylation protocol to the direct side-chain introduction on a non-functionalised glycine unit.

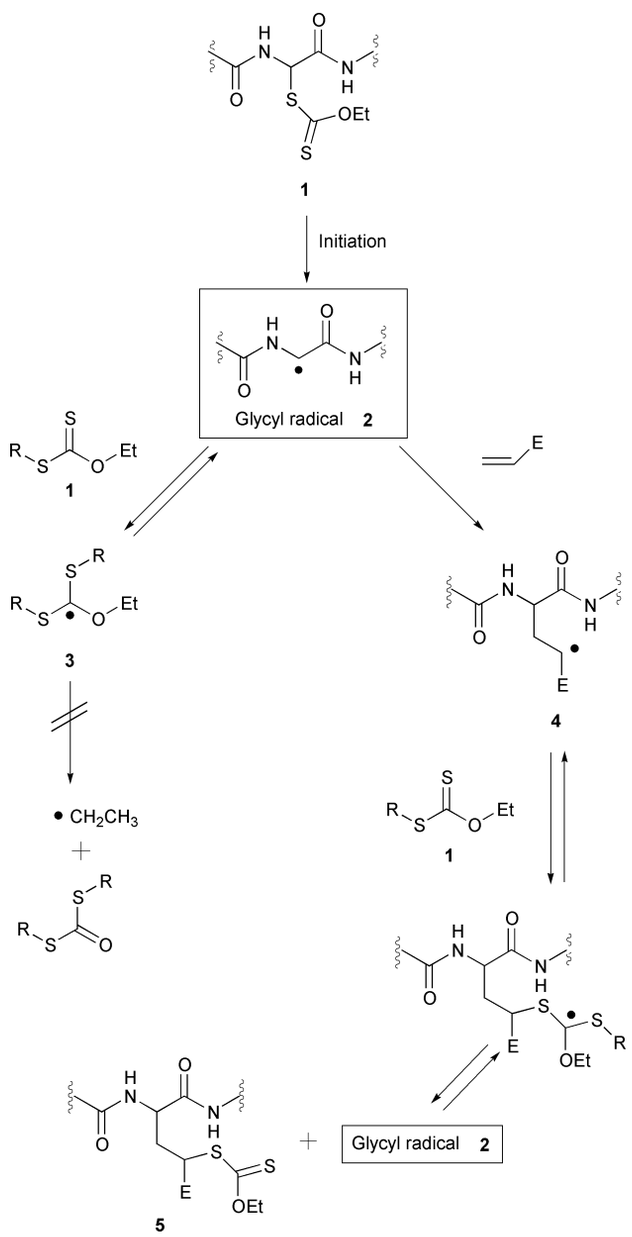
Introduction

We have recently been interested in preparing unnatural peptides by the selective and direct introduction of alkyl side chains onto glycine residues of peptide chains.[1] In comparison with the traditional synthetic approach to such compounds, which incorporates a non-proteinogenic amino acid into the peptide strand by means of a linear synthesis, selective *C*-alkylation allows for the rapid preparation of a series of new peptides from a single parent peptide. Several ways of achieving this goal have previously been explored taking advantage of reactive glycyl species, such as glycine enolates,[2–6] carbocations,[7] and radicals.[8–11] In particular, the *C*-alkylation of peptides by radical-based chemistry is attractive for two reasons. First, glycyl radicals are easily generated owing to the captodative stabilisation of this carbon radical by its two substituents,[12] and second, radical addition reactions to alkenes are performed under essentially neutral conditions.

In this paper, we examine two approaches to a radical-based *C*-alkylation of peptides exploiting the elegant work on the xanthate-transfer radical additions reactions developed by Zard,[13] as well as their novel allylating process.[14] Particularly attractive with these approaches are their ability to promote radical chemistry without the need for organotin-based hydrides of which by-products are generally both toxic and difficult to remove from the desired product. We also disclose our attempts to develop another route to the direct allylation of glycine residues, without the need for a xanthate intermediate.

Results and discussion

The principles for the peptide alkylation approach employing xanthate-containing glycine residues and an olefin are depicted in Scheme 1.[13] An initiation process encompassing an alkyl radical attack on the xanthate functionality in **1** generates the captodatively stabilised glycyl radical **2**. Two possible routes for this radical are then available. The first involves addition of **2** to another glycyl xanthate to afford the intermediate **3**. As β-scission of the C–O bond would lead to the thermodynamically less stable ethyl radical compared with **2**, the more favourable rupture of either of the two weaker C–S bonds regenerates the glycyl radical. This degenerate pathway effectively increases the lifetime of **2**, thus encouraging the characteristically slow but irreversible addition of this stabilised radical to an alkene trap present in the medium. Hence, the subsequent addition of **2** to an olefin leads to a new carbon-centred radical **4** which



