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Photochemical Transformations of Proteinogenic and Non-Proteinogenic Amino Acids

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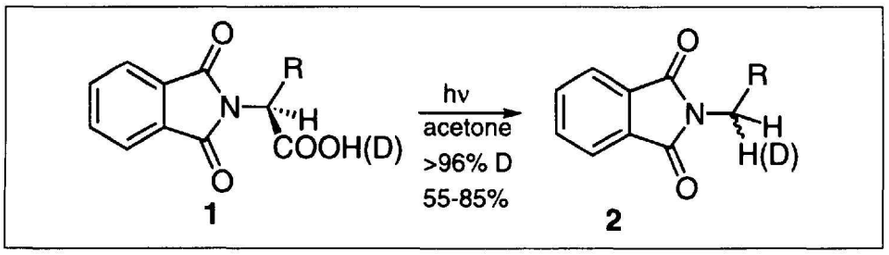
Abstract. The photochemistry of N-activated enantiomerically pure α-amino acids is described with emphasis on chemo-, regio-, stereo-, and spin selectivity. An especially valuable chromophore is the phthalimido group. The first excited singlet states are short-lived and deactivated (chemically) *via* homolytic CH cleavage or (physically) *via* electron-transfer steps. The first excited triplet states are chemically deactivated *via* electron-transfer reactions and subsequent deprotonation/coupling steps. A wide variety of product types were synthesized, and potential target molecules were available by tuning the reaction conditions. Also remote groups can be activated by means of electron-transfer steps, which represents an attractive new synthetic protocol for macrocyclization.

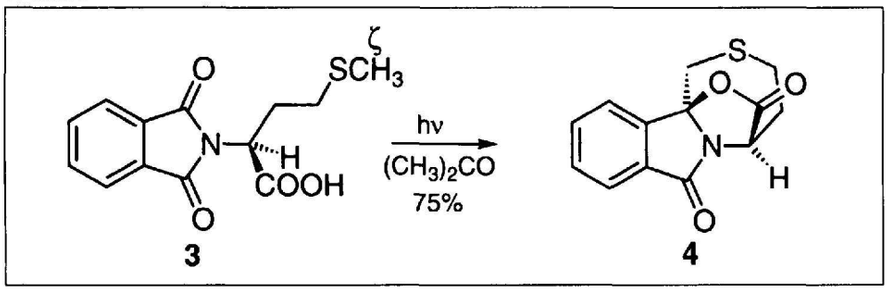
1. Introduction

Amino acids can be photochemically activated by means of chromophoric groups at the nitrogen and the carbon terminus, respectively. Whereas for C-activation only little is known, N-activation *via* acylation is a straightforward and well-studied method, especially in functional group protection chemistry. An especially promising chromophor is the phthalimido group, the photophysics of which has been intensively studied in the last two decades. The major advantages are: long-wavelength-shifted absorption (300–320 nm), low reduction potential (–1.4 V *vs.* SCE in acetonitrile), and clear singlet/triplet differentiation (short-lived $^1n\pi^*$, long-lived $^3\pi\pi^*$) which is a prerequisite for spin-selective transformations. Phthalimide groups can be easily introduced using a variety of chemical methods without loss of enantiomeric purity of the chiral starting materials.

Scheme 1



Scheme 2



2. Results and Discussion

2.1. *Unprotected* N-*Phthaloyl-Amino Acids*

2.1.1. *Photodecarboxylation: Gly, Ala, Abu, Val, Leu, Ile, Tle, Phe, Asp, Glu*

Photodecarboxylation is the dominant pathway for C-unprotected *N*-phthaloyl-α-amino acids **1** (*Scheme 1*). This reaction had already been described by *Kanaoka* and coworkers [1]. We could confirm this observation for H-atom as well as D-atom transfer [2]. The irradiation could be performed by triplet sensitization (acetone or benzophenone) or by direct excitation in solution (*e.g.*, in acetonitrile) or in the solid state. Secondary photoreactions were not observed in the alanine, the phenylalanine, and the phenylglycine case, whereas amino-acid derivatives with longer linear or branched alkyl chains did show additional reactivity. Essential for this efficient reaction seems to be a H-bond in the ground state of the substrate. The most favorable geometry for a strong H-bonding interaction is the seven-membered ring formed intramolecularly in *N*-acylamino acids. Larger ring systems are less favorable, and consequently, β-alanine or higher derivatives of ω-amino acids were completely photostable under the reaction conditions. In the cases of the glutamic-acid and the aspartic-acid derivatives (R = $(CH_2)_nCOOH$ with n = 1, 2) selective decarboxylation of the α-carboxy group was achieved without further decarboxylation of the β- or γ-carboxy group.

Racemic products **2** were formed from chiral (enantiomerically pure) deuterated substrates as was proven at the stage of the free α-[^{2}H]-amines. Thus, (±)-α-[^{2}H]-benzylamine is available from phenylglycine in 60% yield. From quenching and sensitization experiments was concluded that

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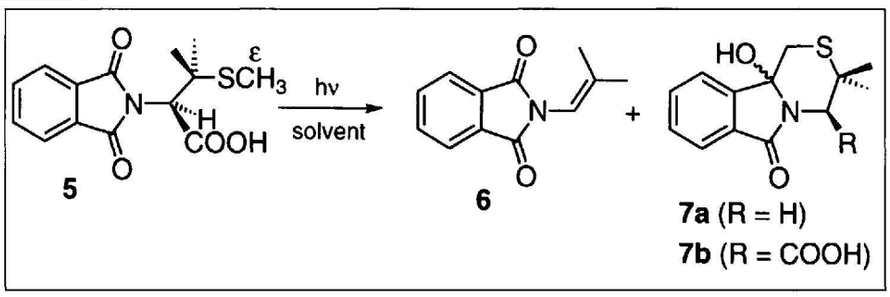
this reaction is initiated by a triplet-sensitized excited state proton-transfer (ESPT)/electron-transfer sequence followed by extrusion of CO_2 and H-(back) migration. Since remote carboxyl groups do not form the H-bond mentioned above, this initial proton-transfer step is less probable.

2.1.2. *Electron-Transfer Chemistry Interfering: Met and Cys, Ser and Thr, Tyr and DOPA*

During our investigation on the photodecarboxylation of C-unprotected α-amino acids, methionine became a substrate of central importance. This amino acid is an useful precursor to vinylglycine in an elegant thermal reaction and we tried to develop a similar efficient photochemical route. There existed already a literature report about the quantitative photodecarboxylation of phthaloylmethionine (PHT = Met **3**) [1]. When repeating this experiment, however, we found an unusual behavior: **3** is stable when irradiated in acetonitrile and cyclized to the tetracyclic product **4** when irradiated in acetone or acetonitrile in the presence of benzophenone [3] (*Scheme 2*).

Under less polar conditions (*e.g.*, in benzene), decarboxylation was observed in low yields. Obviously, in this case the first reaction event must be an electron transfer from the S-atom to the phthalimido acceptor group. Subsequently, the phthalimide radical anion forms the lactone ring *via* nucleophilic attack at the carboxy group. Analogous reactions with intermediate radical cations are well-documented in the literature. Loss of a distal α-proton converts the S radical cation into a C-radical which combines with the imide-localized C-radical to give **4**. Beside the remarkable structure of compound **4** and the efficiency of its formation, a surprising aspect of the methionine photochemistry is its spin selectivity: the singlet state of **3** is deactivated >95% to the ground state whereas the corresponding triplet state cyclizes with a quantum yield of *ca.* 0.25. The 'normal' behavior of phthalimide singlets, however, is rapid intersystem crossing to the triplet manifold. This photophysical process is largely suppressed for the donor-acceptor substrate **3**. A possible explanation is, that the singlets are deactivated by an electron-transfer/back electron-transfer process. If so, other substrates with similar geometry should also be prone to spin-selective reactions. Consequently, we investigated the cysteine skeleton in some detail [4]. The starting materials were easily available from cysteine and penicillamine, respectively.

Scheme 3



Scheme 4

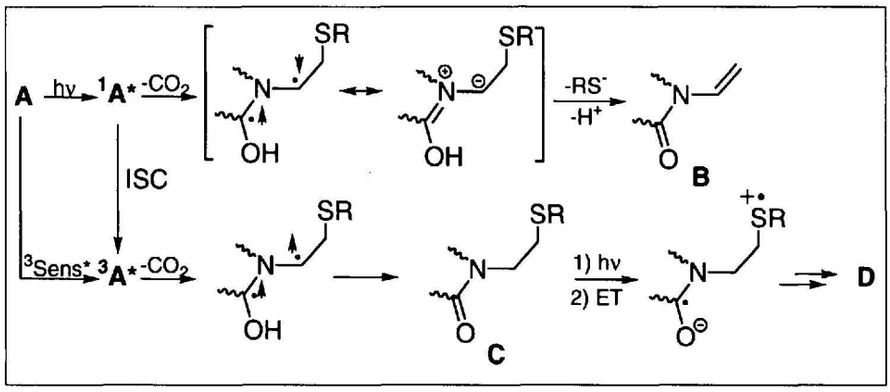


Table 1. *Irradiation of* **5**

Entry	Solvent[a])	Conversion [%][b])	**6** [%]	**7a** [%]	**7b** [%]
1	acetonitrile	17	47	< 3	53
2	acetone	100	9	42	49

[a]) 0.01M soln. of **5**, 300 nm, 15°, 24 h, *RPR-208 Rayonet* reactor.
[b]) ^{1}H-NMR normalized to 100%.

