Photochemistry Of *N*-Phthaloylcysteine Derivatives: Multiplicity-Directed Regioselective CH Activation

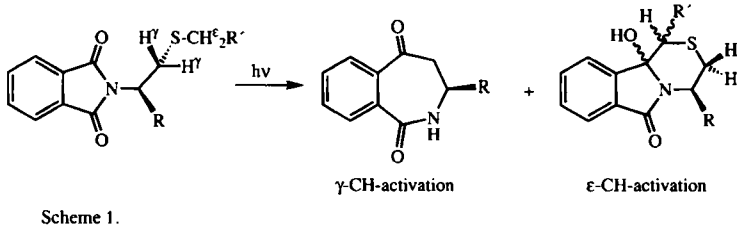
Axel G. Griesbeck,* Joachim Hirt, Karl Peters, Eva-Maria Peters, and Hans Georg von Schnering

Abstract: The photochemistry of the methyl esters of *N*-phthaloylcysteine derivatives **1b**–**5b** was studied. The results are remarkable, because they prove a pronounced, multiplicity-controlled regioselectivity of the initial CH activation step. From substrates **1b**–**4b** the benzazepine-1,5-dione **6** was produced exclusively by the singlet path. The formation of compound **6** is initiated by a γ-H abstraction; this was demonstrated by deuterium labeling experiments. The penicillamine derivative **5b** was unreactive in the singlet manifold. From substrates **1b**–**3b** and **5b** the thiazinoisoindoles **7**–**9** and **11** were produced exclusively by the triplet path. The sterically hindered *S*-isopropylcysteine derivative **4b** also furnished this product type (**10**) as a proportion of the products in the singlet manifold. These annulation products result from a primary photoinduced electron-transfer (PET) step followed by heterolytic ε-H activation. The mechanistic scenario was elucidated by quenching and sensitization experiments. An interplay of CH activation steps and electron back-transfer is probably responsible for this type of spin selectivity.

Keywords
amino acids · C–H activation · electron transfer · photochemistry · state selectivity

Introduction

The concept of "remote photocyclization" has been applied to spacer-linked donor–acceptor couples of the phthalimide (acceptor)–heteroatom donor (O, N, S) type by Kanaoka and coworkers.[1] The key step in these reactions is an electron transfer from the side-chain localized heteroatom to the electronically excited phthalimide chromophore (photoinduced electron transfer, PET[2]). The primary intermediate is a spacer-linked radical ion pair, which is highly acidic at the α-position of the radical cation site and transfers a proton to the ketyl radical anion or to the solvent. The resulting (1,*n*) biradical can combine to give medium to large heterocyclic ring systems in good yields. We have developed other variants of this concept using electron-rich arenes[3] or carboxylates[4] as electron donors in intramolecular PET reactions with concomitant C–C-bond formation. So far only one investigation of the spin selectivity of this type of PET cyclization reactions has been carried out: methionine derivatives show spin-selective cyclization, that is, the triplet excited substrates lead to photoproducts, whereas no reaction occurs from the singlet state.[5] Our observations concerning the conformational situation and the state selectivity of the photochemistry of enantiomerically pure *N*-phthaloyl α-amino acid derivatives[6] have prompted us to examine a series of *N*-phthaloylcysteine derivatives. In contrast to the methionine case, these compounds are capable of γ- and ε-H activation.[7, 8] The products of these two regioisomeric CH activation paths are the benzazepine-1,5-diones and the thiazinoisoindoles, respectively (Scheme 1).



Scheme 1.

Results

As substrates we used the C-protected *S*-methyl, *S*-benzyl, *S*-methoxycarbonylmethyl, and *S*-isopropylcysteine derivatives **1b**–**4b**. In order to study the effect of chemically blocking the γ-CH position we also investigated the photochemistry of the (racemic) penicillamine derivative **5b**. The starting materials were synthesized from the corresponding thiols by *S*-alkylation and transformation into the phthalimides by procedures published by Kidd[9] and Nefkens.[10] The free acids **1a**–**5a**[11] were subsequently transformed into the methyl esters **1b**–**5b** by standard procedures. All starting materials **1b**–**5b** have second ($n\pi^*$) UV absorption maxima of $\lambda = 294(\pm 1)$ nm with extinction coefficients of $\varepsilon = 1850\ (\pm 100)$.

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In order to differentiate between singlet and triplet reactivity, irradiations were performed under direct excitation (in acetonitrile), solvent sensitization (in acetone), triplet sensitization (in acetonitrile/benzophenone), and triplet quenching (in acetonitrile/piperylene) conditions. Furthermore, methanol was used as solvent in order to compare the results in aprotic polar media with protic polar conditions. The results are summarized in Table 1.