Scheme 1

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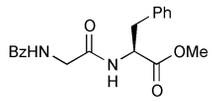
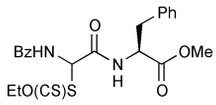
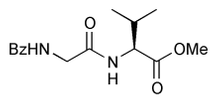
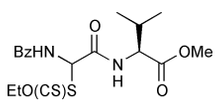
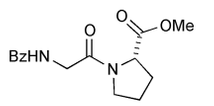
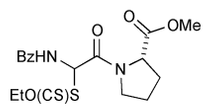
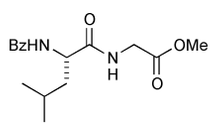
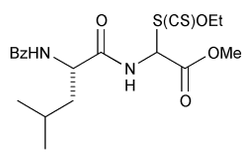
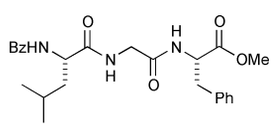
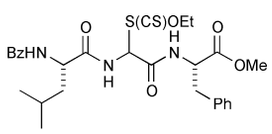
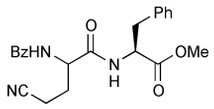
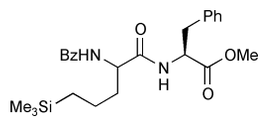
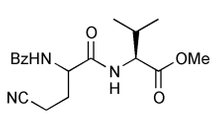
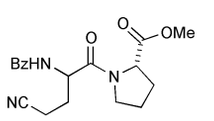
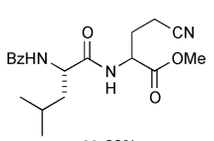
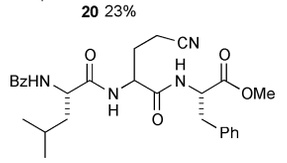
Table 1 Synthesis of the peptide xanthates[a]

Entry	Peptide	Xanthate-yield[b]
1	 **6**	 **11** 63%
2	 **7**	 **12** 75%
3	 **8**	 **13** 57%
4	 **9**	 **14** 40%
5	 **10**	 **15** 51%[c]

[a] For reaction conditions see the Experimental section. [b] Isolated yields after chromatography on silica gel. [c] Based on consumed starting material (33% recovery).

Table 2 *C*-Alkylation of peptides **11**–**15**[a]

Entry	Xanthate[a]	Alkene	Alkylated peptide yield[b]
1	**11**	acrylonitrile	 **16** 50%
2	**11**	allyltrimethyl-silane	 **17** 37%
3	**12**	acrylonitrile	 **18** 43%
4	**13**	acrylonitrile	 **19** 20%
5	**14**	acrylonitrile	 **20** 23%
6	**15**	acrylonitrile	 **21** 14%

[a] For reaction conditions see the Experimental section. [b] Isolated yields after chromatography on silica gel.

eventually undergoes an addition and fragmentation reaction with the starting compound to afford the functionalised peptide **5**. Again, the high stability of the glycyl radical[12] compared with the alkyl radical formed in **4** provides the driving force for this reaction.

Some support for the feasibility of this method for peptide alkylation was provided by Hiemstra and Speckamp, who previously studied alkene addition to simple glycine xanthates by employing di-*tert*-butyl peroxide as the radical-chain initiator under high temperatures (150–160 °C).[15] Variable yields of alkylation were obtained depending on the nature of the olefin used. Removal of the xanthate group was then accomplished under standard tin hydride conditions. However, since their paper was published, several modifications in this radical-alkylation approach have been reported by Zard, including the use of milder reaction conditions with dilauroyl peroxide (DLP) as the radical initiator in solvents such as cyclohexane, benzene or 1,2–dichloroethane.[13] In addition, treatment of the xanthates with stoichiometric amounts of DLP in propan-2-ol was reported as an effective means for the desulfurisation step, hence again avoiding the use of toxic tin reagents.[16] These alterations therefore prompted us to test such alkylation procedures on a series of peptides as discussed below.

The synthesis of the peptide xanthates was easily achieved in two steps from the corresponding glycine-containing peptide. A series of dipeptides **6**–**9** and one tripeptide **10**, as illustrated in Table 1, were first subjected to a radical bromination step according to Easton *et al.* with *N*-bromosuccinimide (NBS).[9,11] Without isolation of the unstable glycyl bromide intermediate, the reaction mixture was immediately treated with the potassium salt of *O*-ethyl dithiocarbonate. In this way, the stable xanthates **11**–**15** could be isolated as an approximately 1.5 : 1 diastereoisomeric mixture, with yields for the sulfide introduction corresponding well to what was previously observed in our reductive samariation studies of glycine pyridyl sulfides.[1]

The results for the radical addition reaction are depicted in Table 2. A refluxing solution of the xanthate and two mole equivalents of the olefin in 1,2-dichloroethane or benzene was treated with small portions of DLP (see Experimental section) until no further evolution of the reaction could be detected. In general, 48 h were required to reach this stage. Without isolation of the new alkene-addition product, the reaction mixture was immediately subjected to the desulfurisation step as described by Zard and co-workers.[16] Hence, replacement of the original medium with propan-2-ol, and then subjection of this hot solution (82 °C) with additional 0.1 mol equiv. portions of DLP (in total 1.3 mol equiv. over a period of 3 days) allowed for the reductive cleavage of the C–S bond. Under these conditions, the intermediate secondary radical is formed as described above, abstracting hydrogen from propan-2-ol to give the corresponding 2–hydroxyisopropyl radical, which itself undergoes a disproportionation reaction to afford acetone and propan-2-ol.