Table 2. *Irradiation of* **8**

Entry	Solvent[a])	Conversion [%][b])	**9** [%]	**10a** [%]	**10b** [%]	**11** [%]
1	acetonitrile	33	12	< 3	66	22
2	acetone	100	< 3	39	61	< 3

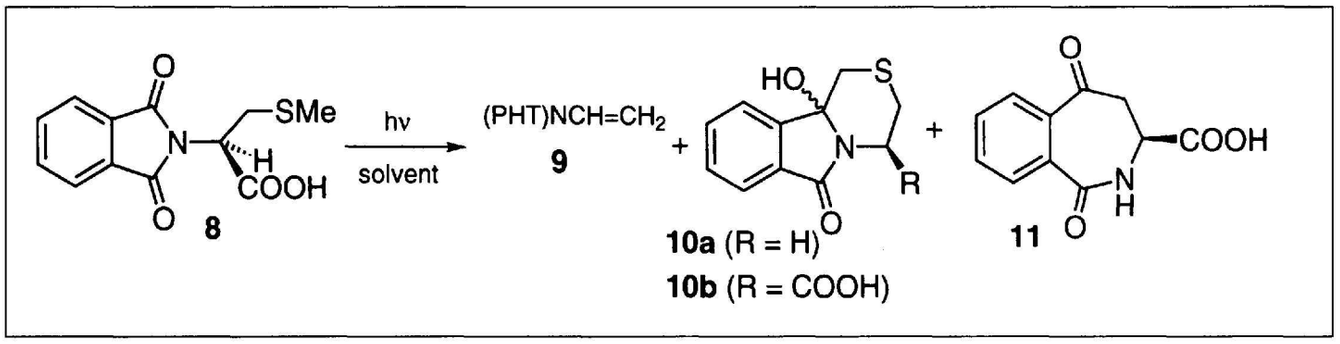
[a]) 0.01M soln. of **8**, 300 nm, 15°, 24 h, *RPR-208 Rayonet* reactor.
[b]) ^{1}H-NMR normalized to 100%.

The results with these starting materials **A** (**5**) (*Schemes 3* and *4*, *Table 1*) were more complex than with the methionine substrate **3**. This is due to the fact that the thioalkyl group is now in the right position for inducing β-elimination. This elimination preferentially occurs in the singlet photochemistry leading to the enamide **B** (**6**). Product **D** (**7a**) derives from a two-photon decarboxylation/electron-transfer cyclization process and is characteristic for the triplet photochemistry. In competition to these two pathways which originate from the same primary process, always products were identified with an intact carboxy group. In the penicillamine example this was the tricyclic compound **7b**.

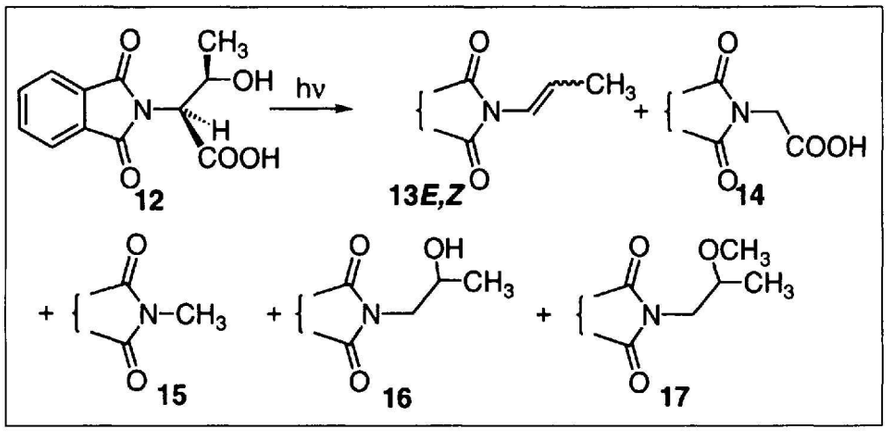
The formation of these products is initiated by primary electron transfer from the thioalkyl group to the excited phthalimide electron acceptor. This PET (photoinduced electron transfer) is much more efficient from the triplet than from the singlet state. It can be concluded from the results obtained with cysteine and penicillamine, that back electron transfer dominates the photochemistry of the singlets (*Scheme 4*).

In the *S*-methylated substrate **8** (*Scheme 5*, *Table 2*) the γ-Hs (γ with respect to the imide-carbonyl groups) are activated solely

Scheme 5



Scheme 6



Scheme 7

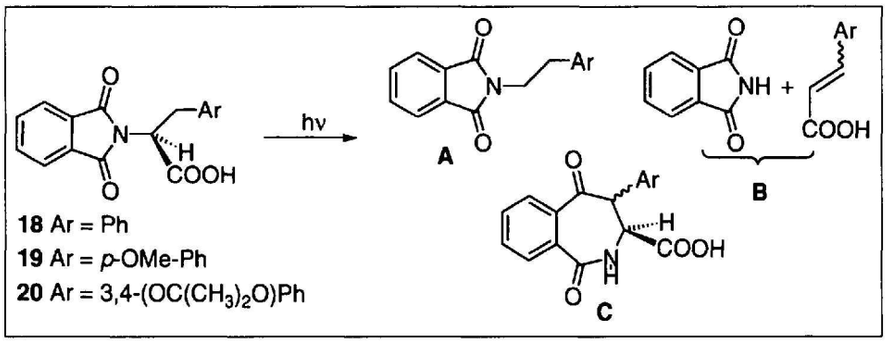


Table 3. *Irradiation of* **12**

Entry	Solvent[a])	Conditions	Conversion [%][b])	**13** [%][b])[c])	**14** [%][b])	**15** [%][b])	**16** [%][b])
1	acetone	pyrex	82	88 (0.69)	6	–	6
2	acetonitrile	pyrex	100	68 (0.94)	15	12	5
3	acetonitrile	pyrex/BP[d])	100	92 (0.80)	–	8	–
4	benzene	pyrex	60	61 (0.91)	13	19	6
5	benzene	pyrex/10% H_2O	100	51 (0.82)	6	25	15
6	methanol	pyrex	100	–	–	35	40[e])
7	water	pyrex	100	–	–	55	45

[a]) 0.01M soln. of **12**, 300 nm, 13°, 24 h, N_2, *RPR-208 Rayonet* reactor.
[b]) ^{1}H-NMR (200 MHz) normalized to 100%.
[c]) Values in parentheses refer to the **13*E*/13*Z***-ratio.
[d]) 0.004M soln. of benzophenone (BP).
[e]) Additionally 25% of **17** formed.

in acetonitrile (singlet path which has also been proven by quenching experiments) with formation of the benzazepinecarboxylic **11**. This compound is *not* formed *via* primary electron transfer from the S-atom because radical ion-pair formation always gives rise to deprotonation from the terminal methyl group and thus leads to the formation of thiazinoindoles **10a** and **10b**, respectively. The precursor to **11** is the corresponding α-methylthio-substituted compound which undergoes *Norrish* II cleavage *ca.* 100 times more efficient than the primary γ-H abstraction.

The C-unprotected amino-acid derivatives of threonine and serine have two possible sites of electron-donor functionalities: the carboxy and the hydroxy group [5] (*Scheme 6*, *Table 3*). The products **13**–**17** (**17** is a photoaddition product of MeOH to the radical cation of **13**) which were formed from the threonine derivative **12** originate from all possible combinations: **13** is formed by decarboxylation and β-elimination of the hydroxide, **14** is the product of ET (electron transfer) from the hydroxy group, **15** the secondary decarboxylation product, and **16** the product of primary decarboxylation.

The diastereoisomeric *N*-propenyl compounds **13*E*** and **13*Z*** were the dominating products deriving from the triplet pathway (solvent-sensitized as for *Entry 1* or benzophenone-sensitized as for *Entry 3*). The **13*E*/13*Z*** ratio in the benzophenone case clearly differs from the acetone photolysis, indicating the possibility of secondary photochemical isomerization. An additional amount of 27% of **14** and the corresponding decarboxylation product **15** resulted in acetonitrile as products of singlet **12**. Low-conversion photolysis clearly showed that **15** is a secondary product from **14**. The carbinol **17** is on one hand the minor product of photodecarboxylation and, on the other hand, the photoaddition product of H_2O to the radical cation of **13**.

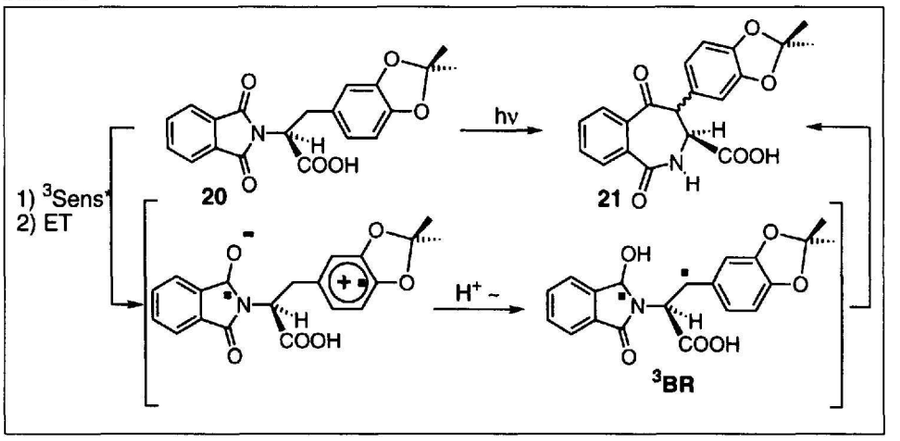
A third group of PET-active donor-acceptor couples were the aromatic amino

acids tyrosine and dihydroxyphenylalanine (protected as the methyl ether **19** and the acetal **20**) (*Scheme 7*, *Table 4*). The phenylalanine substrate **18** has already been reported to undergo exclusively decarboxylation when irradiated in acetone. When, however, acetonitrile was used as solvent, as side reaction a *Norrish* II cleavage to give phthalimide and the diastereoisomeric cinnamic acids (path **B**) was observed (*Entry 2*). This result already indicated the possibility of PET steps leading to a pair of aryl radical cation and phthalimide radical anion. From intermolecular PET reactions of phthalimides with electron-rich arenes, it is known that aryl radical cations serve as efficient source of benzylic radicals. It is remarkable that the C-unprotected DOPA derivative **20** did not even give traces of decarboxylation and solely the ring-enlargement product **21** with excellent diastereoselectivity (*Scheme 8*).

