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Synthesis and photochemical reactivity of phthalimidoadamantane–tyrosine conjugates

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Abstract Dipeptide **3**, tetrapeptide **4** and pentapeptide **5**, containing adamantylphthalimide and tyrosine, were synthesized and their photochemical reactivity investigated. Upon excitation to the triplet excited state, **3** does not give any photoproduct, although the photoinduced electron transfer (PET) should take place based on the thermodynamic properties. Tetrapeptide **4** and pentapeptide **5** are photochemically reactive, undergoing decomposition upon excitation. The lack of anticipated photodecarboxylation reactivity is explained by PET between the tyrosine and the phthalimide. However, deprotonation of the phenoxyl radical-cation giving phenoxyl radicals or back electron transfer giving starting material are probably faster than intrastrand single electron transfer which would lead to carboxyl radical and decarboxylation. The results indicate the importance of fine-tuning the molecular structure to attain the desired photoreactivity by the right choice of the reactants redox potential, as well as their acid/base properties.

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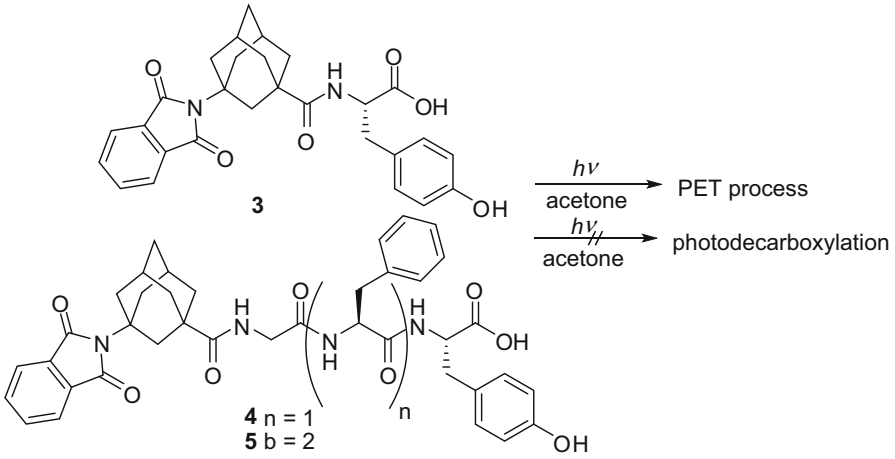
Graphical Abstract



Keywords Phthalimide · Tyrosine · Peptides · Photodecarboxylation · Photoinduced electron transfer

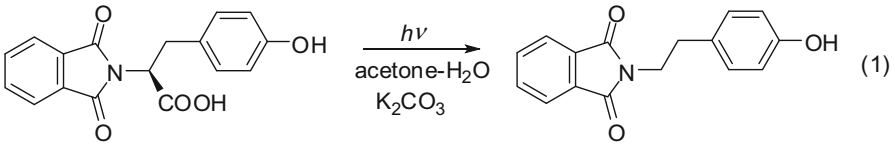
Introduction

Phthalimide is a versatile chromophore utilized in different photochemical reactions [1], and is particularly useful in organic synthesis [2, 3]. Photoinduced reactions of phthalimides include H-abstractions [4], cycloadditions [5] or photoinduced electron transfer (PET) [6, 7]. PET reactions of phthalimides can initiate decarboxylation [8], or elimination of silyl ethers [9, 10]. Thus, PET-promoted decarboxylation has been applied in the synthesis of macrocylic ethers [11–15] and cyclic peptides [16, 17]. Furthermore, intermolecular photodecarboxylations have also been developed [18] and used in photoinduced acetate [19, 20], benzyl [21, 22], and α-amino acid addition to phthalimides [23], or for the formation of cyclic aryl ethers [24].

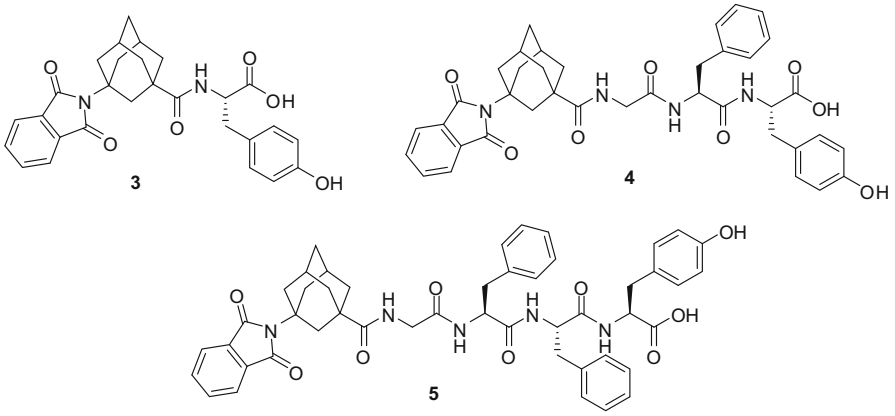
We have turned our attention to the photochemistry of phthalimides as a useful synthetic method for the preparation of complex polycyclic molecules [25] with antiproliferative [26] or antiviral activity [27]. We discovered that adamantylphthalimides undergo photoinduced H-abstractions [28], which can also take place in the solid state [29] or in supramolecular complexes [30]. Moreover, the photochemical reactivity of adamantyl amino acids activated by phthalimides has been investigated [31], where radicals formed in the decarboxylation can be trapped with electron-deficient alkenes giving adducts [32]. Furthermore, phthalimido-activated amino acids have been incorporated into dipeptides which underwent photodecarboxylation affording cyclic compounds with high enantioselectivity [33]. In contrast, *N*-arylphthalimide derivatives gave only simple decarboxylation products [34].

Griesbeck et al. [35] have recently demonstrated that *N*-phthalimido tyrosine **1** underwent photodecarboxylation giving a tyramine derivative **2**. Tyrosine is a good

electron donor in PET reactions with the redox potential of $E^{\circ} = 0.85$ V $_{\text{vs FcFc+}}$ [36]. Thus, PET with phthalimide in the triplet excited state ($E_T = 293$–300 kJmol^{-1}) [37] and the reduction potential of $E^{\circ} = -1.85$ V $_{\text{vs FcFc+}}$ should be exergonic.