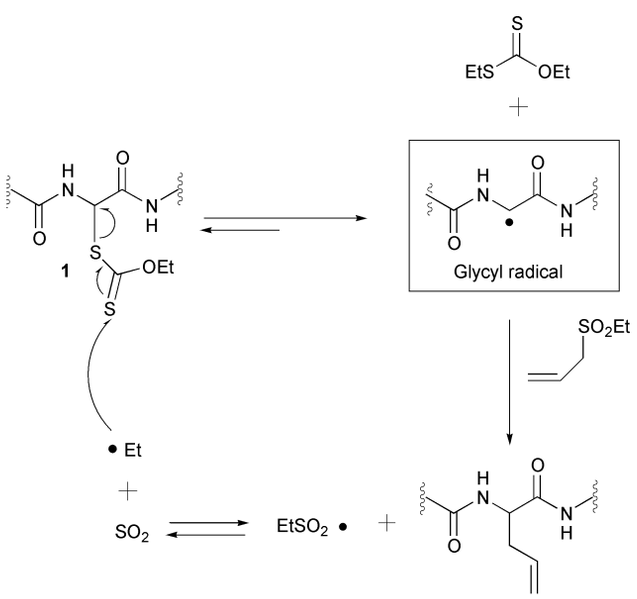
First attempts were made with the dipeptide derivative **11** with either the electron-deficient alkene acrylonitrile (entry 1), or the more electron-rich olefin allyltrimethylsilane (entry 2). As earlier observed with the simple glycine derivatives, best yields in the two-step alkylation process were obtained with acrylonitrile, affording the alkylated peptide **16** in 50% yield in contrast to the 37% yield for **17** with the allylsilane.

The other peptides were also submitted to the same conditions using acrylonitrile as the radical trap. Whereas, with the dipeptide **12**, similar yields in the alkylation step were obtained

as with **11** (entry 3), an approximately two-fold decrease in the yields were observed with the peptide derivatives **13** and **14** (entries 4 and 5), though with the tripeptide **15** the yield dropped to 14% (entry 6). These reactions were nevertheless quite clean with only one other compound being isolated, which was characterised as the corresponding isopropyl ether at the glycine α-carbon. In these reactions, the consumption of the starting xanthate proved to be quite sluggish, and hence this unchanged material underwent simple solvolysis in the subsequent reduction step in propan-2-ol.

Although we do not fully understand the divergence in the yields of the alkylation step, we do note that the low yield obtained with the tripeptide **15** appears to be the result of its low reactivity. This is also confirmed in the previous bromination step with tripeptide **10**, as well as with other larger peptides from our previous work on reductive samariation of pyridyl sulfide-containing peptides,[1] where in general longer reaction times were required and lower yields of the corresponding bromides were obtained compared with the dipeptides. The low diastereoselectivity observed for all the alkylated peptides suggest that sterical effects are not responsible for the reduced yields seen with the tripeptide **15**.

In 1998, Zard and co-workers reported a new non metal-based *C*-allylation procedure, being an attractive alternative to the conventional radical allylation protocols employing allyltributyltin.[14] The essentials for this approach applied to the preparation of *C*-allylated peptides from their corresponding xanthates are formulated in Scheme 2. As in the above alkene-addition protocol, an initiation step is required, which may be promoted by DLP. Addition of the glycyl radical to allyl ethyl sulfone and subsequent elimination generates the allylated peptide and the ethanesulfonyl radical. The latter fragments to give SO_2 and an ethyl radical which propagates the chain.

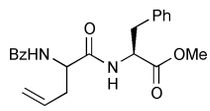
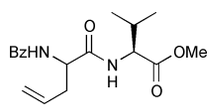
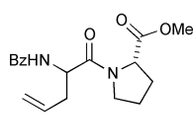
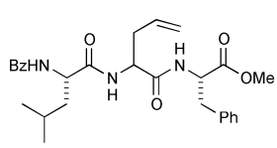


Scheme 2

This simple procedure was therefore put to the test and the results are summarised in Table 3. All reactions were performed in refluxing 1,2-dichloroethane by the slow addition of 0.3–0.4 mole equivalents of DLP to the xanthate and the allyl sulfone (2 equiv.). A similar trend in the yields of allylated products was observed as for the radical additions shown in Table 2. The simple dipeptides **11**–**13** were consumed reasonably well (entries 1–3) with yields of 30–57%, whereas for the tripeptide **15** a yield of only 17% of the allylated derivative **25** could be obtained (entry 4).

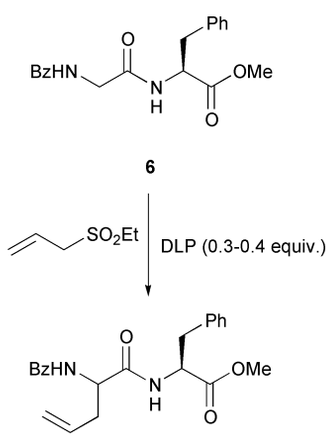
The question then arose as to whether it is necessary for the glycine moiety to possess a xanthate functionality in order for

Table 3 *C*-Allylation of peptides **11**–**13** and **15**[a]

Entry	Xanthate[a]	Allylated peptide yield[b]
1	**11**	 **22** 57%
2	**12**	 **23** 33%
3	**13**	 **24** 30%
4	**15**	 **25** 17%

[a] For reaction conditions see the Experimental section. [b] Isolated yields after chromatography on silica gel.

the *C*-allylation of peptides with allyl ethyl sulfone to be effective. The low C–H bond-dissociation energy (BDE) measured and calculated for the glycine residue (≈ 81 kcal mol^{-1}) [12]† compared with ethane (≈ 100 kcal mol^{-1}), suggested that for the allylation reaction the ethyl radical generated could propagate the chain by hydrogen abstraction of the weak α-C–H bond of glycine (Scheme 3).