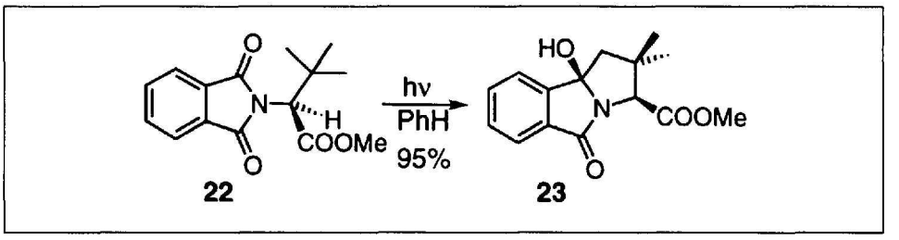
The mechanism of the formation of this interesting (and completely photostable) compound is indicated in *Scheme 8*: After triplet sensitization and electron transfer, a triplet radical ion pair is formed which deprotonates to give the triplet 1,4-biradical **^{3}BR**. This biradical cannot undergo 2,3-bond cleavage due to the additional spin barrier. Thus, ISC and subsequent C–C bond formation are favored for the DOPA case.

In summary, the combination of electron-donating groups (SR, OR, aryl) with the carboxylic-acid functionality leads in some cases to highly complex PET photochemistry which can, however, be selectively tuned by solvent effects and the oxidation potentials of the donor functional groups.

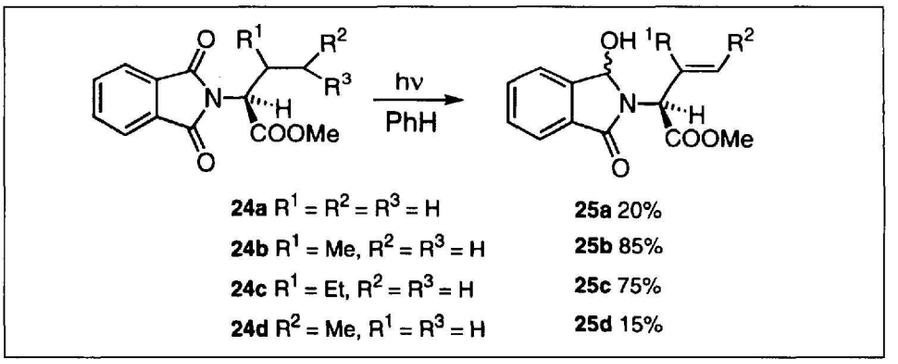
Scheme 8



Scheme 9



Scheme 10



3. C-Protected *N*-Phthaloyl-Amino Acids

3.1. *Homolytic CH Activation: Abu, Val, Leu, Ile, Tle*

The preferred position for homolytic CH cleavage by an electronically excited carbonyl compound is the γ-CH bond. In **22**, only δ-CH's were available, and when irradiated in benzene (or alternatively, in somewhat lower yields, also in acetonitrile) the benzopyrrolizidine **23** was formed in excellent yields and with high diastereoselectivity (*Scheme 9*). In the presence of a suitable triplet sensitizer, no reaction was observed [6].

This spin selectivity was also observed for the substrates **24a–d**, indicating that only the singlet excited states are capable of homolytic γ-CH and δ-CH activation.

Table 4. *Irradiation of* **18**, **19**, *and* **20**

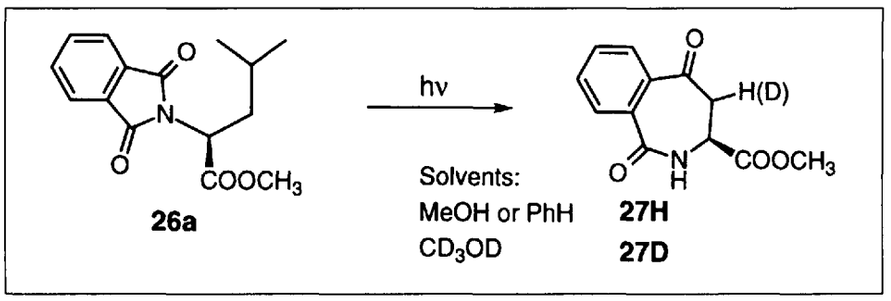
Entry	Substrate	Solvent[a])	Time	Conversion [%][b])	A [%][b])	B [%][b])[c])	C [%][b])[d])
1	**18**	acetone	1d	100	100	–	–
2	**18**	acetonitrile	1d	100	80	20	–
3	**19**	acetone	1d	80	–	65	35
4	**20**	acetone	0.5d	80	–	–	100 (89:11)

[a]) 0.05M solns. of **18–20**, 300 nm, 20°, N_2, *RPR-208 Rayonet* reactor.
[b]) ^{1}H-NMR (250 MHz) normalized to 100%.
[c]) *Ca.* 1:1 *trans/cis*-mixture of α,β-unsaturated acids.
[d]) Values in parentheses refer to the *trans/cis*-ratio.

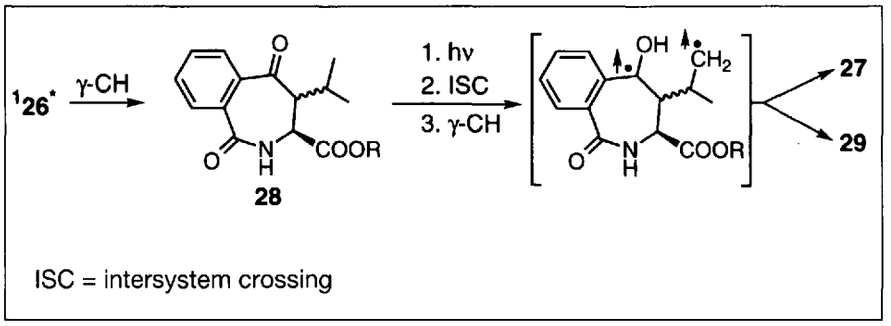
The *N*-phthaloyl methyl ester of 2-aminobutyric acid (**24a**), valine (**24b**), isoleucine (**24c**), and norvaline (**24d**) gave the corresponding photoisomerization products **25** which could be deprotected to give the free β,γ-unsaturated amino acids. For **24a** and **24b**, we showed explicitly that no epimerization occured at the stereogenic center even after prolonged irradiation [7] (*Scheme 10*).

This synthetic approach to the important class of β,γ-unsaturated amino acids worked with high yields for γ-branched substrates, wheras the 2-aminobutyric-acid derivative **24a** gave only 20% (isolated yield) of a 1:1 diastereoisomeric mixture

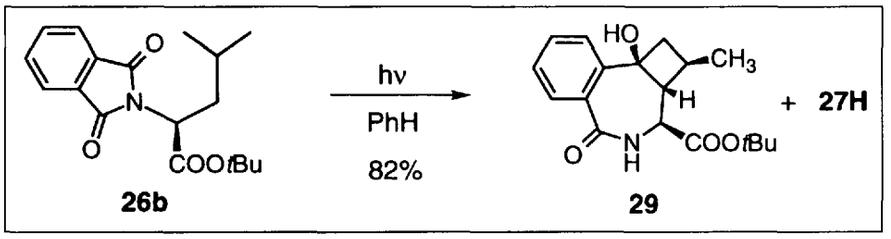
Scheme 11



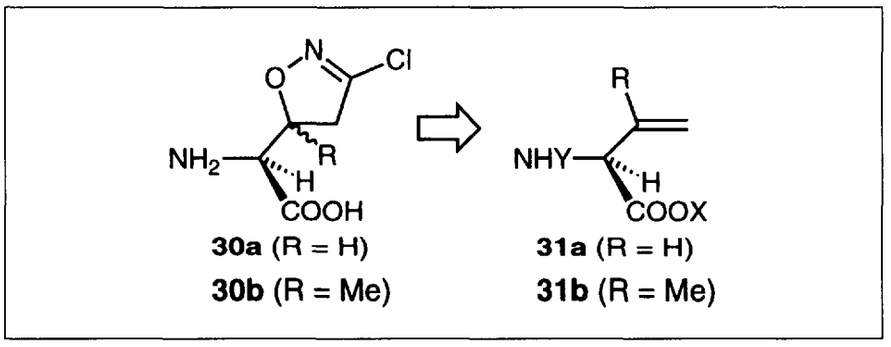
Scheme 12



Scheme 13



Scheme 14

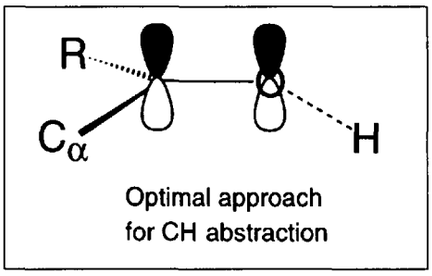


of **25a**. As different reactivity picture appeared with the leucine derivatives **26a** and **26b** (*Scheme 11*).

The one-photon transformation reported for the isoleucine case was not observed for **26a**, *i.e.*, deuterium was incorporated at the α-position of product **27D** when the reaction was performed in deuterated MeOH [8]. Thus, a sequence of a primary (singlet) *Yang* cyclization and a secondary (triplet) *Norrish* II cleavage leads to the formation of the benzazepinecarboxylates **27**. We were not able to detect (by NMR or GC) the intermediary isopropyl-substituted intermediate **28** (*Scheme 12*). Thus, the secondary *Norrish* reaction must be much more efficient, at least by a factor of 50. This assumption is reasonable, because quantum yields for *Norrish* II cleavage reactions (Φ_r) with triplet acetophenone derivatives are in the order of 0.7–1.0 [9], whereas for the corresponding reactions with singlet phthalimides Φ_r are in the order of 0.02–0.05 [4].