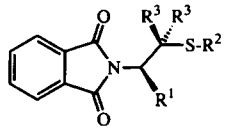
Table 1. Photolysis of cysteine derivatives **1b–5b** [a].

Substrate	Solvent	Conversion [b]	**6**	Annulation products
1b ($R^2 = CH_3$, $R^3 = H$)				
1	CH_3CN	62	26	74 **7** (59:41)
2	Acetone	100	–	>95 **7** (60:40)
3	CH_3CN/BP [c]	100	–	>95 **7** (60:40)
4	CH_3CN/P [d]	21	>95	<5
5	CH_3OH	14	69	31 **7** (65:35)
6	CH_3OH/BP	22	–	>95 **7** (81:19)
2b ($R^2 = CH_2Ph$, $R^3 = H$)				
7	CH_3CN	47	43	31 **8** (4 diast.) [e]/26 **13**
8	Acetone	94	–	48 **8** (82:18)/52 **13**
9	CH_3CN/BP [c]	100	13	40 **8** (90:10)/47 **13**
10	CH_3CN/P [d]	16	>95	<5
11	CH_3OH	35	36	64 **13**
3b ($R^2 = CH_2COOCH_3$, $R^3 = H$)				
12	CH_3CN	60	39	61 **9** (23:5:49:23)
13	Acetone	100	–	>95 **9** (53:10:13:24)
14	CH_3CN/BP [c]	100	21	79 **9** (32:6:38:24)
15	CH_3CN/P [d]	25	>95	<5
16	CH_3OH	71	9	91 **9** (32:4:35:29)
4b ($R^2 = CH(CH_3)_2$, $R^3 = H$)				
17	CH_3CN	24	65	35 **10** (75:25)
18	Acetone	61	32	68 **10** (73:27)
19	CH_3CN/BP [c,f]	50	14	86 **10** (75:25)
20	CH_3CN/BP/364 [g]	92	16	84 **10** (76:24)
21	CH_3CN/P [d]	22	>95	<5
22	CH_3OH	25	54	46 **10** (75:25)
5b ($R^2 = CH_3$, $R^3 = CH_3$)				
23	CH_3CN	24	–	>95 **11** (87:13)
24	Acetone	100	–	>95 **11** (84:16)
25	CH_3CN/BP [c]	100	–	>95 **15**
26	CH_3CN/P [d]	<5	–	–
27	CH_3OH	<5	–	–

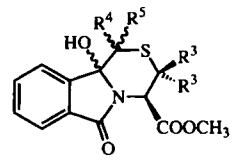
[a] 4.7–11.7 mM solutions of substrates **1b–5b**, Rayonet photochemical reactor, 3000 Å lamps, $T = 23$ °C, N_2, irradiation time: 24 h. [b] By ^{1}H NMR analysis (250 MHz) of the crude product mixtures and comparison with significant signals from the purified products. [c] 10.1 mM solution of benzophenone in acetonitrile. [d] 50–100 mM solution of piperylene in acetonitrile. [e] Diastereoisomeric ratio not determinable by ^{1}H NMR analysis. [f] Rayonet photochemical reactor, 3500 Å lamps. [g] Argon ion laser, $\lambda = 364$ nm, irradiation time: 2 h, 12.0 mM benzophenone.

Three types of products could be detected in these experiments: the benzazepine-1,5-dione **6**, the annulation products **7–11**, and the corresponding dehydrated compounds **13** and **15**. The formation of the olefins **13** and **15** during irradiations (see especially entries 11 and 25) is probably due to autocatalytic processes initiated by the radical cations generated during the reaction or by thermal activation. These products and the alkenes **12** and **14** could be obtained independently from **7–11** by treatment with catalytic amounts of trifluoroacetic acid.

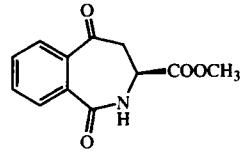
Direct excitation: The reactions in acetonitrile (entries 1, 7, 12, 17) led to complex product mixtures. The annulation products were the major products formed from substrates **1b–3b**, and



1 $R^2 = CH_3$, $R^3 = H$
2 $R^2 = CH_2Ph$, $R^3 = H$
3 $R^2 = CH_2R^1$, $R^3 = H$
4 $R^2 = CH(CH_3)_2$, $R^3 = H$
5 $R^2 = CH_3$, $R^3 = CH_3$
a: $R^1 = COOH$,
b: $R^1 = COOCH_3$.



7 $R^{4,5} = H$, $R^3 = H$
8 $R^4 = Ph$, $R^5 = H$, $R^3 = H$
9 $R^4 = COOCH_3$, $R^5 = H$, $R^3 = H$
10 $R^{4,5} = CH_3$, $R^3 = H$
11 $R^{4,5} = H$, $R^3 = CH_3$.