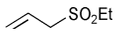
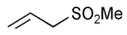
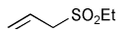
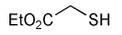
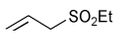
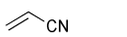
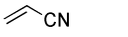


Scheme 3

The results of this study with the dipeptide **6** are shown in Table 4. The reactions were basically performed exactly as those for the xanthates from Table 3 with the exception of the starting peptide. With allyl ethyl sulfone (entry 1), the reaction proved to be quite clean, affording the allylated dipeptide **22** though in a low yield (7%) and the starting compound (92% recovery). Further addition of DLP, even over one mole equivalent with respect to **6**, did not improve this yield. Why these reactions do not go further is not certain, especially as the excess of allyl sulfone is still present after termination. Replacement with allyl methyl sulfone did not ameliorate the yield of the allylated product even though a more reactive methyl radical was

† 1 cal = 4.184 J.

Table 4 Direct *C*-allylation and alkylation of peptide **6**

Entry	Allyl sulfone	Solvent	Thiol (mol equiv.)	Allylated peptide (yield)[a]
1		$C_2H_4Cl_2$		**22** (7%)
2		$C_2H_4Cl_2$		**22** (6%)
3		$C_2H_4Cl_2$		**22** (trace)
4		Benzene	Ph_3SiSH (0.10)	**22** (trace)
5		$C_2H_4Cl_2$	Ph_3SiSH (0.10)	**16** (trace)
6		Benzene	Ph_3SiSH (0.10)	**16** (trace)

[a] Isolated yields after chromatography on silica gel.

expected to be generated under the reaction conditions (entry 2). In the hope that polarity-reversal catalysis according to Roberts would improve the reaction yields, the addition of two electrophilic thiols was also examined.[17] Unfortunately, experiments with either of the two thiols, ethyl thioacetate or triphenylsilanethiol, did not lead to any improvement, as observed by ^{1}H NMR analysis of the crude reaction mixtures (entries 3–6).

Conclusions

In this work, we have disclosed our preliminary studies on the use of peptide xanthates as an alternative method for the introduction of side chains directly onto a peptide chain by either addition of the glycyl xanthate unit onto an alkene or an allylation procedure employing allyl alkyl sulfones. Particularly advantageous with such procedures is the use of non-metal-based radical reactions, hence avoiding the toxic but more common tin compounds. The yields for the side-chain introduction are variable and work best with small peptides, although the reasons for the reduced yields in the case of the tripeptide have not been elucidated. Attempts to adapt the allylation protocol to the direct side-chain introduction on a non-functionalised glycine unit met with limited success, but clearly merits further examination considering the implications and simplicity of such a procedure.

Experimental

IR spectra were measured on a Perkin Elmer Paragon 1000 FT-IR spectrometer; ν_{max}-values are given in cm^{-1}. NMR spectra (^{1}H at 200 MHz and ^{13}C at 50 MHz) were recorded on a Varian Gemini 2000 spectrometer. Chemical shifts (δ in ppm) are given relative to those for Me_4Si; *J*-values are given in Hz. ES mass spectra were recorded with a Micromass LC-TOF instrument. TLC was performed on Kieselgel 60 F_{254} (Merck). Dichloromethane and 1,2-dichloroethane were freshly distilled from P_2O_5, whereas benzene was distilled from calcium hydride. Photic irradiation was carried out with a 150 W household lamp bulb.

General procedure for preparation of xanthate derivatives

A solution of NBS (587 mg, 3.3 mmol) and a di- or tripeptide **6**–**10** (3.0 mmol) in CH_2Cl_2 (20 cm^3) was irradiated with a 150 W lamp for 3 h under an argon atmosphere. The heat from the lamp was sufficient to maintain reflux. The solution was then cooled to 0 °C, after which potassium *O*-ethyl dithiocarbonate (577 mg, 3.6 mmol) was added. After stirring of the mixture for 14 h at 20 °C, water (20 cm^3) and CH_2Cl_2 (20 cm^3) were added to the reaction mixture, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic phases were dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The pure xanthate derivatives **11**–**15** were obtained after purification by flash chromatography using pentane–EtOAc mixtures as eluents. Diastereomeric ratios were measured by integration of the methyl ester signals at the *C*-terminal position of the peptides.

Bz-Gly(SCSOEt)-Phe-OMe 11. Yellow solid (63% yield) as a 1 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 1 to 7 : 3); ν_{max} (KBr) 3278, 1737, 1662, 1636, 1048; δ_H 1.38 (3 H, t, *J* 7.0, CH_2CH_3), 1.42 (3 H, t, *J* 7.0, CH_2CH_3), 3.10 (1 H, dd, *J* 14.0 and 6.4, PhC*H*), 3.11 (1 H, dd, *J* 14.0, 6.6, PhC*H*), 3.20 (1 H, dd, *J* 14.0 and 5.8, PhC*H*), 3.21 (1 H, dd, *J* 14.0, 5.2, PhC*H*), 3.74 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.61 (2 H, q, *J* 7.0, OCH_2), 4.64 (2 H, q, *J* 7.0, OCH_2), 4.81–4.97 [2 H, m, 2 × C_αH(Phe)], 6.40 (1 H, d, *J* 7.6, SCH), 6.44 (1 H, d, *J* 8.0, SCH), 7.02–7.32 (12 H, m, Ph, NH), 7.40–7.60 (8 H, m, Aryl, NH), 7.77–7.83 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{22}H_{24}N_2NaO_5S_2$ (*M* + Na): 483.1024. Found: *m*/*z*, 483.1028.