A remarkable effect was observed with the *N*-phthaloylleucine *tert*-butyl ester **26b**: beside 50% of the regular *Yang* cyclization/*Norrish* II cleavage product **27H**, another 50% of a cyclobutanol **29** was observed (*Scheme 13*). The tricyclic 'double *Yang* product' showed one set of resonance lines in ^{1}H-and ^{13}C-NMR, indicating that only one out of eight possible diastereoisomers was formed. The X-ray structure analysis of **29** showed that the cyclobutane ring is *trans*-fused with respect to the ester group. Thus, the isoproyl group in the corresponding precursor molecule **28** also must be located *trans*.

Molecular mechanics (MM2) and semiempirical (PM3) calculations indicated that the most important factor for the reactivity of *N*-alkyl-phthalimide singlets is the angle Δ (C–**H**··**O**=**C**)



which is 100±5° for reactive substrates and 82±5° for unreactive substrates (basis of calculation: twelve substrates). The dihedral angle ω(**C$_\alpha$–C=O··H**) can approach optimal values of 0° to maximum 35° for all substrates. This correlation is the basis of the competition between (slow, but thermodynamically favorable) β- *vs.* (rapid) γ- or δ-CH abstraction in the photochemistry of *N*-phthaloyl-α-amino acids.

Another important feature of this spin selectivity is the stereoselectivity of the second H-migration step in the formation of the isomerization products **25**: beside **25d**, all products were formed diastereomerically (and consequently enantiomerically) pure, *i.e.*, the stereogenic α-hydroxyamide center is formed highly stereoselective. We suppose that the second H-migration (which involves always the δ-H) is rapid and rotation about the C$_\alpha$–N-bond cannot compete at the singlet 1,4-biradical stage. Thus, the second H-transfer always involves the same diastereotopic face of both the imide-carbonyl groups.

3.2. *Application: Syntheses of Isodehydrovaline and Vinylglycine*

Acivicin (**30a**) has been characterized as an antimicrobial, antimetabolitic and effective antitumor agent. The retrosynthesis of this compound and of the corresponding β-alkylated derivatives leads to β,γ-unsaturated amino acids as 1,3-dipolarophiles. For the synthesis of **30a**, we

needed vinylglycine **31a** which was at this time not available by a photochemical route (*Scheme 14*).

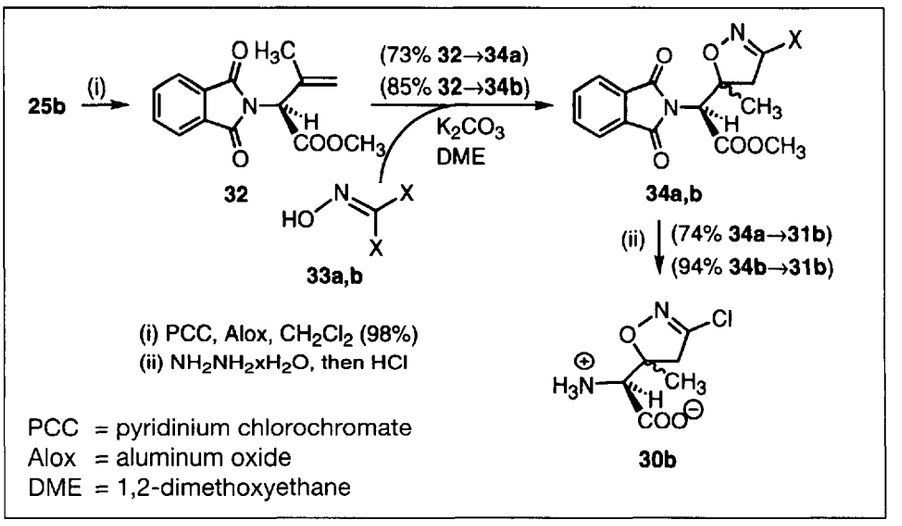
Isodehydrovaline (**31b**) was available by the photoisomerization process in good yields and high diastereoselectivity. Thus, we have focused on the preparation of branched derivatives of **30** and investigated 1,3-dipolar cycloaddition reactions of chloro- and bromonitrile oxide with isodehydrovaline substrates [10]. Optimal results were obtained with the reoxidized substrate **32** which added to the nitrile oxides *in situ* prepared from the oximes **33** with good diastereoselectivity (83:17). The adducts **34a,b** were deprotected to give the desired **30b** (*Scheme 15*).

The synthesis and use of vinylglycine was another challenge. Vinylglycine (**31a**, X = Y = H), a natural amino acid, acts as an inhibitor of pyridoxal-dependent aspartate aminotransferases and is also considered as an important intermediate in several biogenetic pathways. A number of thermal processes leading to vinylglycine have been developed using other amino acids such as homoserine, glutamic acid, and methionine or carbohydrates as starting materials. The most successful synthetic approach up to now is the thermolysis of N,C-protected methionine sulfoxide, developed and optimized by *Rapoport* and coworkers [11]. Simple photoisomerization of the methyl 2-phthalimidobutyrate **24a** gave only low yields. In this case, radical combination is faster than the second H-migration step. Assuming, that an increase in migratory ability or in leaving group ability of the second fragment X should favor the formation of a C=C-bond, we investigated several possible substrates with X = OH, OR, SR, S(O)R, Br, und Cl [12]. The most efficient approach to vinylglycine uses the *N*-phthaloyl derivative of methionine sulfoxide (**35**) (*Scheme 16*).

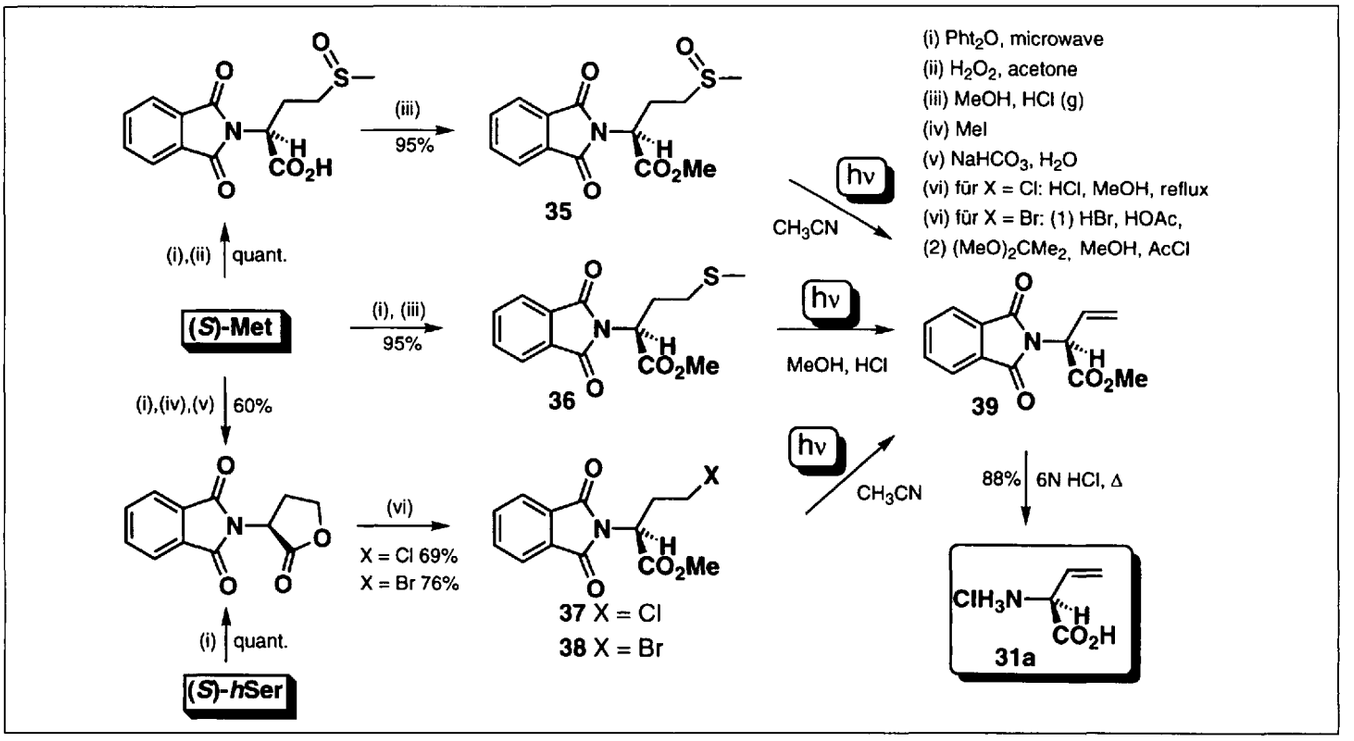
Other useful substrates in this context were the δ-chloro- and δ-bromo-substituted amino acids **37** and **38** (from homoserine lactone). Even the simple methionine ester **36**, available in two steps from methionine, gave C,N-protected vinylglycine **39** upon irradiation in HCl-saturated MeOH (in contrast to the photochemistry in acetonitrile – *vide infra*). The overall yields for the photoeliminations are between 75–85% and thus can compete with the most efficient thermal processes. A further advantage of this reaction is its applicability in peptide transformations, *i.e.*, N-terminal Met-substituted peptides could be selectively transformed into N-terminal vinylglycine-substituted peptides.