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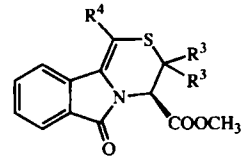


12 $R^4 = H$, $R^3 = H$
13 $R^4 = Ph$, $R^3 = H$
14 $R^4 = COOCH_3$, $R^3 = H$
15 $R^4 = H$, $R^3 = CH_3$.

the benzazepine-1,5-dione **6** dominated in the case of substrate **4b**. In the case of the penicillamine derivative **5b**, the thiazinoisoindole **11** was the sole product detected in the reaction mixture. The conversion was incomplete in all experiments and remarkably low for the sterically hindered *S*-isopropyl compound **4b** and the penicillamine **5b**. The annulation products **7–11** were formed as mixtures of diastereoisomers. Except for **8**, the diastereoisomeric ratios could be determined from characteristic signals in the ^{1}H NMR spectra (vide infra). That four isomers of **8** were formed in the direct photolysis of **2b** (entry 7) was indicated by four sets of signals in the corresponding ^{13}C NMR spectrum.

Triplet sensitization: When the experiments were conducted under solvent-sensitization conditions (entries 2, 8, 13, 18, 24), the product mixtures were simpler for substrates **1b–3b**. In these cases, only the annulation products **7–9** were formed. Again, for the *S*-benzyl derivative **2b**, a partial conversion of **8** into the dehydrated product **13** was detected. The conversion was near 100% for all photolyses. Only the *S*-isopropyl derivative **4b** showed a lower degree of conversion (entry 18). The same effect as sensitization by the solvent acetone was achieved by the use of benzophenone as triplet sensitizer in acetonitrile. The formation of the benzazepine-1,5-dione **6** by **2b** and **3b** could not be completely suppressed (entries 9, 14). The *S*-isopropyl substrate **4b** behaved differently and showed an increase in selectivity from 32:68 (in acetone) to 14:86 (in acetonitrile/benzophenone) in favor of the annulation products (entries 18 and 19). In order to check if the latter ratio, which derives from irradiation at 350 nm, is the limiting number for the pure triplet-sensitization pathway for substrate **4b**, we conducted this photolysis at $\lambda = 364$ nm with an argon ion laser (entry 20). In this case benzophenone is excited exclusively and therefore the singlet path for **4b** is completely suppressed. Comparison of the results of entries 19 and 20 reveal that both product compositions derive exclusively from the triplet excited phthalimide. In the error limits the diastereoisomeric ratios for the annulation products **7–11** were not dependent on the activation mode. Only for substrate **3b** was the ratio of the stereoisomeric prod-

ucts **9** slightly different when produced in acetone (entry 13) compared with the other experiments.

Triplet quenching: The triplet reactivity of electronically excited phthalimides **1b–5b** could be completely suppressed by performing the photolyses in the presence of piperylene as triplet quencher. The penicillamine derivative **5b**, which has no abstractable γ-CH position, was unreactive under these conditions. All other substrates **1b–4b** gave solely the benzazepine-1,5-dione **6** as product. Due to complete triplet deactivation, a decrease in conversion is detected in all quenching experiments (entries 4, 10, 15, 21).

Relative configuration of the annulation products 7–11: All annulation products were purified by column chromatography and completely characterized. The assignment of the relative configuration of thiazinoisoindoles **7–11** is based on the X-ray structure of the major diastereoisomer **11** from the photolysis of the penicillamine derivative **5b**.[12] This compound was isolated in diastereoisomerically pure form in 52% yield from photolysis of **5b** in acetone after two recrystallizations (entry 24).

The significant signals in the ^{1}H NMR spectra of *cis*- and *trans*-**11** come from the hydrogens (H_α) at the stereogenic, ester-substituted center. A strong deshielding effect is observed for H_α for all *cis*-diastereoisomers. In Table 2 the shift and coupling

Table 2. Characteristic ^{1}H NMR data (H_α) of thiazinoisoindoles **7–11** and thioenolethers **12–15** [a].

		7	**8**	**9**	**10**	**11**
trans	δ	4.52	4.67	4.49–4.82	4.32	4.38
	^3J	3.1/8.2	3.4/6.6	2.6/11.8–3.0/6.0	3.0/11.6	
cis	δ	5.44	5.54	5.45–5.58	5.45	5.16
	^3J	2.0/4.8	2.1/5.5	2.4/4.8–2.0/5.0	2.1/4.9	
trans:*cis* [b]		40:60	90:10	38:62	75:25	84:16 [c]

		12	**13**	**14**	**15**
	δ	5.51	5.63	5.60	4.97
	^3J	3.1/3.6	3.3/3.3	3.1/3.5	–

[a] 250 MHz, $CDCl_3$, J in Hz. [b] Photolysis in acetonitrile/benzophenone. [c] Photolysis in acetone (entry 24).

data for these hydrogens are summarized. Except for the *S*-methyl case (product **7**), the *trans*-diastereoisomers are the major products from the triplet photoreactions.