Bz-Gly(SCSOEt)-Val-OMe 12. Yellow solid (75% yield) as a 1.1 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 1); ν_{max} (KBr) 3366, 1747, 1651, 1636, 1050; δ_H 0.89 (3 H, d, *J* 6.8, Me), 0.93 (3 H, d, *J* 6.8, Me), 0.95 (3 H, *J* 6.8, Me), 0.98 (3 H, d, *J* 6.8, Me), 1.46 (3 H, d, *J* 7.0, Me), 1.47 (3 H, d, *J* 7.0, Me), 2.13–2.35 (2 H, m, 2 × C*H*Me$_2$), 3.74 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.55 [1 H, t, *J* 9.0, C_αH(Val)], 4.57 [1 H, t, *J* 9.0, C_αH(Val)], 4.72 (4 H, q, *J* 6.8, 2 × OCH_2), 6.52 (1 H, d, *J* 7.6, SCH), 6.53 (1 H, d, *J* 7.6, SCH), 7.31 (1 H, d, *J* 9.0, NH), 7.36 (1 H, d, *J* 9.0, NH), 7.40–7.56 (6 H, m, Aryl), 7.61 (2 H, d, *J* 7.6, 2 NH), 7.78–7.87 (4 H, m, Aryl); HR-MS (ESI) Calc. for $C_{18}H_{24}N_2NaO_5S_2$ (*M* + Na): 435.1024. Found: *m*/*z*, 433.1022.

Bz-Gly(SCSOEt)-Pro-OMe 13. Yellow solid (57% yield) as a 1 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 2 to 1 : 1); ν_{max} (KBr) 3312, 1748, 1640, 1043; δ_H 1.46 (3 H, t, *J* 7.2, Me), 1.48 (3 H, t, *J* 7.2, Me), 1.95–2.34 (8 H, m, 2 × $NCH_2CH_2CH_2$), 3.62–3.92 (4 H, m, 2 × NCH_2), 3.74 (3 H, s, OMe), 3.75 (3 H, s, OMe), 4.50–4.58 [2 H, m, 2 × C_αH(Pro)], 4.70 (1 H, q, *J* 7.2, OCH), 4.71 (1 H, q, *J* 7.2, OCH), 4.72 (1 H, q, *J* 7.2, OCH), 4.73 (1 H, q, *J* 7.2, OCH), 6.62 (1 H, d, *J* 8.4, SCH), 6.67 (1 H, d, *J* 8.2, SCH), 7.39–7.57 (6 H, m, Aryl), 7.64 (1 H, d, *J* 8.4, NH), 7.69 (1 H, d, *J* 8.2, NH), 7.79–7.85 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{18}H_{22}N_2NaO_5S_2$ (*M* + Na): 433.0868. Found: *m*/*z*, 433.0852.

Bz-Leu-Gly(SCSOEt)-OMe 14. Yellow solid (40% yield) as a 1.8 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 1); ν_{max} (KBr) 3270, 1752, 1637, 1047; δ_H 0.96–1.01 (12 H, m, 4 × Me), 1.41 (3 H, t, *J* 6.8, Me), 1.42 (3 H, t, *J* 7.0, Me), 1.64–1.87 (6 H, m, 2 × Me), 3.75 (3 H, s, OMe), 3.82 (3 H, s, OMe), 4.46–4.82 [6 H, m, 2 × C_αH(Leu), 2 × OCH_2], 5.99 (1 H, d, *J* 8.8, SCH), 6.03 (1 H, d, *J* 8.8, SCH), 6.56 (1 H, d, *J* 8.8, NH), 6.61 (1 H, d, *J* 8.8, NH), 7.38–7.60 (6 H, m, Aryl), 7.72–7.86 (6 H, m, Aryl, 2 × NH); HR-MS (ES) Calc. for $C_{19}H_{26}N_2NaO_5S_2$ (*M* + Na): 449.1181. Found: *m*/*z*, 449.1198.

Bz-Leu-Gly(SCSOEt)-Phe-OMe 15. Yellow solid (51%, based on 33% recovered starting material) as a 1 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (8 : 3); ν_{max} (KBr) 3275, 1748, 1636, 1046; δ_H 0.91–0.97 (12 H, m, 4 × Me), 1.32 (3 H, t, *J* 7.0, Me), 1.35 (3 H, t, *J* 7.0, Me), 1.65–1.74 (4 H, m, 2 × CH_2), 2.14–2.36 (2 H, m, 2 × C*H*Me$_2$), 3.04 (2 H, dd, *J* 14.3, 6.2, 2 × PhC*H*), 3.15 (2 H, dd, *J* 14.3, 5.1, 2 × PhC*H*), 3.70 (3 H, s, OMe), 3.72 (3 H, s, OMe), 4.54 (4 H, q, *J* 7.0, 2 × OCH_2), 4.77–4.93 [4 H, m, 2 × C_αH(Leu), 2 C_αH(Phe)], 6.19 (1 H, d, *J* 8.1, SCH), 6.24 (1 H, d, *J* 8.4, SCH), 7.04–7.51 (20 H, m, Aryl, 2 × NH), 7.66–

7.85 (4 H, m, Aryl), 7.92 (1 H, d, *J* 6.6, NH), 7.96 (1 H, d, *J* 7.0, NH); HR-MS (ES) Calc. for $C_{28}H_{35}N_3NaO_6S_2$ (*M* + Na): 596.1865. Found: *m*/*z*, 596.1858.