Summarizing the reactivity of simple alkyl-substituted phthalimides, three types of products can be obtained: photoisomer-

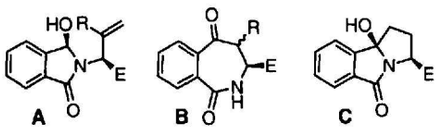
Scheme 15



Scheme 16



ization (**A**), ring-enlargement (**B**), and cyclization (**C**) products. In most cases, these products were formed with high diastereoselectivity, in all cases enantiomerically pure.



3.3. *Electron-Transfer Chemistry: Met and Cys, Ser and Thr, Tyr and DOPA*

As already described, methionine behaved rather unusual when irradiated as its *N*-phthaloyl derivative in acetone (formation of the tetracyclic lactone **4**). In contrast, the methyl ester **36** behaved decent: only an 1:1 mixture of the diastereoisomeric tricyclic lactames **40** was formed as result of triplet sensitization [3] (*Scheme 17*). We could not detect any product from the excited singlet state. A slight change in reaction conditions, however, opened a photochemical channel also for the singlet state (HCl/MeOH – *vide supra*).

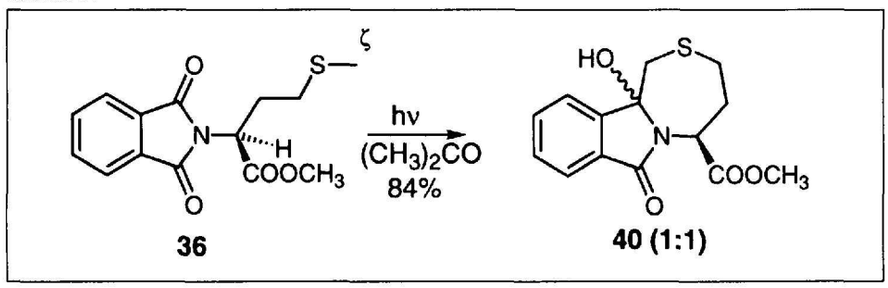
Thus, homolysis of the γ-CH bond which is the dominant process for singlet excited phthalimides is avoided in electron-donor-substituted substrates. This effect can be circumvented by reducing the bond energy of the γ-CH bond *via* heteroatom incorporation. The C-protected cysteine derivatives **41** are attractive substrates for this purpose. Two product families were formed under the reaction conditions: the benzazepine-1,5-diones **A** derive from a two-photon sequence, *i.e.*, ring enlargement and subsequent *Norrish* II cleavage of the α-thioalkylated intermediate. The isoindolothiazines **B** derive from a one-photon process, *i.e.*, photoinduced electron transfer, generating the S radical cation, subsequent deprotonation of the terminal thioalkyl group, and C–C bond formation [13] (*Scheme 18*, *Table 5*).

Furthermore, as shown by the experiments with the *S*-methyl-cysteine **41a** and the penicillamine derivatives **44**, the products are formed with high spin selectivity. In the presence of an excess of triplet quencher, solely product **42** was formed from **41a**. Consequently, the γ-blocked substrate **44** remained unchanged under these conditions (*Scheme 19*).

Under triplet sensitization, the isoindolothiazines **43** and **45** were the only detectable (primary) products. For all substrates investigated in this series, both PET and γ-CH-bond homolysis can be postulated as primary reaction events. The distance between the S-atom and the proximate carbonyl O-atom of the excited phthalimido group is between 2.2 Å (*gauche*-conformation) and 4.3 Å (*anti*-conformation, from AM1 calculations) in the ground-state conformers. Thus, electron transfer is not restricted by the donor-acceptor distance. Form an energetic point of view, both singlet and triplet excited states are capable of exergonic intramolecular electron transfer. Using the redox potentials for the model substrates dimethylsulfide (+1.21 V *vs.* SCE) and *N*-methylphthalimide (–1.37 V *vs.* SCE) and the singlet/triplet energies of *N*-methylphthalimide (3.8 eV and 3.1 eV), free energies were calculated for the electron transfer of –1.2 eV (27.6 kcal/mol) from the first excited singlet state and of –0.5 eV (11.9 kcal/mol) from the first excited triplet state, respectively. For compound **41**, $E_{red.}$ of –1.40 (peak potential) and $E_{ox.}$ of *ca.* 1.60 V (irreversibel) were determined. Using these values, ΔG^0_{ET} is – 0.8 eV for the singlet and – 0.2 eV for the triplet process.

Analogous PET reactions for γ-alkyl thioketones have been studied in detail by *Wagner* and *Lindstrom* [14]. They used acetophenone substrates in order to completely circumvent the singlet channel. For substrates comparable to ours, a ratio of PET reaction to homolytic γ-CH activation of *ca.* three was reported. In case of the cysteine derivatives described here,

Scheme 17



Scheme 18

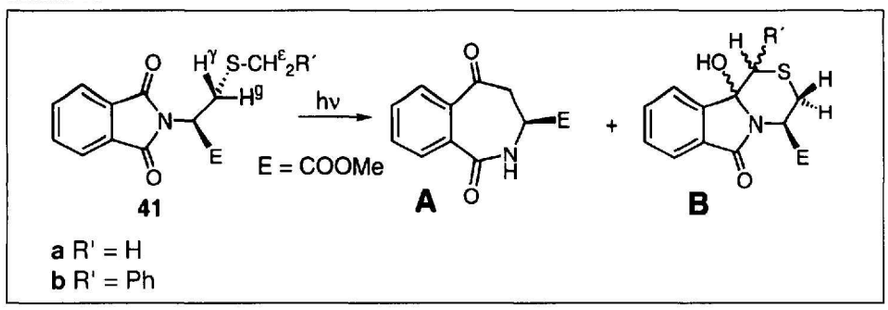


Table 5. *Irradiation of* **41** *and* **42**

Entry	Substrate	Solvent	Conversion [%][b]	A (42)	B
				ratio	
	41 (R' = H)				
1		acetone	100	–	> 95 **43** (60:40)
2		CH_3CN	62	26	74 **43** (59:41)
3		CH_3CN/BP[c]	100	–	> 95 **43** (60:40)
4		CH_3CN/P[d]	21	> 95	< 5
	44				
5		acetone	100	–	> 95 **45** (84:16)
6		CH_3CN	24	–	> 95 **45** (87:13)
7		CH_3CN/BP[c]	100	–	> 95 **46**
8		CH_3CN/P[d]	< 5	–	–

[a]) 11.0 mM solns. of substrates, *Rayonet* reactor, 300 nm, 23°, N_2, irrad. time: 24 h.
[b]) By ^{1}H-NMR analysis (250 MHz) of the crude product mixtures and comparison with significant signals from the purified products.
[c]) 10.1 mM soln. of benzophenone in acetonitrile.
[d]) 50–100 mM soln. of piperylene in acetonitrile.

this ratio must be higher than twenty. Both the experiments with acetone and benzophenone (E_T = 69 kcal/mol) as triplet sensitizers led to this conclusion. Less than 5% benzazepine-1,5-dione **42** was found in the acetone-sensitized experiments. Due to the relatively low concentrations of benzophenone in the respective experiments, a small amount of singlet reactivity was always detected due to direct excitation of the phthalimide chromophore. The photolysis of **41b** (with R' = Ph) with 364 nm light (argon ion laser) indicated that in this special case also the γ-CH position is active in the triplet photochemistry. We assign this phenomenon to the pronounced steric shielding of the ε-CH position.

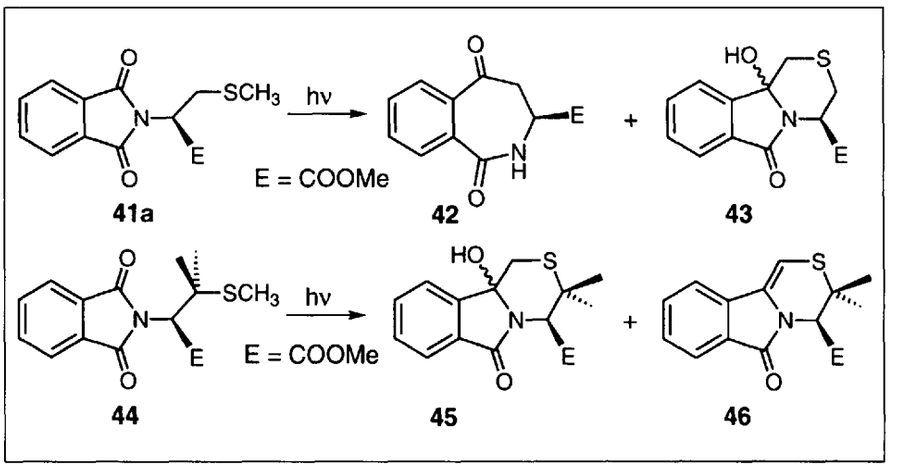
In the presence of piperylene (E_T = 59.2 kcal/mol), the triplet states of **41** and **44** should be completely quenched. The experiments clearly showed that **42** is preferentially formed *via* the singlet channel and that the isoindoles are *exclusively* formed *via* the triplet channel.

Apparently, the triplet radical ions ^{3}**RI** formed after intramolecular electron transfer from ^{3}**A*** are selectively deprotonated from the (kinetically more acidic) ε-CH position. The resulting 1,6-biradicals combine to the isoindoles **43** and **45** after spin inversion (*Scheme 20*).