Here, we describe the synthesis of di-, tetra-, and pentapeptides **3**–**5** containing *N*-phthalimido adamantane amino acid at the *N*-terminus and tyrosine at the *C*-peptide terminus. The molecular structures were designed to probe for selectivity in the PET reactions between two electron donors, carboxylate or tyrosine, and the dependence of the PET efficiency on the distance between the electron donor and the acceptor (phthalimide).



Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance Spectrometer at 300 or 600 MHz. All NMR spectra were measured in $CDCl_3$, DMSO-d_6, CD_3CN or CD_3OD using tetramethylsilane as a reference. High-resolution mass spectra (HRMS) were measured on an Applied Biosystems 4800 Plus ESI TOF/TOF instrument. IR spectra were recorded on a FT-IR ABB Bonem MB 102 spectrophotometer. Melting points were obtained using an Original Köfler Mikroheitztisch apparatus (Reichert, Wien) and are uncorrected. Silica gel or alumina was used for the chromatographic purifications. Solvents were purified by

distillation. The chemicals for the synthesis were obtained from the usual commercial sources and used as received. Photochemical reactions were carried in a Luzchem reactor in quartz cuvettes or quartz Erlenmeyer flasks. The CH_3CN used in the irradiation experiments was of HPLC purity, whereas the p.a. acetone was additionally purified by refluxing over $KMnO_4$ and distillation. The synthesis of all known precursors is given in the supporting information.

Phth-Ad-Tyr(OH)-OBn (3OBn)

A flask was charged with 3-(*N*-phthalimidoadamantane)-1-carboxylic acid **6** (175 mg, 0.54 mmol), HBTU (224 mg, 0.59 mmol), HOBT (80 mg, 0.59 mmol), triethylamine (TEA; 157 μL, 1.13 mmol) and CH_2Cl_2 (dried over molecular sieves 4Å). After stirring for 10 min at rt under inert N_2-atmosphere, L-tyrosine benzyl ester (228 mg, 0.59 mmol) was added and the reaction was stirred for 3 days. When the reaction was completed, brine (30 mL) was added to the reaction mixture. The product was extracted with ethyl acetate (3 × 20 mL), and the extracts were washed with HCl (1 M, 15 mL), H_2O (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed on a rotary evaporator, furnishing the product (270 mg, 87%) which was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (0–10%) as eluent.

(S)-2-{[3-(N-Phthalimido)a-1-yl]carboxamido}-3-(4-hydroxyphenyl)propanoic acid benzyl ester ***(3OBn)*** Colorless solid; m.p. 190–192 °C; IR (KBr) $\tilde{\nu}_{max}/cm^{-1}$: 3371, 2912, 2856, 1741, 1706, 1636, 1614, 1513, 1456, 1374, 1315, 841, 721; ^1H NMR (CD_3OD, 300 MHz) δ/ppm: 7.80–7.70 (m, 4H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.34–7.18 (m, 5H), 6.96 (d, $J = 8.4$ Hz, 2H), 6.67 (d, $J = 8.4$ Hz, 2H), 5.12 (d, $J = 12.2$ Hz, 1H), 5.10 (d, $J = 12.2$ Hz, 1H), 4.65–4.54 (m, 1H), 3.09 (dd, $J = 5.6$, 13.9 Hz, 1H), 2.95 (dd, $J = 8.8$, 13.9 Hz, 1H), 2.59-2.37 (m, 6H), 2.22 (s, 2H), 1.86–1.58 (m, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ/ppm: 179.1 (s, 1C), 173.1 (s, 1C), 170.9 (s, 2C), 157.3 (s, 1C), 137.0 (s, 2C), 135.3 (d, 2C), 133.1 (s, 1C), 131.4 (d, 2C), 129.5 (d, 2C), 129.3 (d, 1C), 128.9 (s, 1C), 123.6 (d, 2C), 116.2 (d, 2C), 68.0 (t, 1C), 61.3 (s, 1C), 55.5 (d, 1C), 43.9 (s, 1C), 42.2 (t, 1C), 43.30 (t, 1C), 43.29 (t, 1C), 38.7 (t, 2C), 37.0 (t, 1C), 36.2 (t, 1C), 31.0 (d, 2C); HRMS (ESI-qTOF) *m/z*: $[M + H]^+$Calcd. for $C_{35}H_{34}N_2O_6$ 579.2495, Found 579.2504.

Phth-Ad-Tyr(OH)-OMe (3Me)

This compound was prepared according to the procedure for the preparation of **3OBn** from **6** (477 mg, 1.47 mmol), HBTU (612 mg, 1.61 mmol), HOBT (217 mg, 1.61 mmol), TEA (430 μL, 3.09 mmol) L-tyrosine methyl ester (498 mg, 1.61 mmol). The crude product was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (0–10%) and CH_2Cl_2/MeOH (0–10%). The pure product was isolated in the form of a colorless solid (71%, 523 mg).

(S)-2-{[3-(N-Phthalimido)adamantan-1-yl]carboxamido}-3-(4-hydroxyphenyl)propanoic acid methyl ester ***(3Me)*** Colorless solid; m.p. >350 °C; IR (KBr) $\tilde{\nu}_{max}/cm^{-1}$: 3489,

1725, 1635, 1378, 1080, 876; ^{1}H NMR (CD_3CN, 600 MHz) δ/ppm: 7.73 (s, 4H), 7.03 (d, $J = 8.5$ Hz, 2H), 6.72 (d, $J = 8.5$ Hz, 2H), 6.37 (d, $J = 7.5$ Hz, 1H), 4.55-4.45 (m, 1H), 3.65 (s, 3H), 3.08 (dd, $J = 5.1$, 14.0 Hz, 1H), 2.92 (dd, $J = 8.3$, 14.0 Hz, 1H), 2.52–2.38 (m, 6H), 2.23 (br.s, 2H), 1.82–1.59 (m, 6H); ^{13}C NMR (CD_3CN, 75 MHz) δ/ppm: 177.0 (s, 1C), 173.2 (s, 1C), 170.5 (s, 2C), 156.7 (s, 1C), 134.9 (d, 2C), 132.9 (s, 2C), 131.4 (d, 2C), 128.9 (s, 1C), 123.2 (d, 2C), 116.1 (d, 2C), 60.9 (s, 1C), 54.5 (d/q, 1C), 52.7 (d/q, 1C), 43.5 (s, 1C), 42.0 (t, 1C), 40.0 (t, 2C), 38.6 (t, 2C), 37.0 (t, 1C), 35.8 (t, 1C), 30.5 (d, 2C); HRMS (ESI-qTOF) *m/z*: $[M + H]^+$ Calcd. for $C_{29}H_{30}N_2O_6$ 503.2182; Found 503.2190.