An additional supporting argument for the relative configuration of compounds **7–11** comes from the comparison with the chemical shifts of H_α in the unsaturated compounds **12–15**. A 1,3-diaxial interaction between H_α and the hydroxy group in **7–11** does not exist in the *cis*-diastereomers. Therefore, these hydrogens are expected to have chemical shifts similar to those in the alkenes **12–15**. Additionally, the coupling constants $^3J_{HH}$ (Table 2) correlate nicely with the assumption of a preferred chair-like conformation (see Fig. 1), with the methoxycarbonyl substituent in an equatorial position. For the products **8** and **9** an additional stereogenic center is formed during the radical combination step. For the *S*-benzyl derivative **8** we could only isolate two diastereoisomers. From the ^{1}H NMR data we assign the relative configurations shown in Scheme 2 to the major and minor diastereoisomers of **8**. The similarity in the chemical shifts of the benzylic hydrogens as well as the existence of W-coupling ($^4J_{HH}$ = 1.2 Hz) in both cases led to this assignment.

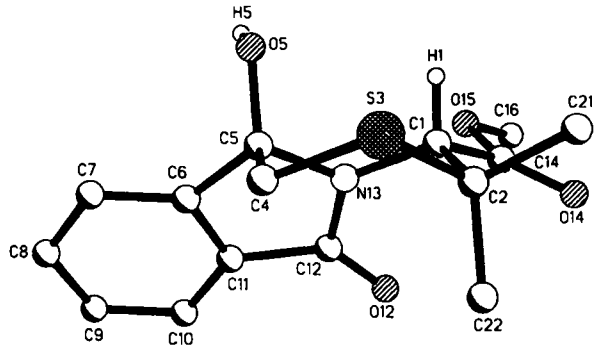
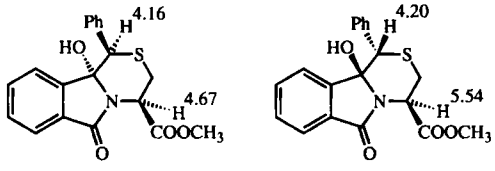


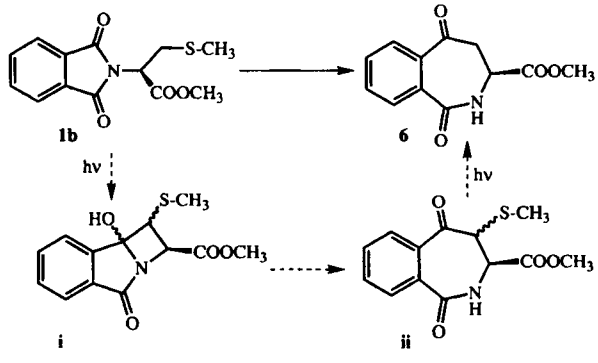
Fig. 1. Structure of *trans*-**11** in the crystal.



Scheme 2.

We were not able to determine the relative configuration of all four stereoisomers of **9** formed in the photocyclization of the *S*-methoxycarbonylmethyl derivative **3b**. From the chemical shifts of the H_α protons, we assume that the major products have *trans*-configuration with respect to the hydroxy and methoxycarbonyl groups.

Mechanism of formation of the benzazepine-1,5-dione 6: Prior to this investigation it was assumed[13,14] that the formation of benzazepine-1,5-diones such as **6** proceeds by a photochemical two-step reaction, which is initiated by a γ-CH abstraction (depicted in Scheme 3 for **1b** as substrate). We could, however,



Scheme 3.

never detect an intermediary azetidine **i** or the corresponding ring-opened alkylthio-substituted benzazepine-1,5-dione **ii**. For the analogous 1,2:4,5-benzene biscarboximides, the second Norrish II reaction was reported to be sufficiently slow to allow detection of the intermediate.[13] This approach, however, was not successful for phthalimides.[14] In order to prove the proposed reaction sequence, we conducted the photolysis with the deuterium-labeled **1b-D$_3$**[15] in methanol and [D_4]methanol, respectively (Scheme 4). The product composition from both experiments matched the result from entry 5 within a deviation of ±6%. In methanol, no deuterium atoms were incorporated into the benzazepine ring system. When, however, deuterated