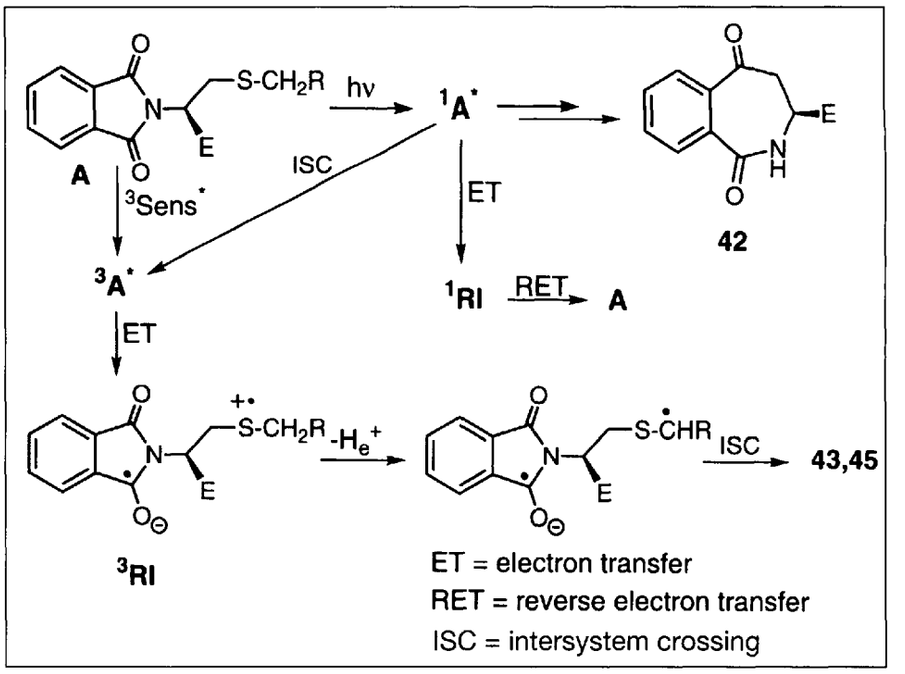
From an energetic point of view (*vide supra*), electron transfer from the singlet excited state ^{1}**A*** should be even more efficient. There is, however, a pronounced decrease in conversion when the direct irradiations are compared with the triplet-sensitized reactions. Additionally, ε-CH activation was not observed for the singlet reactions. Thus, there must be a competing process much faster than the deprotonation reaction. We assume that this process is reverse electron transfer (RET) from the singlet radical ions ^{1}**RI** which regenerates the ground states. Firstly, this process is highly exergonic, secondly, no spin barrier exists for this reaction. The formation of the precursor to **42** is therefore assumed to be due to a homolytic CH abstraction from the geometrical preferred γ-position and not to a PET process. In case of the triplet radical ion pairs, spin inversion must preceed the RET process. Therefore, an efficient competition between this deactivation process and the heterolysis of the ε-CH bond exists.

The hydroxy-substituted amino acids serine and threonine were studied as the methyl esters **47a** and **47b**. Irradiation in acetone or acetonitrile led to cleavage of the central C–C bond with formation of *N*-phthaloylglycine **48** and the corresponding aldehydes [5] (*Scheme 21*). Use of the O-deuterated starting materials led to α-deuterated **48** in racemic form. This cleavage is probably initiated by PET from the hydroxy group to the excited imide triplet followed by fast intramolecular proton transfer and cleavage of the C_α–C_β bond. Several catechol-protected derivatives of methyl ester **49** (R = Me, H) have been investigated in order to synthesize new structures for pharmaceuticals [15]. The photochemical ring-enlargement reactions proceeded with high efficiency and in high yields. It is remarkable to mention that no thermal processes are known which give benzazepinedione structures enantiomerically pure (*Scheme 22*).

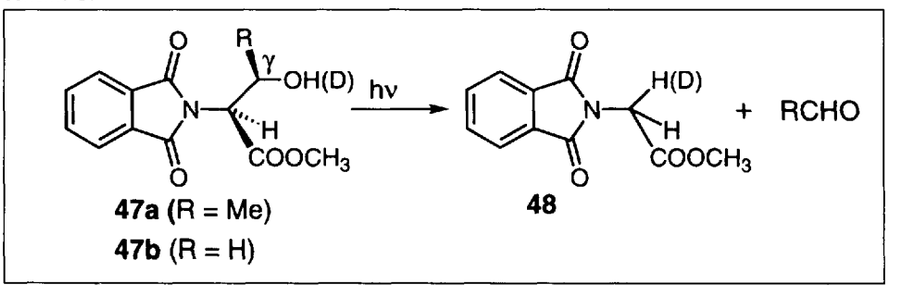
Scheme 19



Scheme 20



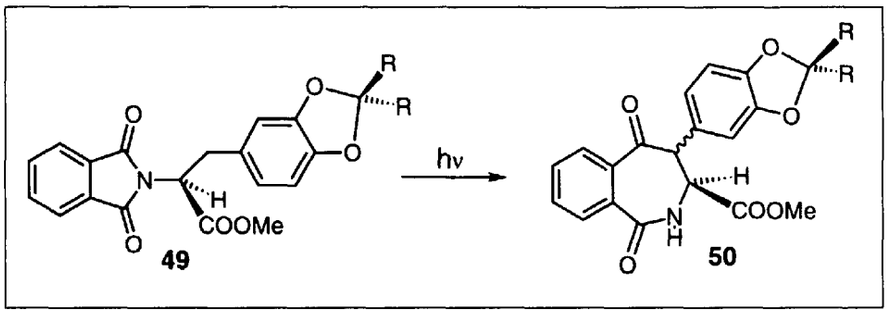
Scheme 21



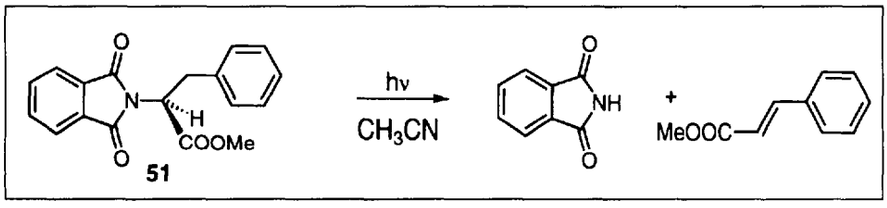
3.4. *Unreactive Substrates: Gly, Ala, and Phe*

When irradiated for standard conversion times, the methyl esters of *N*-phthaloylglycine, alanine, and phenylalanine behaved photostable. This behavior was not surprising for glycine and alanine: in general, β-Hs are abstracted slowly, and this is also valid for γ-Hs, if a primary radical is produced *and* the geometry for H abstraction is unfavorable. For *tert*-leucine for example, the formation of a primary radical *via* δ-H abstraction is effective due to the favorable geometry, *i.e.*, the short C=O···H distance and the *ca.* 100° C=O···H angle. Thus, the reduced photochemical reactivity of the phenylalanine substrate is striking. Ground-state geometry is expected to be correct for abstraction of a benzylic H (like in the leucine case **26**), and the radical produced thereafter is strongly stabilized. Long-term (2–3 d) irradiation of **51** in acetonitrile resulted in complete β-cleavage (*Scheme 23*). This might mean that radical combination is less favored due to fast methylcinnamate formation or due to the geometry of the intermediate 1,4-biradical with aryl-aryl interaction. Could there also be PET deactivation for **51**? A hint came from the fluorescence decay data [5]. In nonpolar solvents (benzene, toluene) the singlet decay time was *ca.* 4 ns, in acetonitrile, this time increased by a factor of 3.6 (dual fluorescence with a 4- and a 22-ns contribution). A plausible explanation is delayed fluorescence *via* repopulation of the first excited singlet by back electron transfer from the radical ion pair. This process, similar as for other PET substrates, deactivates the singlets. Additionally, in this case the triplet of **51** is too low in energy to enable exergonic ET. Thus, due to different reasons, singlet *and* triplet states are less reactive than normal.