General procedure for peptide alkylation

DLP was added to a refluxing solution of a xanthate derivative **11**–**15** (0.2 mmol) and the alkene (acrylonitrile or allyltrimethylsilane) (0.4 mmol) in 1,2-dichloroethane (2 cm^3). The addition was carried out either by employing a syringe pump with a solution of DLP (0.08 M) in 1,2-dichloroethane and an addition rate of 0.02 mol equiv. per hour, or simply by adding 0.02 mole equiv. per hour of DLP as a solid. The addition of DLP was maintained until no further evolution of the reaction was observed by TLC analysis. The reaction mixture was then cooled to room temperature and 1,2-dichloroethane was removed by evaporation under vacuum. The residue was re-dissolved in propan-2-ol (2 cm^3), heated to reflux, and 1.3 mol equiv. of dilauroyl peroxide was added as 0.1 mol equiv. portions per 5 h. When the xanthate intermediate could not be detected by TLC analysis, the reaction mixture was cooled to room temperature and evaporated to dryness. Purification by flash chromatography using pentane–EtOAc mixtures as eluents afforded the alkylated peptide derivatives **16**–**21**.

Bz-Gly[$(CH_2)_2$CN]-Phe-OMe 16. Colourless solid (50% yield) as a 1.5 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (7 : 3 to 1 : 1); ν_{max} (KBr) 3300, 2218, 1751, 1654; δ_H 1.79–2.36 (4 H, m, 2 × C*H*$_2$CH$_2$CN), 2.39–2.61 (4 H, m, 2 × CH$_2$CN), 2.95 (1 H, dd, *J* 11.8, 8.6, PhC*H*), 3.02 (1 H, dd, *J* 11.8, 7.6, PhC*H*), 3.16 (1 H, dd, *J* 14.0, 5.6, PhC*H*), 3.25 (1 H, dd, *J* 14.0, 5.2, PhC*H*), 3.70 (3 H, s, OMe), 3.74 (3 H, s, OMe), 4.78–4.98 (4 H, m, 4 × C$_\alpha$H), 7.04–7.32 (14 H, m, Aryl, 4 × NH), 7.32–7.58 (6 H, m, Aryl), 7.75–7.83 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{22}H_{23}N_3NaO_4$ (*M* + Na): 416.1586. Found: *m*/*z*, 416.1598.

Bz-Gly[$(CH_2)_3$SiMe$_3$]-Phe-OMe 17. Colourless solid (37% yield) as a 1.2 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (7 : 3 to 1 : 1); ν_{max} (KBr) 3280, 1750, 1636; δ_H −0.06 (9 H, s, SiMe$_3$), −0.05 (9 H, s, SiMe$_3$), 0.42–0.54 (4 H, m, 2 × SiCH$_2$), 1.20–2.10 [8 H, m, SiCH$_2$(C*H*$_2$)$_2$], 3.10 (1 H, dd, *J* 14.0, 6.0, PhCH), 3.13 (1 H, dd, *J* 14.0, 6.0, PhCH), 3.21 (1 H, dd, *J* 14.0, 6.0, PhCH), 3.23 (1 H, dd, *J* 14.0, 6.0, PhCH), 3.68 (3 H, s, OMe), 3.72 (3 H, s, OMe), 4.60–4.73 [2 H, m, 2 × C*H*(CH$_2$)$_3$Si], 4.87 [2 H, dt, *J* 8.0, 6.0, 2 × C$_\alpha$H(Phe)], 6.69 (1 H, d, *J* 8.0, NH), 6.76 (1 H, d, *J* 8.2, NH), 6.83 (1 H, d, *J* 8.0, NH), 6.87 (1 H, d, *J* 8.0, NH), 7.04–7.30 (10 H, m, Aryl), 7.38–7.57 (6 H, m, Aryl), 7.71–7.85 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{25}H_{34}N_2NaO_4$ (*M* + Na): 477.2185. Found: *m*/*z*, 477.2185.

Bz-Gly[$(CH_2)_2$CN]-Val-OMe 18. Colourless solid (43% yield) as a 1.4 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 2 to 2 : 3); ν_{max} (KBr) 3303, 2249, 1744, 1640; δ_H 0.89 (3 H, d, *J* 5.1, Me), 0.92 (3 H, d, *J* 4.9, Me), 0.93 (3 H, d, *J* 7.3, Me), 0.97 (3 H, d, *J* 7.0, Me), 2.05–2.43 (6 H, m, 2 × C*H*Me$_2$, 2 × C*H*$_2$CH$_2$CN), 2.43–2.57 (4 H, m, 2 × CH$_2$CN), 3.68 (3 H, s, OMe), 3.76 (3 H, s, OMe), 4.48 [1 H, dd, *J* 8.7, 4.7, C$_\alpha$H(Val)], 4.55 [1 H, dd, *J* 9.1, 4.7, C$_\alpha$H(Val)], 4.96–5.10 [2 H, m, 2 × C*H*(CH$_2$)$_2$CN], 7.28–7.56 (10 H, m, Aryl, 4 × NH), 7.79–7.86 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{18}H_{23}N_3NaO_4$ (*M* + Na): 368.1586. Found: *m*/*z*, 368.1591.