Phth-Ad-Tyr(OH)-OH (3)

A flask was charged with benzyl ester **3OBn** (270 mg, 0.47 mmol), 10% Pd/C ($\sim$70 mg) and abs. MeOH (15 mL). The flask was closed with a septum and purged with nitrogen in order to remove air. Et_3SiH (0.75 ml, 4.7 mmol) was added to the suspension in the flask during 1 h. The reaction was monitored on TLC. When the reaction was completed, Pd/C was removed by filtration through filter paper (blue ribbon) and the solvent was removed on a rotary evaporator. The pure product (173 mg, 76%) was isolated after purification by column chromatography on silica gel using CH_2Cl_2/MeOH (0–10%) as eluent.

(S)-2-{[3-(N-Phthalimido)adamantan-1-yl]carboxamido}-3-(4-hydroxyphenyl)propanoic acid (3) Colorless solid; m.p. >350 °C; IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 3363, 1701, 1631, 1374, 1086, 886; ^{1}H NMR (CD_3CN, 300 MHz) δ/ppm: 7.74 (s, 4H), 7.03 (d, $J = 8.5$ Hz, 2H), 6.72 (d, $J = 8.5$ Hz, 2H), 6.37 (d, $J = 7.5$ Hz, 1H), 4.55-4.45 (m, 1H), 3.08 (dd, $J = 5.1$, 14.0 Hz, 1H), 2.92 (dd, $J = 8.3$, 14.0 Hz, 1H), 2.52–2.38 (m, 6H), 2.23 (br.s, 2H), 1.82–1.59 (m, 6H); ^{13}C NMR (CD_3CN, 75 MHz) δ/ppm: 177.4 (s, 1C), 173.2 (s, 1C), 170.5 (s, 2C), 156.7 (s, 1C), 135.0 (d, 2C), 132.9 (s, 2C), 131.5 (d, 2C), 129.1 (s, 1C), 123.2 (d, 2C), 116.1 (d, 2C), 60.9 (s, 1C), 54.5 (d, 1C), 43.5 (s, 1C), 42.0 (t, 1C), 39.9 (t, 2C), 38.6 (t, 2C), 36.6 (t, 1C), 35.8 (t, 1C), 30.5 (d, 2C); HRMS (ESI-qTOF) *m/z*: $[M + H]^+$ Calcd. for $C_{28}H_{28}N_2O_6$ 489.2026; Found 489.2038.

General procedure for the activation of carboxylic acid by DCC-NHS procedure [40]

A flask was filled with Boc-protected aminoacid (10 mmol), DCC (11 mmol), NHS (11 mmol) and CH_2Cl_2 (25 mL, dried over molecular sieves 4Å). The reaction mixture was stirred at −5 °C for 5 h, and left in a refrigerator overnight. The next day, the precipitate was filtered off and the solvent was removed on a rotary evaporator. The residue was dissolved in ethyl acetate and the remaining precipitate was filtered off. The solution was washed with 0.5 M $NaHCO_3$ (30 mL), H_2O (30 mL), 0.5 M HCl (30 mL), and H_2O (30 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was removed on a rotary evaporator. The crude succinimido-activated amino acid was used in the coupling step without additional purification.

Phth-Ad-Gly-OSu (8)

This compound was prepared according to the general procedure from dipeptide **7** (0.32 g, 0.8 mmol), NHS (0.11 g, 0.9 mmol) and DCC (0.19 g, 0.9 mmol). The product was isolated in the form of a colorless amorphous solid (0.37 g, 91%) which, without purification, was used in the next step.

Colorless amorphous solid; ^{1}H NMR (CD_3OD, 300 MHz) δ/ppm: 7.75 (s, 4H), 3.52–3.36 (m, 2H), 2.82 (s, 4H), 2.65–2.45 (m, 6H), 2.29 (br.s, 2H), 1.98–1.67 (m, 6H).

General procedure for the peptide coupling via succinimide-activated amino acid [40]

A round-bottom flask was charged with amino acid (2.5 mmol), $NaHCO_3$ (5 mmol, or 7.5 mmol in the case of using TFA salt of amino acid) and THF-H_2O (1:1, 20 mL). A solution of succinimide-activated amino acid (2.75 mmol) in THF (15 mL) was added dropwise to the mixture, and the reaction was stirred at rt for 1–2 days. THF was removed on a rotary evaporator, the reaction mixture was acidified with 0.5 M HCl to pH 2, and the product was extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with water and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel.

PhthAd-Gly-Phe-Tyr(OH)-OH (4)

This compound was prepared according to the general procedure from dipeptide H-**PheTyr-OH** (0.70 g, 1.6 mmol) and **8** (0.83 g, 1.7 mmol). The product was isolated by column chromatography on silica gel with MeOH/CH_2Cl_2 (5-10%) as eluent in the form of a colorless solid (0.85 g, 78%).

N-[3-(N′-phthalimido)-1-adamantanecarbonyl]glycyl-L-phenylalanyl-L-tyrosine ***(4)*** Colorless solid; m.p. 256–258 °C; IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 3563, 2937, 2875, 2375, 2354, 1729, 1708, 1687, 1646, 1563, 1542, 1500, 1458, 1354, 1083, 833, 625, 604; ^{1}H NMR (CD_3OD, 300 MHz) δ/ppm: 7.78 (s, 4H), 7.26–7.15 (m, 5H), 7.06 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 4.55–4.51 (m, 1H), 4.43–4.39 (m, 1H), 3.91 (d, J = 16.4 Hz, 1H), 3.74 (d, J = 16.4 Hz, 1H), 3.16-3.07 (m, 2H), 2.94-2.84 (m, 2H), 2.60-2.42 (m, 6H), 2.29 (s, 2H), 1.88-1.75 (m, 2H), 1.69 (d, J = 12.5 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz) δ/ppm: 180.5 (s, 1C), 172.9 (s, 1C), 172.0 (s, 1C), 170.9 (s, 1C), 157.0 (s, 2C), 138.2 (s, 1C/2C), 135.3 (d, 2C), 133.1 (s, 1C/2C), 131.5 (d, 2C), 130.2 (d, 2C), 130.0 (s, 1C), 129.6 (d, 2C), 127.8 (d, 1C), 123.6 (d, 2C), 116.1 (d, 2C), 61.4 (s, 1C), 57.4 (d, 1C), 56.4 (d, 1C), 44.1 (s, 1C), 43.8 (t, 1C), 42.1 (t, 1C), 40.3 (t, 2C), 38.8 (t, 2C), 38.2 (t, 1C), 37.9 (t, 1C), 36.2 (t, 1C), 31.0 (d, 2C), one singlet was not seen; HRMS (ESI-qTOF) m/z: $[M + H]^+$ Calcd. for $C_{39}H_{40}N_4O_8$ 693.2924; Found 693.2932.