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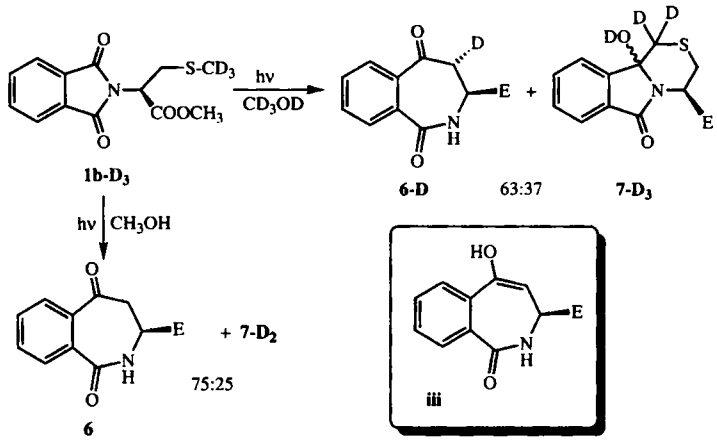


Scheme 4.

methanol was used as solvent, the bisdeuterated **6-D$_2$** was observed with a relative yield of 63% after 40% conversion. From the coupling constants of the remaining AM spin system ($^3J_{HH}$ = 11.2 Hz), it became clear that the *trans*-diastereoisomer was formed with a selectivity > 90%. These results clearly prove the existence of the intermediary enol **iii**, which could only be formed by the reaction sequence depicted in Scheme 3. The second Norrish II reaction followed by C–S cleavage must therefore proceed with much higher quantum yield than the primary Norrish II step. The formation of thioaldehydes from Norrish II cleavage of α-alkylthio ketones has been well studied,[16] and the thioaldehydes trapped by several reagents.[17]

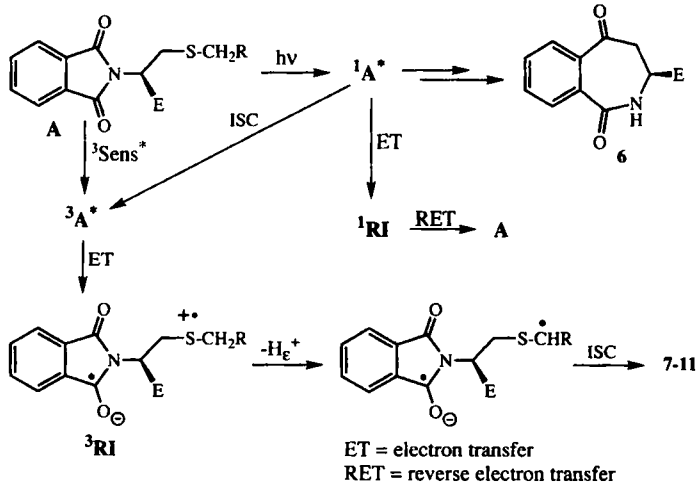
There was no deuterium effect on the diastereoselectivity of the thiazinoisoindole formation: a *trans*:*cis* ratio of 40:60 was detected for **7-D$_3$**, identical to the diastereoisomeric ratio of **7** from the nonlabeled substrate **1b** in methanol (see Table 2).

Discussion

The activation of a remote position in an electronically excited molecule can be attributed to special conformational effects (in these cases the remote position approaches the chromogenic part of the molecule and interacts in the ground state, for example, by charge-transfer interaction or by metal-mediated chelation) or to long-range transfer of energy or electrons. The macrocyclization developed for phthalimide chromophores and heteroatom donors by Kanaoka et al.[1] is initiated by a photoinduced electron-transfer (PET) step. No spectral evidence for charge-transfer interactions has been reported for these examples. For PET reactions of phthalimido alkylcarboxylates, chelation effects have been postulated to be crucial for the rate of cyclization.[4] For the cysteine derivatives which are discussed in the present report, both PET and CH-bond homolysis steps can be postulated as the primary reaction processes. The distance between the sulfur atom and the proximate carbonyl oxygen 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. From an energetic point of view, both singlet and triplet excited states are capable of exergonic intramolecular electron transfer. With the redox potentials for the model substrates dimethylsulfide (+1.21 V vs. SCE[18]) and *N*-methylphthalimide (−1.37 V vs. SCE[19]) and the singlet/triplet energies of *N*-methylphthalimide (3.8 eV and 3.1 eV[20]), free energies for the electron transfer are −1.2 eV (27.6 kcal mol^{-1}) for the first excited singlet state and −0.5 eV (11.9 kcal mol^{-1}) for the first excited triplet state, respectively.[21] We measured the redox potentials for the *S*-methylcysteine derivative **1b** and found values for E_{red} of −1.40 (peak potential) and for E_{ox} of ca. 1.60 V (irreversible). From these values, ΔG°_{ET} is −0.8 eV for the singlet and −0.2 eV for the triplet process.