Bz-Gly[$(CH_2)_2$CN]-Pro-OMe 19. Colourless solid (20% yield) as a 1 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (7 : 3); ν_{max} (KBr) 3422, 2233, 1752, 1654; δ_H 1.90–2.42 (12 H, m, 2 × C*H*$_2$CH$_2$CN, 2 × NCH$_2$C*H*$_2$C*H*$_2$), 2.42–2.60 (4 H, m, 2 × CH$_2$CN), 3.60–3.85 (4 H, m, 2 × NCH$_2$), 3.74 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.48–4.60 [2 H, m, 2 × C$_\alpha$H(Pro)], 5.10 [1 H, dt, *J* 7.5, 6.4, C*H*(CH$_2$)$_2$CN], 5.16 [1 H, dt, *J* 7.3, 6.4, C*H*(CH$_2$)$_2$CN], 7.21 (2 H, d, *J* 6.4 Hz, 2 × NH), 7.39–7.58 (6 H, m, Aryl), 7.78–7.88 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{18}H_{21}N_3NaO_4$ (*M* + Na): 366.1430. Found: *m*/*z*, 366.1427.

Bz-Leu-Gly[$(CH_2)_2$CN]-OMe 20. Colourless solid (23% yield) as a 1.1 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (7 : 3); ν_{max} (KBr) 3289, 2235, 1744, 1640; δ_H 0.96 (6 H, d, *J* 5.5, 2 × Me), 0.99 (6 H, d, *J* 5.9, 2 × Me), 1.62–1.91 (10 H, m, 2 × C*H*$_2$C*H*Me$_2$, 2 × C*H*$_2$CH$_2$CN), 2.21–2.52 (4 H, m, 2 × CH$_2$CN), 3.72 (3 H, s, OMe), 3.79 (3 H, s, OMe), 4.57–4.81 (4 H, m, 4 × C$_\alpha$H), 6.71 (1 H, d, *J* 7.3, NH), 6.75 (1 H, d, *J* 8.1, NH), 6.84 (1 H, d, *J* 7.3, NH), 7.12 (1 H, d, *J* 8.1, NH), 7.29–7.62 (6 H, m, Aryl), 7.73–7.81 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{19}H_{25}N_3NaO_4$ (*M* + Na): 382.1742. Found: *m*/*z*, 382.1736.

Bz-Leu-Gly[$(CH_2)_2$CN]-Phe-OMe 21. Colourless solid (14% yield) as a 2.5 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (1 : 1); ν_{max} (KBr) 3313, 2231, 1744, 1648; δ_H 0.91–1.01 (12 H, m, 4 × Me), 1.60–2.20 (10 H, m, 2 × C*H*$_2$C*H*Me$_2$, 2 × C*H*$_2$CH$_2$CN), 2.30 (2 H, t, *J* 6.6, CH$_2$CN), 2.33 (2 H, t, *J* 6.6, CH$_2$CN), 2.92–3.24 (4 H, m, 2 × PhC*H*$_2$), 3.63 (3 H, s, OMe), 3.73 (3 H, s, OMe), 4.48–4.70 (4 H, m, 4 × C$_\alpha$H), 4.70–4.89 (2 H, m, 2 × C$_\alpha$H), 6.71 (1 H, d, *J* 8.4, NH), 6.79 (1 H, d, *J* 8.4, NH), 6.98–7.30 (14 H, m, Aryl, 4 × NH), 7.37–7.58 (6 H, m, Aryl), 7.71–7.89 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{28}H_{34}N_4NaO_5$ (*M* + Na): 529.2427. Found: *m*/*z*, 529.2424.

Typical procedure for the peptide allylation of xanthate derivatives 11–15

DLP was added to a refluxing solution of a xanthate derivative **11**–**15** (0.2 mmol) and allyl alkyl sulfone (0.4 mmol) in 1,2-dichloroethane (2 cm^3). The addition was carried out either with a syringe pump using a solution of DLP (0.08 M) in 1,2-dichloroethane with an addition rate of 0.02 mol equiv. per hour or simply by adding 0.02 mol equiv. per hour as a solid. The addition of DLP was maintained until no further evolution of the reaction was observed by TLC analysis. The reaction mixture was then cooled to room temperature and 1,2-dichloroethane was removed by evaporation in vacuum. The residue was purified by flash chromatography using pentane–ethyl acetate mixtures as eluents to afford the allylated peptide derivatives **22**–**25**.