PhthAd-Gly-Phe-Phe-Tyr(OH)-OBn (5OBn)

A flask was charged with PhthAd-Gly-OSu **8** (0.59 g, 1.54 mmol), HBTU (0.64 g, 1.70 mmol), HOBt (0.23 g, 1.70 mmol), TEA (450 μL, 3.23 mmol) and dry DMF (20 mL). The reaction mixture was stired at rt under N_2 for 10 min and then **TFA × H-Phe-Phe-Tyr-OBn** (1.13 g, 1.7 mmol) was added. The reaction was conducted for 3 days. When the reaction finished, DMF was removed on a rotary evaporator and CH_3CN (10 mL) and brine (70 mL) were added. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 5% HCl (15 mL), H_2O (15 mL), 5% $NaHCO_3$ (15 mL), H_2O (15 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed on a rotary evaporator and the residue chromatographed on a column of silica gel with 0–10% $MeOH/CH_2Cl_2$. The product (0.60 g, 42%) was isolated in the form of a colorless solid.

N-[3-(N′-phthalimido)-1-adamantanecarbonyl]glycyl-L-phenylalanyl-L-phenylalanyl-L-tyrosine benzyl ester ***(5OBn)*** Colorless solid; m.p. 115–117 °C; IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 3403, 3072, 3039, 2942, 2885, 2789, 2462, 2404, 1712, 1635, 1519, 1462, 1366, 1308, 1192, 1135, 1077, 750, 731, 519; ^{1}H NMR (CD_3OD, 300 MHz) δ/ppm: 7.33 (s, 4H), 7.36-7.08 (m, 15H), 6.94 (d, $J = 8.5$ Hz, 2H), 6.63 (d, $J = 8.5$ Hz, 2H), 5.04 (s, 2H), 4.63–4.47 (m, 3H), 3.79 (d, $J = 16.2$ Hz, 1H), 3.67 (d, $J = 16.2$ Hz, 1H), 3.15–2.73 (m, 6H), 2.62–2.39 (m, 6H), 2.25 (br.s, 2H), 1.93–1.63 (m, 6H); ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm: 9.23 (br.s, 1H), 8.75-8.67 (m, 1H), 8.41 (d, $J = 7.2$ Hz, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 8.00–7.93 (m, 1H), 7.85–7.74 (m, 4H), 7.37–7.08 (m, 15H), 6.98 (d, $J = 8.4$ Hz, 2H), 6.64 (d, $J = 8.4$ Hz, 2H), 5.06 (d, $J = 12.0$ Hz, 1H), 5.04 (d, $J = 12.0$ Hz, 1H), 4.60-4.40 (m, 3H), 3.74–3.62 (m, 2H), 3.00–2.64 (m, 6H), 2.47-2.32 (m, 6H), 2.19 (br.s, 2H), 1.75–1.56 (m, 6H); ^{13}C NMR (CD_3OD, 150 MHz) δ/ppm: 173.1 (s, 1C), 172.5 (s, 1C), 138.1 (s, 1C), 131.4 (d, 2C), 130.3 (d, 2C), 130.2 (d, 2C), 129.6 (d, 2C), 129.5 (d, 2C), 129.4 (d, 4C), 129.3 (d, 1C),129.2 (s, 1C), 128.4 (s, 1C), 127.8 (d, 1C), 127.7 (d, 1C), 123.6 (d, 2C), 116,3 (d, 2C), 67,9 (t, 1C), 61.3 (s, 1C), 55.9 (d, 3C), 44.1 (s, 1C), 42.3 (t, 2C), 40.4 (t, 2C), 38.9 (t, 2C), 38.5 (t, 1C), 38.3 (t, 1C), 37.8 (t, 1C), 36.3 (t, 1C), 31.0 (d, 2C).

PhthAd-Gly-Phe-Phe-Tyr(OH)-OH (5)

A flask (20 mL) was charged with ester **5OBn** (0.15 g, 0.2 mmol), 10% Pd/C (0.03 g) and dry methanol (5 mL). The reaction mixture was purged with nitrogen for 15 min. Et_3SiH (0.32 ml, 2.0 mmol) was added dropwise and the stirring was continued over 1 h. The progress of the reaction was monitored on TLC with 5% $MeOH/CH_2Cl_2$ as an eluent. When the reaction was completed, Pd/C was filtered off through filter paper (blue ribbon), and the solvent was removed on a rotary evaporator. The pure product was obtained in the form of a colorless solid (0.13 g, quantitatively).

N-[3-(N′-phthalimido)-1-adamantanecarbonyl]glycyl-L-phenylalanyl-L-phenylalanyl-L-tyrosine ***(5)*** Colorless solid; m.p. 124–126 °C; IR (KBr) $\tilde{\nu}_{max}$ /cm^{-1}: 3383, 2907,