Analogous PET reactions for γ-alkylthioketones have been studied in detail by Wagner and Lindstrom.[16] They used acetophenone derivatives in order to completely circumvent the singlet channel. For substrates comparable to ours, a ratio of PET reaction to homolytic γ-CH activation of about three was reported. In the case of the cysteine derivatives **1b**, **2b**, and **3b** this ratio must be greater than twenty: both the experiments with acetone and benzophenone (E_T = 69 kcal mol^{-1}[22]) as triplet sensitizers led to this conclusion. Less than 5% benzazepine-1,5-dione **6** 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 owing to direct excitation of the phthalimide chromophore. The photolysis of **4b** by irradiation at 364 nm (entry 20) indicated that in this special case the γ-CH position is also active in the triplet photochemistry. We ascribe this phenomenon to the pronounced steric shielding of the ε-CH position.

In the presence of piperylene (E_T = 59.2 kcal mol^{-1}[23]), the triplet states of **1b–5b** should be completely quenched. These experiments (entries 4, 10, 15, 21 in Table 1) clearly show that the benzazepine-1,5-dione **6** is preferentially formed by the singlet pathway, and that the isoindoles **7–11** are formed *exclusively* by the triplet pathway (Scheme 5). Experiment 26 is in accord with this interpretation: no trace of the annulation product **11** was detected when the triplet reactivity was suppressed.



Scheme 5. E = COOMe.

Apparently, the (triplet) radical ions **^{3}RI** formed after intramolecular electron transfer from **^{3}A*** are selectively deprotonated at the (kinetically more acidic) ε-CH position. The resulting 1,6-biradicals combine to the isoindoles **7–11** after spin inversion.

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 in the direct irradiations 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[24]) from the singlet radical ions ^{1}**RI** to restore the ground states. Firstly, this process is highly exergonic ($\Delta G^\circ_{ET} \approx -2.6$ to -3.0 eV); secondly, no spin barrier exists for the reaction.[25] The formation of the precursor to the benzazepine-1,5-dione **6** is therefore assumed to result from homolytic CH abstraction from the geometrically preferred γ-position and not from a PET process. In the case of the triplet radical ion pairs, spin inversion must precede the reverse electron-transfer process.[25] Therefore, an efficient competition between this deactivation process and the heterolysis of the ε-CH bond exists.

Conclusion

A pronounced spin correlation effect that controls the regioselectivity of CH activation was observed. The cysteine derivatives are ideal substrates for the study of these effects because they show clean photoreactions without any side products in most solvents studied so far. We are currently undertaking experiments to elucidate a) the nature and lifetime of the radical-ion intermediates, and b) conformational effects on the multiplicity-directed regioselectivity of the CH-activation using more constrained substrates.

Experimental Section

General: ^{1}H NMR: Bruker AC200 (200 MHz), AC250 (250 MHz), AC300 (300 MHz). ^{13}C NMR: Bruker AC200 (50.3 MHz), AC250 (63.4 MHz); carbon multiplicities were determined by DEPT. UV/Vis: Hitachi U-3200. Column chromatography: silica gel (Merck) 60–230 mesh; petroleum ether (PE, 40–60 °C), ethyl acetate (EA). Optical rotations: Perkin-Elmer 241 MC polarimeter. All melting points were determined with a Büchi melting point apparatus (type 535) and are uncorrected. Combustion analyses: Institut für Anorganische Chemie der Universität Würzburg and Institut für Anorganische Chemie der Universität zu Köln. Rayonet chamber photoreactors RPR-208 (8×3000 Å lamps, ca. 800 W, $\lambda = 300 \pm 10$ nm) and RPR-100 (16×3500 Å lamps, ca. 400 W, $\lambda = 350 \pm 20$ nm) and immersion-well reactors ($\lambda > 280$ nm) were used for irradiations. For experiment 20 the 364 nm line of an INNOVA 100 argon-ion laser (W. Adam laser group, University of Würzburg) was used.

General procedure for the synthesis of (*R*)-*N*-phthaloyl α-amino acids:
Procedure A: Phthalic anhydride (0.01 mol) was heated in a stoppered flask to 140–145 °C. The appropriate amino acid (0.01 mol) was added over 5 min with vigorous stirring. This mixture was kept at 140 °C for about 10 min. In the last 5 min the flask was left open in order to evaporate the condensate. After cooling, the crystalline residue was used for esterification without further purification.

Procedure B: Phthalic anhydride (0.01 mol) and the corresponding amino acid (0.01 mol) were suspended in 1 mL of water. This mixture was placed in a commercial microwave oven (800 W) for 2 min until the water was evaporated. The oily residue which crystallized on standing in the refrigerator was used for esterification without further purification.

General procedure for the synthesis of (*R*)-*N*-phthaloyl α-amino acid methyl esters (*Procedure C*): A stream of gaseous HCl was bubbled through a precooled (0 °C) solution of (*R*)-*N*-phthaloyl amino acid (0.01 mol) in methanol (50 mL) for 2 min. After cooling back to 0 °C the solution was again saturated with gaseous HCl for 2 min and stirred for complete conversion (12 h); the excess methanol was then removed at reduced pressure. Product formation was monitored by TLC. The oily colorless residue was dried at reduced pressure and crystallized.