Bz-Gly(All)-Phe-OMe 22. Colourless solid (57% yield) as a 1.6 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (7 : 3); ν_{max} (KBr) 3275, 1748, 1636; δ_H 2.56 (2 H, t, *J* 7.0, CH$_2$CHC*H*$_2$), 2.59 (2 H, t, *J* 7.0, allylic CH$_2$), 3.05 (1 H, dd, *J* 13.8, 6.6, PhC*H*), 3.07 (1 H, dd, *J* 13.8, 6.8, PhC*H*), 3.17 (2 H, dd, *J* 13.8, 5.8, 2 × PhC*H*), 3.70 (3 H, s, OMe), 3.74 (3 H, s, OMe), 4.69 (1 H, dt, *J* 7.5, 7.0, CH$_2$CHCH$_2$C*H*), 4.71 (1 H, dt, *J* 7.5, 7.0, CH$_2$CHCH$_2$C*H*), 4.81–4.93 [2 H, m, 2 × C$_\alpha$H(Phe)], 5.04–5.21 (4 H, m, 2 × C=CH$_2$), 5.69 (1 H, ddt, *J* 17.6, 9.1, 7.0, *H*C=CH$_2$), 5.78 (1 H, ddt, *J* 17.0, 9.9, 7.0, *H*C=CH$_2$), 6.67 (2 H, d, *J* 8.0, 2 × NH), 6.75 (2 H, d, *J* 7.5, 2 × NH), 7.04–7.28 (10 H, m, Aryl), 7.37–7.58 (6 H, m, Aryl), 7.72-7.80 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{22}H_{24}N_2NaO_4$ (*M* + Na): 403.1634. Found: *m*/*z*, 403.1638.

Bz-Gly(All)-Val-OMe 23. Colourless solid (33% yield) as a 1.4 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 1); ν_{max} (KBr) 3298, 1747, 1636; δ_H 0.90 (3 H, d, *J* 6.8, Me), 0.91 (3 H, d, *J* 6.8, Me), 0.92 (3 H, d, *J* 6.8, Me), 0.97 (3 H, d, *J* 6.8, Me), 2.10–2.28 (2 H, m, 2 × C*H*Me$_2$), 2.65 (4 H, t, *J* 6.8, 2 × CH$_2$CHC*H*$_2$), 3.69 (3 H, s, OMe), 3.75 (3 H, s, OMe), 4.52 [1 H, dd, *J* 9.0, 5.0, C$_\alpha$H(Val)],

4.55 [1 H, dd, *J* 9.0, 4.0, $C_{\alpha}H$(Val)], 4.80 (1 H, dt, *J* 7.8, 6.5, CH_2CHCH_2CH), 4.84 (1 H, dt, *J* 7.8, 6.5, CH_2CHCH_2CH), 5.12–5.26 (4 H, m, $C{=}CH_2$), 5.84 (1 H, ddt, *J* 17.4, 10.1, 7.1, $HC{=}CH_2$), 5.86 (1 H, ddt, *J* 17.4, 10.1, 7.1, $HC{=}CH_2$), 6.89 (1 H, d, *J* 9.0, NH), 6.97 (1 H, d, *J* 7.8, NH), 7.38–7.57 (6 H, m, Aryl), 7.76–7.83 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{18}H_{24}N_2NaO_4$ (*M* + Na): 355.1634. Found: *m*/*z*, 355.1635.

Bz-Gly(All)-Pro-OMe 24. Colourless solid (30% yield) as a 2 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 2 to 2 : 3); ν_{max} (KBr) 3319, 1748, 1637; δ_H 1.92–2.32 (12 H, m, $2 \times NCH_2CH_2CH_2$, $2 \times CH_2CHCH_2$), 3.60–3.92 (4 H, m, $2 \times NCH_2$), 3.69 (3 H, s, OMe), 3.75 (3 H, s, OMe), 4.44–4.59 [2 H, m, $2 \times C_{\alpha}H$(Pro)], 4.99–5.23 (6 H, m, $2 \times CH_2CHCH_2CH$, $2 \times C{=}CH_2$), 5.68–6.01 (2 H, m, $2 \times HC{=}CH_2$), 7.08 (2 H, d, *J* 8.0, $2 \times$ NH), 7.36–7.55 (6 H, m, Aryl), 7.74–7.85 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{18}H_{22}N_2NaO_4$ (*M* + Na): 353.1477. Found: *m*/*z*, 353.1471.

Bz-Leu-Gly(All)-Phe-OMe 25. Colourless solid (17% yield) as a 2 : 1 diastereoisomeric mixture as determined by ^{1}H NMR analysis; eluted with pentane–EtOAc (3 : 1 to 2 : 1); ν_{max} (KBr) 3292, 1752, 1636; δ_H 0.93–1.00 [12 H, m, $2 \times CH(CH_3)_2$], 1.57–1.84 [6 H, m, $2 \times CH_2CH(CH_3)_2$], 2.40–2.56 (4 H, m, $2 \times CH_2CHCH_2$), 2.95–3.30 (4 H, m, $2 \times PhCH_2$), 3.62 (3 H, s, OMe), 3.72 (3 H, s, OMe), 4.38–4.77 [4 H, m, $2 \times CH_2$-$CHCH_2CH$, $2 \times C_{\alpha}H$(Leu)], 4.77–4.92 [2 H, m, $2 \times C_{\alpha}H$(Phe)], 4.93–5.14 (4 H, m, $2 \times C{=}CH_2$), 5.45–5.79 (2 H, m, $2 \times HC{=}CH_2$), 6.56–6.77 (6 H, m, $6 \times$ NH), 6.99–7.31 (10 H, m, Aryl), 7.39–7.55 (6 H, m, Aryl), 7.71–7.82 (4 H, m, Aryl); HR-MS (ES) Calc. for $C_{28}H_{35}N_3NaO_5$ (*M* + Na): 516.2474. Found: *m*/*z*, 516.2473.

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