1704, 1646, 1502, 1200, 720; ^{1}H NMR (DMSO-d_6, 300 MHz) δ/ppm: 12.39 (br.s, 1H), 9.16 (s, 1H), 8.16 (d, $J = 8.5$ Hz, 1H), 8.10 (d, $J = 7.5$ Hz, 1H), 7.85–7.73 (m, 4H), 7.73 (d, $J = 8.5$ H, 2H), 7.60 (t, $J = 5.5$ Hz, 1H), 7.27–7.07 (m, 10H), 7.01 (d, $J = 8.0$ Hz, 2H), 6.65 (d, $J = 8.0$ Hz, 2H), 4.59–4.41 (m, 2H), 4.39–4.29 (m, 1H), 3.68 (dd, $J = 16.0$, 5.4 Hz, 1H), 3.51 (dd, $J = 16.0$, 5.4 Hz, 1H), 3.07–2.65 (m, 6H), 2.47–2.40 (m, 4H), 2.33 (d, $J = 12.2$ Hz, 2H), 2.19 (br.s, 2H), 1.76–1.63 (m, 5H), 1.57 (d, $J = 12.2$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ/ppm 176.0 (s, 1C), 172.7 (s, 1C), 170.8 (s, 1C), 170.5 (s, 2C), 169.0 (s, 2C), 168.7 (s, 1C), 155.9 (s, 2C), 137.6 (s, 1C), 137.4 (s, 1C), 134.3 (d, 2C), 131.2 (s, 1C), 130.0 (d, 2C), 129.2 (d, 2C), 129.2 (d, 2C), 128.0 (d, 2C), 127.9 (d, 2C), 127.8 (d, 1C), 126.2 (d, 1C), 126.1 (d, 1C), 122.4 (d, 2C), 114.9 (d, 2C), 59.7 (s, 1C), 53.9 (d, 1C), 53.7 (d, 1C), 53.4 (d, 1C), 42.2 (s, 1C), 42.1 (t, 1C), 42.0 (t, 2C), 40.8 (t, 1C), 38.8 (t, 2C), 37.5 (t, 1C), 37.4 (t, 1C), 36.0 (t, 1C), 34.8 (t, 1C), 28.9 (d, 2C); HRMS (ESI-qTOF) *m/z*: $[M + H]^+$ Calcd. for $C_{48}H_{49}N_5O_9$ 840.3609; Found 840.3609.

Irradiation experiments

Solutions of peptides **3–5** (100 mg) were prepared in acetone–H_2O (3:1 or 10:3, 100 mL) poured into a quartz Erlenmeyer flask to which K_2CO_3 was added (0, 0.5 or 1 equiv.). The solution was purged with N_2 for 20 min, sealed and irradiated at 300 nm in a Luzchem reactor equipped with 8 lamps (1 lamp, 8 W). During the irradiation, the solution was continuously stirred and cooled with a fan integrated in the reactor. After the irradiation, the solvent was removed on a rotational evaporator and the crude reaction mixture analyzed by NMR. For the product, isolation preparative HPLC was performed on a Varian, using a Phenomenex Jupiter column and eluting by CH_3OH/H_2O + 0.1% TFA (0–50%) for 15 min and 100% MeOH for 10 min, followed by chromatography on preparative TLC on SiO_2 using CH_2Cl_2/MeOH 8% as eluent.

(S)-2-{[3-(N-Phthalmyl)adamantan-1-yl]carboxamido}-3-(4-hydroxyphenyl)propanoic acid (9) Dipeptide **3** (5 mg, 0.01 mmol) and K_2CO_3 (1.4 mg, 0.010 mmol) were dissolved in acetone (5 mL) and H_2O (1.5 mL) and left for 3 days at rt in the dark. The solvent was evaporated to afford the pure product **9** isolated in the form of a colorless solid, 20 mg (44%); m.p. 144–146 °C; IR (KBr) $\tilde{\nu}_{max}/cm^{-1}$: 3340, 2914, 2858, 1719, 1644, 1516, 1449, 1364, 1308, 1270, 1228, 1202, 1134, 835, 722, 710, 607; ^{1}H NMR (CD_3CN, 300 MHz) δ/ppm: 7.78 (dd, $J = 1.0$, 7.5 Hz, 1H), 7.56 (dt, $J = 1.4$, 7.4 Hz, 1H), 7.48 (dt, $J = 1.5$, 7.5 Hz, 1H), 7.42 (dd, $J = 1.2$, 7.4 Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 2H), 6.72 (d, $J = 8.5$ Hz, 2H), 6.47–6.38 (m, 2H), 4.56–4.46 (m, 1H), 3.78 (s, 2H), 3.08 (dd, $J = 5.1$, 14.0 Hz, 1H), 2.92 (dd, $J = 8.1$, 14.0 Hz, 1H), 2.18 (br.s, 2H), 2.12-1.95 (m, 6H), 1.78–1.57 (m, 6H); ^{13}C NMR (CD_3CN, 75 MHz) δ/ppm: 177.6 (s, 1C), 173.6 (s, 1C), 169.5 (s, 1C), 168.4 (s, 1C), 156.8 (s, 1C), 140.2 (s, 1C), 132.6 (d, 1C), 131.5 (d, 2C), 130.4 (d, 1C), 130.3 (d, 1C), 129.1 (s, 2C), 128.6 (d, 1C), 116.1 (d, 2C), 54.6 (d, 1H), 53.6 (s, 1H), 52.9 (q, 1C), 43.3 (s, 1C), 43.1 (t, 1C), 41.1 (t, 2C), 38.84 (t, 1C), 38.79 (t, 1C), 36.7 (t, 1C), 36.0 (t, 1C), 30.3 (d, 2C); HRMS (ESI-qTOF) *m/z*: $[M + H]^+$ Calcd. for $C_{29}H_{32}N_2O_7$ 521.2288; Found 521.2289.