(*R*)-*N*-Phthaloyl-*S*-methylcysteine (1a): (*R*)-*S*-methylcysteine (5.00 g, 37.0 mmol) and phthalic anhydride (5.48 g, 37.0 mmol) were condensed following procedure B. After crystallization from MeOH/H_2O, **1a** (8.02 g, 81%) was isolated as beige needles. M.p. 185–186 °C (185–186 °C [26]); IR (Nujol): $\tilde{\nu}$ = 3150 (br m), 2880 (w), 1765 (m), 1745 (s), 1690 (s), 1170 (m), 925 (m), 840 (s), 740 (m), 720 (s) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 293.5 (1778), 219.3 (37746) nm; ^{1}H NMR (250 MHz, [D$_6$]acetone): δ = 2.10 (s, 3H, CH_3), 3.30 (m, 2H, CH_2S), 5.10 (dd, J = 6.9, 9.2 Hz, 1H, NCH), 7.91 (m, 4H, Ar-H); ^{13}C NMR (63 MHz, [D$_6$]acetone): δ = 14.9 (q), 33.4 (t), 51.1 (d), 124.2 (d, 2C), 132.5 (s, 2C), 135.5 (d, 2C), 168.1 (s, 2C), 169.8 (s).

(*R*)-*N*-Phthaloyl-*S*-methylcysteine methyl ester (1b): Compound **1b** (1.15 g, 95%) was prepared from (*R*)-*N*-phthaloyl-*S*-methylcysteine (1.15 g **1a**, 4.33 mmol) according to procedure C. M.p. 107 °C; IR (CCl_4): $\tilde{\nu}$ = 3020 (w), 2940 (w), 2900 (w), 1735 (vs), 1705 (vs), 1425 (m), 1380 (vs), 1095 (s), 1015 (s), 910 (m) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 295.4 (1863), 239.8 (11925), 218.6 (46548) nm; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.10 (s, 3H, CH_3), 3.31 (d, J = 6.1 Hz, 1H, CH_2S), 3.34 (d, J = 9.9 Hz, 1H, CH_2S), 3.75 (s, 3H, OCH_3), 5.03 (dd, J = 6.9, 9.8 Hz, 1H, NCH), 7.74 (m, 2H, Ar-H), 7.87 (m, 2H, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.2 (q), 33.1 (t), 50.5 (d), 53.0 (q), 123.6 (d, 2C), 131.7 (s, 2C), 134.2 (d, 2C), 167.4 (s, 2C), 168.8 (s); $C_{13}H_{13}NO_4S$ (279.31): calcd. C 55.96, H 4.69, N 5.01, S 11.48; found C 55.65, H 4.65, N 4.95, S 11.43.

(*R*)-*N*-Phthaloyl-*S*-benzylcysteine (2a): The condensation of phthalic anhydride (1.91 g, 12.9 mmol) and (*R*)-*S*-benzylcysteine (2.73 g, 12.9 mmol) according to procedure A yielded **2a** (4.20 g, 95%) as a yellowish oil, which was used for esterification without further purification. UV (CH_3CN): λ_{max} (ε) = 293.8 (2004), 218.4 (48143) nm; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.24 (m, 2H, CH_2S), 3.74 (s, 2H, CH_2Ph), 4.99 (dd, J = 5.6, 9.5 Hz, 1H, NCH), 7.21 (m, 5H, Ar-H), 7.70 (m, 2H, Ar-H), 7.84 (m, 2H, Ar-H), 9.07 (br s, 1H, COOH); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 29.8 (t), 35.5 (t), 50.6 (d), 123.6 (d, 2C), 127.1 (d), 128.5 (d, 2C), 128.8 (d, 2C), 131.5 (s, 2C), 134.2 (d, 2C), 137.0 (s), 167.3 (s, 2C), 172.6 (s).

(*R*)-*N*-Phthaloyl-*S*-benzylcysteine methyl ester (2b): Compound **2a** (2.30 g, 6.74 mmol) was esterified in methanol (30 mL) according to procedure C. After evaporation of the solvent the crude product was crystallized from methanol/H_2O to yield **2b** (2.00 g, 84%) as colorless crystals. M.p. 68 °C (66 °C [27]); UV (CH_3CN): λ_{max} (ε) = 293.2 (1856), 216.4 (42471) nm; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.27 (d, J = 7.5 Hz, 1H, CH_2S-Benzyl), 3.28 (d, J = 8.5 Hz, 1H, CH_2S), 3.74 (s, 2H, CH_2Ph), 3.75 (s, 3H, OCH_3), 5.00 (dd, J = 7.5, 8.5 Hz, 1H, NCH), 7.26 (m, 5H, Ar-H), 7.77 (m, 2H, Ar-H), 7.90 (m, 2H, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 30.2 (t), 35.6 (t), 50.8 (d), 52.9 (q), 123.6 (d, 2C), 127.2 (d), 128.6 (d, 2C), 128.9 (d, 2C), 131.7 (s, 2C), 134.2 (d, 2C), 137.2 (s), 167.4 (s, 2C), 168.6 (s).