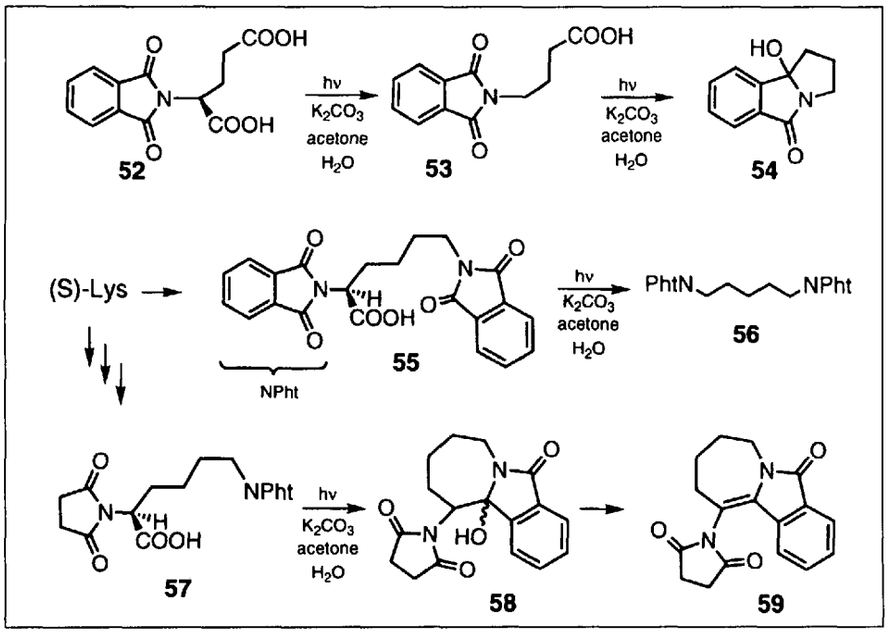
Scheme 22



Scheme 23



Scheme 24



4. Remote Photodecarboxylation

4.1. *The Glutamic-Acid Substrate Series*

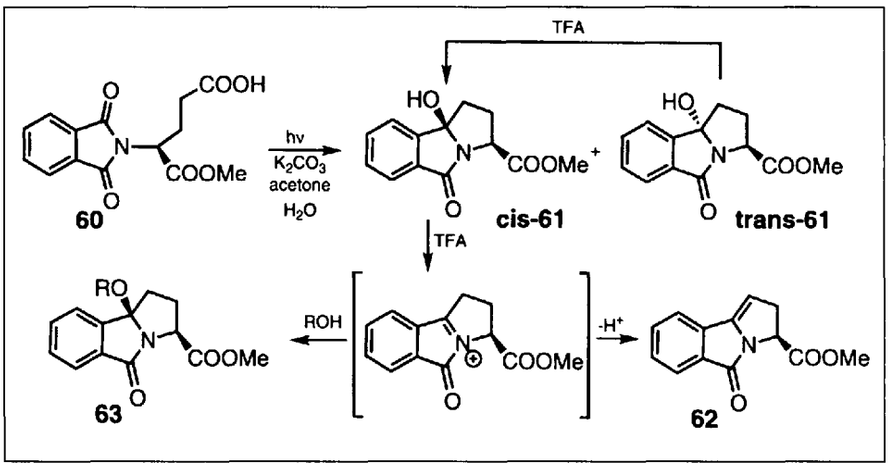
Apparently, there is a substantial difference between α- and ω-decarboxylation with respect to spin selectivity and the secondary processes. The α-decarboxylation of *N*-phthaloylamino acids occurs efficiently under a variety of conditions (*vide supra*), whereas ω-decarboxylation was never observed in the aspartic or glutamic cases. The 'remote' carboxy group could be activated by transformation into the corresponding potassium salts [16][17]. Two illustrative examples for the effect of deprotonation were the *N*-phthaloyl derivatives of glutamic acid (**52**) and lysine (**55**) [18]. The first substrate, when irradiated under salt conditions (excess K_2CO_3 in an acetone/water mixture), was rapidly converted into the γ-aminobutyric-acid derivative **53**. The subsequent cyclization step to give the benzopyrrolizidinone **54** was *ca.* 10 times slower. This ratio of >10:1 for α- *vs.* ω-decarboxylation was also observed for the *bis*-phthaloyl-lysine derivative **55**. In this case, only the 1,5-diaminopentane derivative **56** was formed indicating that the quantum yields for α- *vs.* ε-decarboxylation differ by at least a factor of 5 (assuming identical probability for excitation of each of the chromophoric groups). When the mixed protected lysine **57** was irradiated, clean formation of an 1:1 mixture of the two diastereoisomeric products **58** was observed (*Scheme 24*).

When trying to crystallize one of the stereoisomers, we received the dehydration product **59**. We could show independently that this acid-catalyzed reaction proceeds with remarkable ease and efficiency with both stereoisomers. The low diastereoselectivity observed in the reaction of the lysine derivative **57** was also apparent in the photocyclization of the glutamic-acid derivative **60**. In this case, an 1:1 mixture of *cis*- and *trans*-**61** resulted after relatively short irradiation time. When directly using the potassium salt of **60**, no trace of the simple decarboxylation prod-

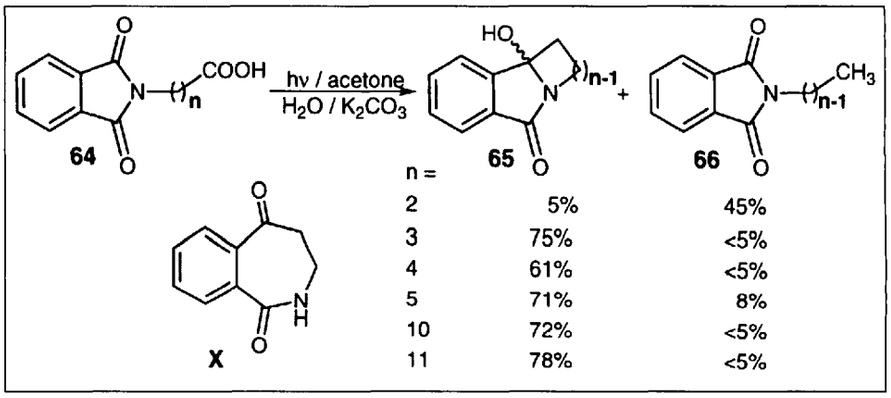
uct was observed after quantitative conversion in an 1:1 acetone/water mixture. The two diastereoisomeric benzopyrrolizidinones were easily distinguishable by ^{1}H-NMR: both $^3J_{HH}$ couplings to H_α were 8.5 Hz in the *cis*-isomer, whereas one $^3J_{HH}$ coupling was no longer detectable in the *trans*-isomer. Treatment of this 1:1 product mixture with catalytic amounts of trifluoroacetic acid (TFA) led to near quantitative epimerization of *trans*-**61** into the *cis*-diastereoisomer. By this method, we were able to isolate diastereomerically pure *cis*-**61** which was also identified by X-ray structure analysis (*Scheme 25*).

Epimerization at the stereogenic center of hydroxy lactames resulting in an 1:1 equilibrium has already been reported by us for the product of the *N*-phthaloylvaline-ester photolysis [7]. In the glutamic-acid case reported herein, however, the epimerization equilibrium is >9:1 in favor of *cis*-**61**. Further treatment of *cis*-**61** with TFA in an inert solvent led to the enamide **62**, whereas in the presence of alcohols the *cis*-alkoxy lactames **63** were formed in high (>95:5) diastereoselectivity. These reactions proceed *via* intermediary acyliminium cations which are known to be reactive with a multitude of nucleophiles. Benzopyrrolizidines of this type have also been synthesized using the azomethine-ylide route developed for *N*-(trialkylsilylmethyl)imides [19]. The low diastereoselectivity observed for the photocyclization of **60** is typical for an 1,5-triplet biradical combination (in contrast to 1,4-triplet biradical reactions). The corresponding *singlet* reactions which also led to the benzopyrrolizidine skeleton, *e.g.*, for the *N*-phthaloyl-*tert*-leucine substrate (**22**→ **23**), proceeded highly diastereoselective.

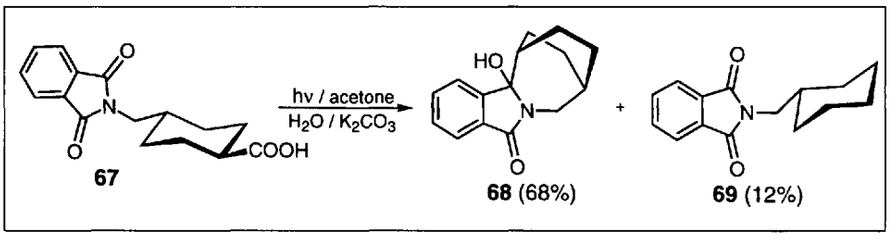
Scheme 25



Scheme 26



Scheme 27



4.2. *Applications: Synthesis of Macrocyclic Products*

The synthesis of macrocyclic ring systems *via* photoinduced electron-transfer cyclization is an attractive alternative to many ground-state reactions [20]. Dilution conditions could be avoided if there exist already strong donor-acceptor interactions in the ground state or the electron transfer occurs preferentially intramolecular (through-space- or through-bond-mediated). The reaction principle described in *Chapt 4.1* was highly promising in this context. In order to elaborate scope and limitations of this decarboxylative cyclization reaction, we focused on the synthesis of medium- and large-ring compounds testing a variety of ring sizes (from 4 to 26), spacer groups (alkyl chains, ester, ether, amide, amine linker), and polyheterocyclic target arrangements [18].

Firstly, alkyl chains were used to separate the phthalimide and the carboxylate part. There was no trace of a cyclization product when *N*-phthaloylglycine was irradiated under standard conditions, only *N*-methylphthalimide was formed. The homologous substrate, 3-phthalimidobutyric acid **64** ($n = 2$), did already give 10% of the benzazepine-1,5-dione **X**, a secondary product of the primarily formed cyclobutane **65** ($n = 2$) (*Scheme 26*).

Substrates with longer alkylchains did result in the formation of the corresponding annulation products **65** in yields not lower than 61%. In all cases, also small amounts (*ca.* 5–10%) of the 'simple' decarboxylation products **66** were detected. Only the starting material with a *trans*-1,4-cyclohexane spacer (**67**) did show a slightly higher degree of decarboxylation leading to the monosubstituted cyclohexane **69**. But also in this case, the cyclization product **68** was formed in good yield (*Scheme 27*). The latter example already indicated that a decrease in conformational flexibility of the connecting hydrocarbon chain is not crucial for the efficiency of the ring formation. Furthermore, the conversion of **67** into **68** showed that also α-branched carboxylic acids can be used as substrates in the title reaction. All medium- and large-ring hydroxy lactames could be easiliy crystallized from acetone, and the X-ray structures were determined for a series of macrocycles. No dimeric products could be detected through NMR or MS analysis, nor '*Kolbe* dimers' neither cross-cyclization products.