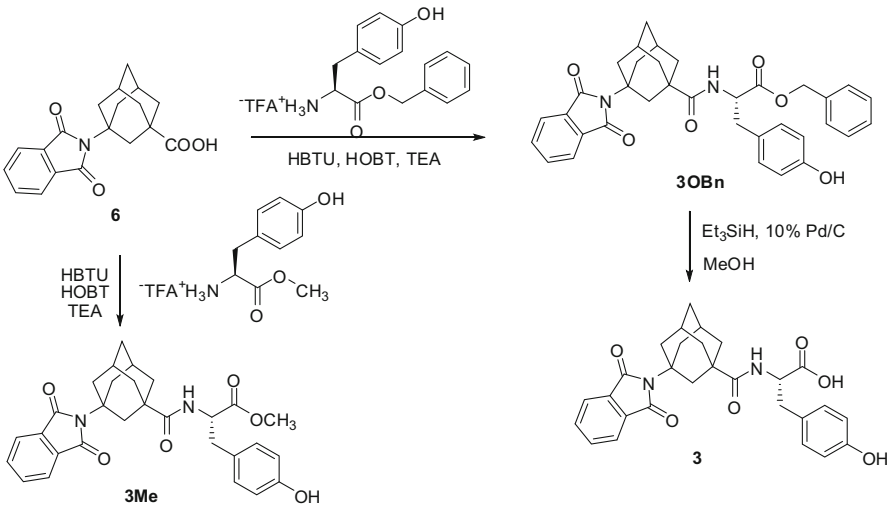
(S)-2-{[3-(N-Phthalmyl)adamantan-1-yl]carboxamido}-3-(4-hydroxyphenyl)propanoic acid methyl ester ***(9Me)*** Dipeptide ester **3Me** (20 mg, 0.04 mmol) and K_2CO_3 (2.7 mg, 0.02 mmol) were dissolved in a mixture of acetone (20 mL) and H_2O (6 mL) and stirred for 2 h in the dark or irradiated. The solvent was removed on a rotary evaporator to afford the pure product isolated in the form of a colorless solid, 30 mg (42%); m.p. 90–93 °C; IR (KBr) $\tilde{\nu}_{max}$ /cm^{-1}: 3353, 2912, 2856, 1729, 1644, 1511, 1442, 1311, 1270, 1225, 1085; ^{1}H NMR (CD_3CN, 600 MHz) δ/ppm: 7.78 (d, $J = 7.7$ Hz, 1H), 7.56 (dt, $J = 1.2$, 7.5 Hz, 1H), 7.48 (dt, $J = 1.2$, 7.7 Hz, 1H), 7.42 (d, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 8.5$ Hz, 2H), 6.72 (d, $J = 8.5$ Hz, 2H), 6.42 (s, 1H), 6.38 (d, $J = 7.5$ Hz, 1H), 4.58–4.53 (m, 1H), 3.79 (s, 1H), 3.66 (s, 2H), 3.04 (dd, $J = 5.3$, 14.0 Hz, 1H), 2.92 (dd, $J = 8.0$, 14.0 Hz, 1H), 2.18 (br.s, 2H), 2.11–2.05 (m, 4H), 2.01–1.97 (m, 2), 1.76–1.66 (m, 5H), 1.63 (d, $J = 12.6$ Hz, 1H); ^{13}C NMR (CD_3CN, 150 MHz) δ/ppm: 177.2 (s, 1C), 173.3 (s, 1C), 169.5 (s, 1C), 168.5 (s, 1C), 156.8 (s, 1C), 140.2 (s, 1C), 132.7 (d, 1C), 131.4 (d, 2C), 130.4 (d, 1C), 130.2 (d, 1C), 129.0 (s, 2C), 128.6 (d, 1C), 116.2 (d, 2C), 54.6 (d, 1H), 53.6 (s, 1H), 52.9 (q, 1C), 52.7 (q, 1C), 43.3 (s, 1C), 43.2 (t, 1C), 41.11 (t, 1C), 41.10 (t, 1C), 38.9 (t, 1C), 38.85 (t, 1C), 37.1 (t, 1C), 36.1 (t, 1C), 30.3 (d, 2C); HRMS (ESI-qTOF) *m/z*: $[M + H]^+$ Calcd. for $C_{30}H_{34}N_2O_7$ 535.2444; Found 535.2448.

Results and discussion

Synthesis

Dipeptide esters **3OBn** and **3Me** were prepared from *N*-protected tyrosine and phthalimido amino acid **6** [32] using *N,N,N′,N′*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) and 1-hydroxybenzotriazole (HOBT) activation protocol [38]. The benzyl deprotection from **3OBn** by use of triethylsilane and Pd/C, according to the modification of the known procedure [39], afforded dipeptide with the free carboxylic acid **3** (Scheme 1).

The synthesis strategy for the preparation of tetra- and pentapeptides was based on the coupling of adamantyl glycine dipeptide **7** with a Phe-Tyr or Phe-Phe-Tyr fragment, respectively. Dipeptide **7** [33, 34] was prepared from **6** and unprotected glycine by use of *N*-hydroxysuccinimide (NHS) and *N,N'*-Dicyclohexylcarbodiimide (DCC) activation [40]. The synthesis of H-Phe-Tyr-OH and H-Phe-Phe-Tyr-OH fragments is shown in Scheme S1 in the supporting information. *N*-Boc-protected phenylalanine reacted with unprotected tyrosine using the NHS and DCC coupling protocol, and afforded dipeptide from which the *N*-Boc group was removed by trifluoroacetic acid (TFA) giving TFA × H-Phe-Tyr-OH. The same coupling protocol was applied to prepare *N*-Boc-Phe-Phe-OH. The introduction of Tyr as the third amino acid was performed in the same manner using unprotected amino acid. In addition, succinimide ester *N*-Boc-Phe-Phe-OSu was coupled with benzyl-protected L-Tyr, giving benzyl-protected tripeptide *N*-Boc-Phe-Phe-Tyr-OBn. Alternatively, the coupling with L-Tyr(OH)-OBn was also performed by use of a stronger activation reagent, HBTU and HOBT, yielding *N*-Boc-Phe-Phe-Tyr-



Scheme 1 Synthesis of **3** and **3Me**

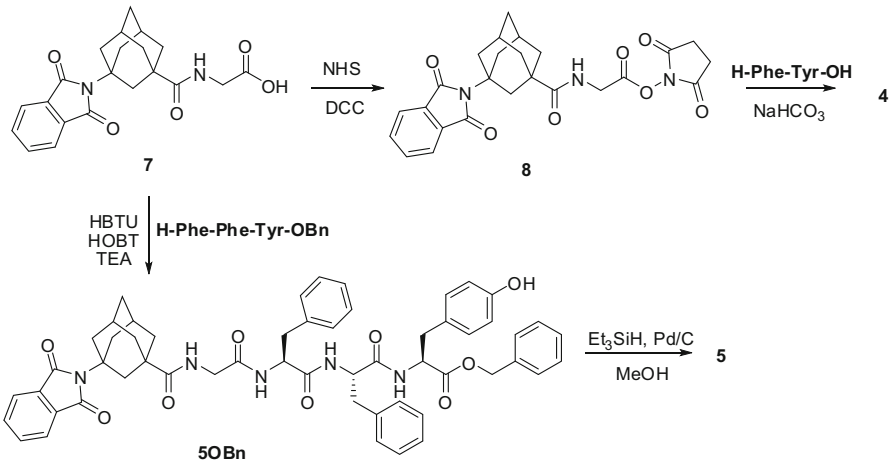
OBn. The Boc deprotection by TFA gave tripetide TFA × H-Phe-Phe-Tyr-OBn which was used in the synthesis of pentapeptide.

To prepare tetrapeptide, adamantylglycine **7** was activated by NHS and DCC to the succinimide derivative **8** and coupled with dipeptide H-Phe-Tyr-OH to afford **4** in 78% yield. Attempts to prepare pentapeptide using the same strategy, from **8** and tripeptide H-Phe-Phe-Tyr-OH, gave very low yields on the desired pentapeptide **5** which was very difficult to purify due to the formation of gel. Therefore, we prepared benzyl *C*-protected pentatpeptide derivative **5OBn**. Since we used protected tripeptide H-Phe-Phe-Tyr-OBn, a stronger coupling reagent HBTU and HOBT could be employed, giving higher yields on the peptide **5OBn**. Benzyl deprotection to free carboxylic acid pentapeptide **5** was achieved by in situ-formed H-radicals using Et_3SiH and Pd/C (Scheme 2).

Peptides **3–5** were fully characterized by spectroscopic methods, and, for **4** and **5**, CD spectra were recorded (see Fig S1 in the supporting information). It is interesting that the CD spectra of **4** and **5** have significantly different patterns, indicating different structure. Probably, the introduction of an additional Phe into the backbone introduces peptide turns, resulting in a helicoidal structure.

Photochemistry

Based on a literature precedent [35], it is anticipated that irradiation of **3–5** in the presence of a base, needed to deprotonate the carboxylic acid, would give rise to photodecarboylation and cyclization products [33]. Irradiation was performed in CH_3CN under direct excitation conditions ($\lambda_{ex} = 300$ nm) or in acetone which acts as a triplet sensitizer ($E_T = 332$ kJ/mol) [41]. The results are summarized in Table 1.



Scheme 2 Synthesis of **4** and **5**

Irradiation of dipeptide **3** performed in acetone is expected to selectively excite phthalimide by energy transfer from acetone. Since the triplet state energy of tyrosine (E_T = 340–350 kJ/mol) [42, 43] is higher than the E_T of acetone, only phthalimide sensitization is exergonic. On excitation of the phthalimde to the triplet excited state, the photodecarboxylation reaction should be feasible when the carboxylic acid is deprotonated, and in principle only one-half of the K_2CO_3 equivalent is needed. However, in the presence of 0.5 equiv. of K_2CO_3, dipeptide **3** upon irradiation showed unexpected photochemical stability. Irradiation of **3** in the presence of a higher K_2CO_3 concentration led to almost complete conversion of **3**, but the transformation was shown to take place in a thermal rather than a photochemical reaction. Products **9** and **9Me** were formed in a base-catalyzed phthalimide ring opening in the presence of 2.2 mM K_2CO_3 (Scheme 3); they were isolated and characterized by spectroscopic methods. Interestingly, base concentration of 1 mM did not catalyze the imide ring opening (Table 1).

Based on phthalimide and tyrosine redox potential, PET should take place between the tyrosine as electron donor and the triplet excited state of phthalimide as electron acceptor. Furthermore, Mariano et al. suggested that primary PET is followed by intrachain single ET (ISET), giving equilibrated ET states that eventually give rise to stable products if there is a reversible process such as decarboxylation or desilylation [44, 45]. Mariano's hypothesis is in accord with the photodecarboxylation of **1**, demonstrated by Griesbeck et al. [35]. Consequently, it is surprising that **3** is photochemically stable. The presumed reason for the observed photostability may be a very fast back electron transfer (BET) so that ISET cannot compete with it. The other plausible reason for the lack of ISET may be a very fast deprotonation of phenoxyl radical-cation **3CT** which gives phenoxyl radical **3PhO**. Acidity of phenoxyl radical-cations and fast deprotonation in aqueous solution is well known [46]. Furthermore, the lack of reactivity of tyrosine-containing peptides in the photocatalytic decarboxylation reactions initiated by phenanthrene and

Table 1 Irradiation conditions and conversions of peptides **3–5**[a]

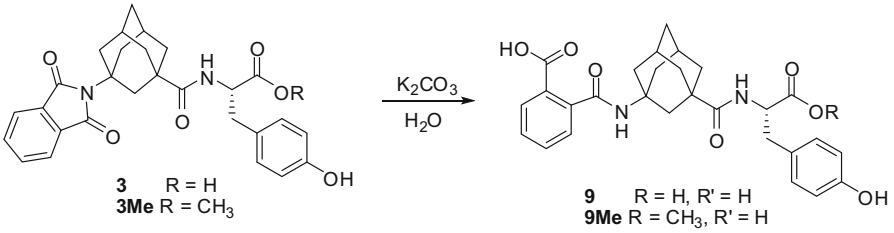
Comp.	Phthalimide conc./ mM	K_2CO_3 conc./ mM	Solvent	Irradiation time	Conversion %[b] (isolated %)
3	2.20	0	Acetone–H_2O 10:3	3 h	<5
3	1.90	0.95	Acetone–H_2O 10:3	2 h	<5
3	2.20	2.20	Acetone–H_2O 10:3	3 h	98 (83)[c]
3Me	4.75	0	Acetone–H_2O 10:3	3 h	<5
3Me	4.75	2.38	Acetone–H_2O 10:3	3 h	91 (86)[c]
4	1.40	0.70	Acetone–H_2O 3:1	40 min	30 (–)[d]
4	1.40	0.70	CH_3CN–H_2O 3:1	40 min	0
5	1.20	0.60	Acetone–H_2O 3:1	20 min	20 (–)[d]
5	1.20	0.60	CH_3CN–H_2O 3:1	20 min	15 (–)[d]
5	0.79	0	Acetone	2 h	42 (–)[d]
5	0.79	2.37	Acetone–H_2O 3:1	2 h	93 (–)[d]
5	0.79	0	CH_3CN	2 h	30 (–)[d]

[a] Irradiation was performed in quartz test tubes (13–15 mL) in a Luzchem reactor by use of 8 lamps with the output at 300 nm (1 lamp, 8 W). Prior to irradiation, the solutions were purged for 30 min with N_2