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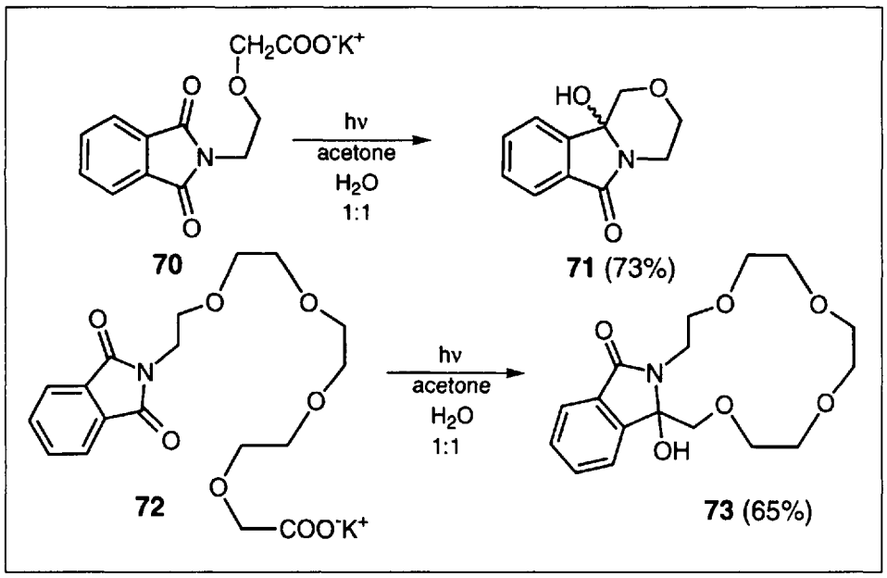
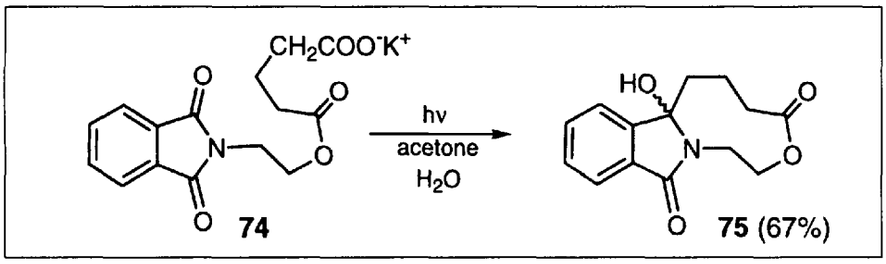
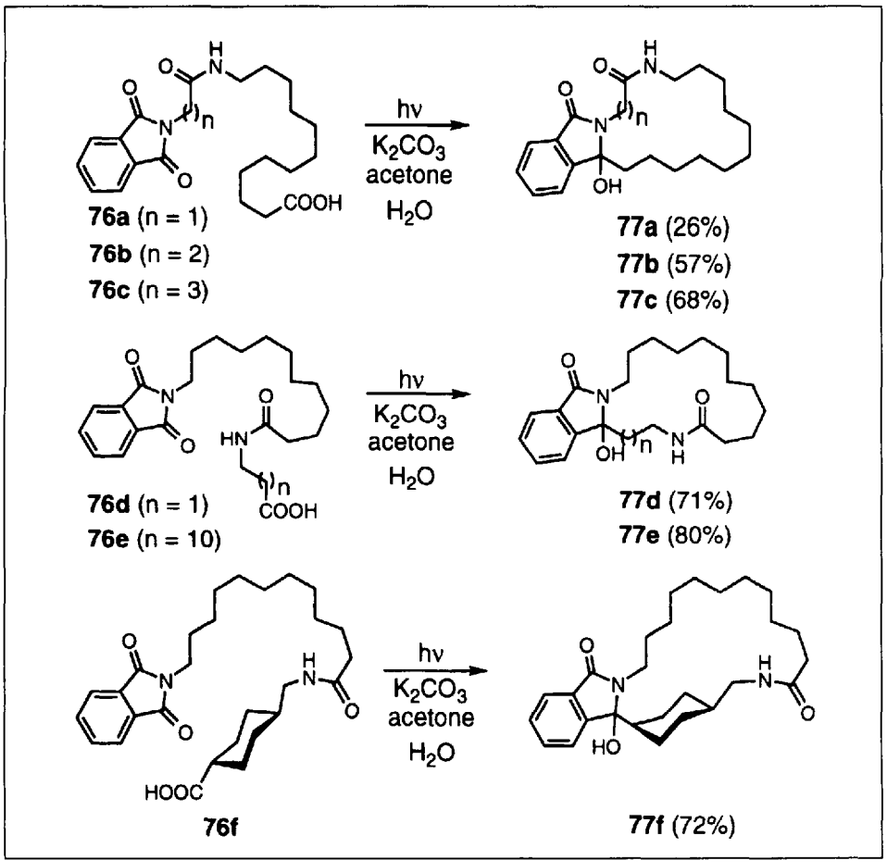
Scheme 28



Scheme 29



Scheme 30



In order to elaborate this photocyclization methodology further, we investigated other spacers connecting the electron-donating carboxylate and the electron-accepting phthalimide groups. The use of ether linkages was tested for substrate **70** and the crown-ether precursor **72**. In both examples, the α-hydroxyacetic-acid moiety serves as the terminal building block.

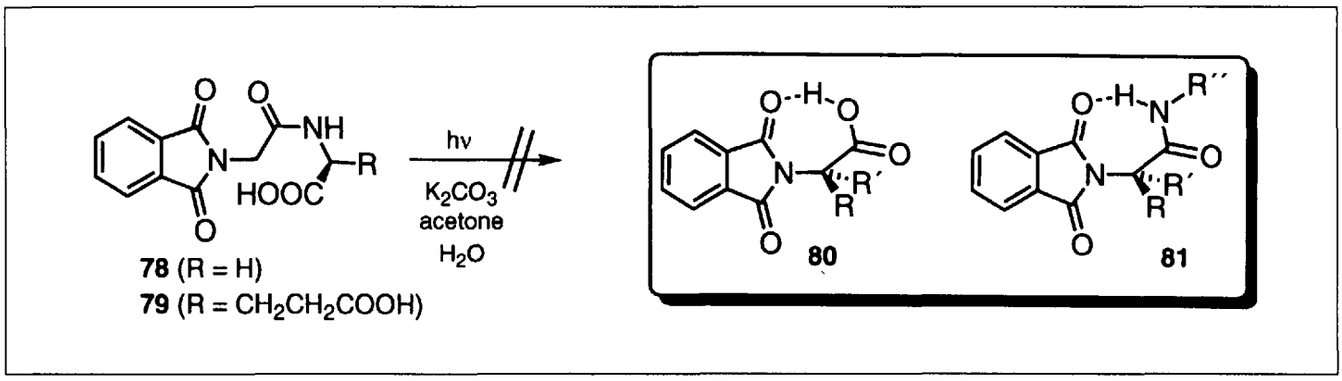
Alternatively, the α-trimethylsilylmethoxy substituent has been developed by *Yoon* and *Mariano* as a versatile electron-donor group, which after oxidation *via* PET and desilyation is converted into an α-oxo-stabilized carbon radical [21]. Thus, the intermediate biradicals are identical in both approaches, however, the PET-decarboxylation route is not limited to substrates with terminal alkyl groups substituted by an electron donor at the α-position. The photocyclization products **71** and **73** were formed in high yields (73%, 65% after recrystallization) and essentially without by-products [18][22] (*Scheme 28*).

Medium- and large-ring lactones (macrolides) also constitute an interesting class of compounds which should be accessible by our method. The glutaric acid-derivative **74** could be successfully applied and the nine-membered azalactone **75** was formed in 67% yield and characterized by an X-ray structure analysis (*Scheme 29*).

Another highly important class of macrocyclic compounds are cyclic oligopeptides. In order to optimize the procedure for preparation of these targets, we investigated six substrates **76a–f** with different spacer pattern [18][23]. The *N*-terminal spacer groups used in compounds **76a–c** were glycine, β-alanine, and γ-aminobutyric acid. Similar as already described for the methylene-linked ester **72b**, the glycine derivative **76a** gave mainly reductive decarboxylation and only 26% of cyclization product **77a**. A functional group which is linked in close proximity to the phthalimide chromophore seems to reduce the cyclization capacity of the (1,*n*)-biradical formed after PET decarboxylation. When using the 'more flexible' substrates **76b** and **76c**, the yields for the macrocycles **77b** and **77c** became acceptable (57% and 68%) (*Scheme 30*).

Increasing the chain length of the N-terminal spacer to C_{11} additionally leads to an increase in cyclization efficiency as was shown for the two examples **76d** and **76e**. It is remarkable that the substrate with the longest and most flexible spacer between donor and acceptor gave the highest yield of cyclization product (**77e**, 80%). Even the *trans*-1,4-cyclohexane-linked dipeptide **76f** gave the macrocycle **77f** in

Scheme 31



excellent yields (comparable with the directly connected donor-acceptor pair **67**). It was this series of experiments in combination with the results obtained for the variation of the countercation (*vide supra*) which led to the idea of a ground-state intramolecular stabilization, similar to template effects in other macrocyclization reactions. An alternative concept involves a long-lived excited phthalimide triplet, however, does not explain the high tendency for intramolecular reaction with essentially no intermolecular electron-transfer competition. Another hint for the role of ground-state stabilization came from the fact, that the 'real' dipeptides **78** (Pht = Gly-Gly) and **79** (Pht = Gly-Glu) were unreactive under the given reaction conditions, *i.e.*, did *neither* give cyclization *nor* reductive decarboxylation. It is highly probable that the same effect which makes the α-decarboxylation exceedingly effective (**80**) also deactivates the glycine-linked dipeptides (**81**) (*Scheme 31*).

5. Conclusion and Perspectives

For a confirmed photochemist it is a banality to describe the two lowest excited singlet and triplet states as 'electronic isomers' of the ground state. These 'isomers' exhibit, nearly always, distinct differences in reactivity, chemo-, regio-, and stereoselectivity. It might be, however, worthwhile to recall these properties when developing new applications for synthetic organic chemistry. In the last six years, we have developed a number of useful transformations in the phthalimide series. These transformations allow to synthesize photochemically elimination, ring-expansion, cyclization, cycloaddition as well as fragmentation products. Spin selectivity is pronounced for many reactions, *i.e.*, singlet states preferentially gave (highly stereoselective) products deriving from homolytic CH activation, whereas triplets preferentially gave PET-initiated products. Tuning the electronic properties of these 'electronic isomers' allows to improve efficiency and selectivity which will lead to more effective photochemical processes in the future. Interesting heterocyclic target families, we are currently concentrating on chiral mitosene derivatives, pyrrolizindines, benzazepines, and pyrroloisoindolines.

I thank the *Grammaticakis-Neumann* prize committee for providing the opportunity to present our recent results at the 1997 meeting of the Swiss Society of Photochemistry and Photophysics in Lausanne.

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