[b] From NMR spectra

[c] Formed in a thermal reaction

[d] Only high molecular weight products



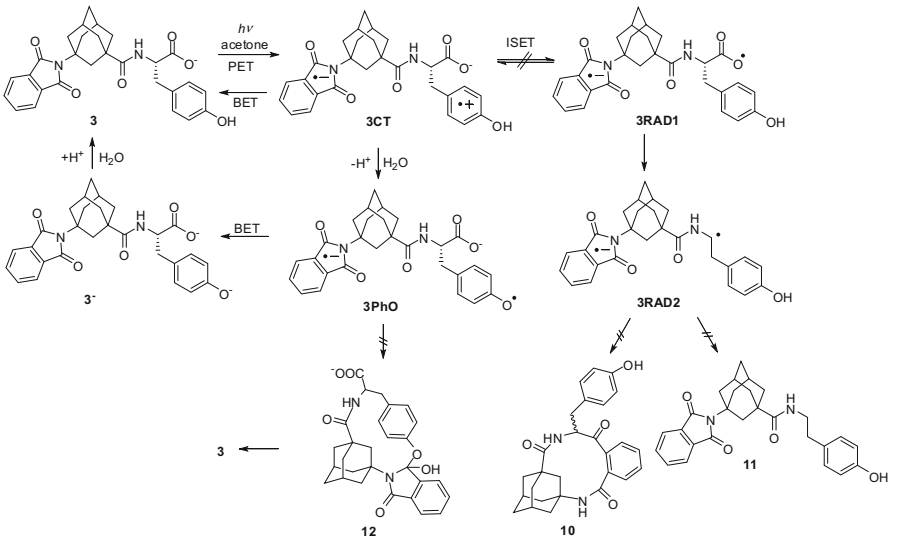
Scheme 3 Thermal base-catalyzed reaction of **3** and **3Me**

dicyanonabenzene has been demonstrated by Yoshimi et al. [47]. In contrast, tyrosine-containing peptides that were substituted at the tyrosine phenolic oxygen underwent decarboxylation and radical addition to electron-deficient alkenes [47]. Therefore, ISET probably does not take place due to **3CT** deprotonation. **3RAD1** and **3RAD2** are never populated, so decarboxyltion of **3** giving the anticipated

products **10** and **11** does not take place (Scheme 4). It is interesting that **3PhO** also does not lead to any stable photoproduct. The presumed reason is depopulation by BET and protonation back to **3**. If the cyclization to strained **12** took place, the hemiaminal would not be stable, so it would revert back to **3**. The other plausible lack of reactivity for **3** may be due to the quenching of the phthalimide triplet state by intermolecular H-transfer from phenol OH. However, H-transfer reactions usually take place several orders of magnitude slower compared to SET, so this pathway is less probable, although it cannot be fully disregarded.

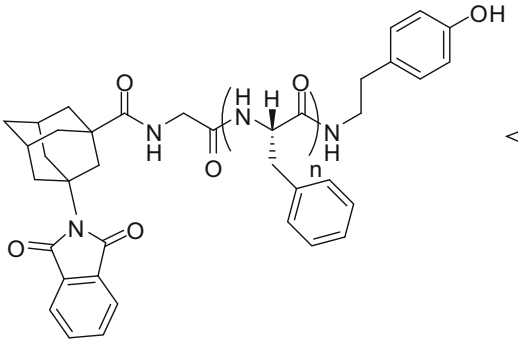
Contrary to dipeptide **3**, tetrapeptide **4** and pentapeptide **5** were photochemically reactive. Thus, 40 min of irradiation of an acetone–H_2O solution of **4** resulted in 30% conversion of the starting material (Table 1). However, NMR and HPLC analysis of the photolysis mixture indicated the formation of numerous products. The anticipated decarboxylation product **13** or cyclization product **14** were not detected. Contrary to the acetone solution, **4** in CH_3CN–H_2O was photochemically stable, indicating that photodecomposition was initiated only upon excitation of phthalimide to the triplet state by energy transfer from acetone.

Pentapeptide **5** was photochemically reactive in both acetone–H_2O and CH_3CN–H_2O solution. A short 20 min of irradiation resulted in a similar 15–20% conversion for both solutions. Similar to the photodecomposition of **4**, decarboxylation product **15** or cyclization product **16** were not detected. Instead, decomposition of the material took place, giving high molecular weight products. Thus, at the high K_2CO_3 concentration of 2.4 mM, almost a complete conversion of the peptide was achieved. However, photodecomposition of the peptide in CH_3CN and acetone, in the same concentration (0.79 mM), was also feasible without the base, although the process was less efficient (Table 1). This finding indicates that the decomposition is not connected to the reactivity of the carboxylic functional group or the thermal

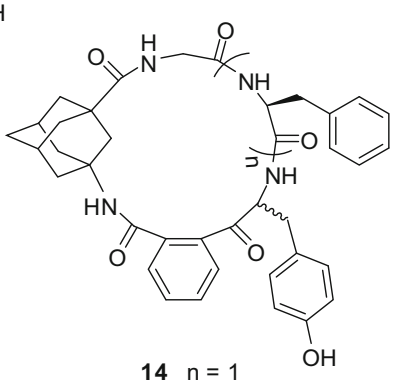


Scheme 4 Plausible mechanism for photochemical reaction of **3**

imide ring opening, as seen with **3**. Most probably, photodecomposition is caused by PET between the phthalimide and the tyrosine, giving a long-lived phenoxyl radical which initiates further radical reactions.



13 n = 1
15 n = 2



14 n = 1
16 n = 2

Conclusion

Adamantylphthalimide tyrosine conjugates dipeptide **3**, tetrapeptide **4** and pentapeptide **5** were synthesized and their photochemical reactivity investigated. Upon excitation to the triplet excited state, **3** probably undergoes PET between the phthalimide and tyrosine, but not between the carboxylate and the phthalimide. Therefore, decarboxylation does not take place and **3** does not lead to any stable photochemical product. On the other hand, direct excitation, or acetone sensitization of tetrapeptide **4** and pentapeptide **5**, lead to photodecomposition. Photodecomposition is similarly efficient, independent of the distance between the electron donor (tyrosine) and the phthalimide. Simple decarboxylation or cyclization products were not obtained, presumably due to a faster formation of a phenoxyl radical by PET followed by decomposition. Although PET probably takes place, ISET cannot compete with BET and the deprotonation of phenol, which leads to no product from **3**, or material decomposition from **4** and **5**. The results presented indicate the importance of a thorough investigation of the photochemical reactivity in diverse molecular structures for the rational design of molecules to attain high reactivity in photocyclization reactions. The molecular structure of reactants undergoing PET has to be wisely designed, not only by the right choice of the reactants' redox potential but also by their acid/base properties.

Supporting information

Supporting information contains synthetic procedures for the preparation of known precursors, CD spectra of **4** and **5** and ^{1}H and ^{13}C NMR spectra of all known compounds. It can be obtained free of charge at the web site.

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