(*R*)-*N*-Phthaloyl-*S*-carboxymethylcysteine (3a): *N*-(Ethoxycarbonyl)phthalimide (12.28 g, 56.0 mmol) was added in one portion to a solution of (*R*)-*S*-carboxymethylcysteine (10.0 g, 56.0 mmol) and Na_2CO_3 (16.2 g, 56.0 mmol) in H_2O (100 mL). The mixture was stirred at room temperature overnight. The resulting clear solution was acidified (pH 2) with 2 N HCl and extracted with ethyl acetate (3×300 mL). The organic phase was washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated to yield **3a** (19.0 g, 99%) as a colorless oil, which was used for esterification without further purification. IR (CCl_4): $\tilde{\nu}$ = 3025 (m), 1775 (m), 1720 (vs), 1385 (vs), 1280 (m), 1080 (m), 910 (w), 730 (m) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 291.4 nm (1870), 218.2 (38617); ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 3.28 (d, J = 15.0 Hz, 1H, SCH_2), 3.40 (dd, J = 11.3, 14.7 Hz, 1H, CH_2S), 3.45 (d, J = 15.0 Hz, 1H, SCH_2), 3.63 (dd, J = 4.7, 14.3 Hz, 1H, CH_2S), 5.20 (dd, J = 4.7, 11.3 Hz, 1H, NCH), 7.93 (m, 4H, Ar-H); ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 31.6 (t), 32.9 (t), 51.2 (d), 124.2 (d, 2C), 131.8 (s, 2C), 135.6 (d, 2C), 168.1 (s), 169.5 (s, 2C), 171.1 (s, 2C).

(*R*)-*N*-Phthaloyl-*S*-methoxycarbonylmethylcysteine methyl ester (3b): Compound **3b** (colorless oil, 2.80 g, 60%) was prepared from **3a** (4.33 g, 14.0 mmol) according to procedure C. R_f = 0.26 (EA/PE 1:2) [28]; IR (CCl_4): $\tilde{\nu}$ = 2930 (m), 1760 (s), 1735 (vs), 1700 (vs), 1375 (vs), 1275 (s), 1235 (s), 1125 (m), 1090 (m), 1010 (m) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 293.9 nm (1697), 217.8 (36332); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.12 (d, J = 14.7 Hz, 1H, SCH_2), 3.35 (d, J = 14.7 Hz, 1H, SCH_2), 3.37 (dd, J = 11.1, 14.5 Hz, 1H, CH_2S), 3.54 (dd, J = 4.8, 14.5 Hz, 1H, CH_2S), 3.70 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 5.06 (dd, J = 4.8, 11.1 Hz, 1H, NCH), 7.74 (m, 2H, Ar-H), 7.83 (m, 2H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.1 (t), 32.4 (t), 50.3 (d), 52.4 (q), 52.9 (q), 123.6 (d, 2C), 131.5 (s, 2C), 134.2 (d, 2C), 167.3 (s), 168.3 (s), 170.1 (s, 2C).

(*R*)-*N*-Phthaloyl-*S*-isopropylcysteine (4a): (*R*)-*S*-Isopropylcysteine was prepared from L-cysteine (10.0 g, 0.08 mol) and isopropylbromide (21.0 g, 0.17 mol) in 2 N NaOH (100 mL) and ethanol (100 mL) following the method of ref. [29]. Recrystallization from H_2O/ethanol yielded (*R*)-*S*-isopropylcysteine (5.20 g, 40%) as a colorless solid. M.p. 235–236 °C (237 °C [29]); ^{1}H NMR (250 MHz, D_2O): δ = 1.18 (d, J = 6.6 Hz, 3H, CH_3), 1.19 (d, J = 6.8 Hz, 3H, CH_3), 2.98 (dd, J = 7.2, 14.7 Hz, 1H, CH_2S), 3.00 (qq, J = 6.6, 6.8 Hz, 1H, CH), 3.08 (dd, J = 4.5, 14.7 Hz, 1H, CH_2S), 3.89 (dd, J = 4.5, 7.2 Hz, 1H, NCH); ^{13}C NMR (50 MHz, D_2O): δ = 24.9 (q), 25.0 (q), 33.0 (t), 37.6 (d), 56.2 (d), 175.2 (s).

Compound **4a** (6.40 g, 98%) was prepared according to procedure A from the (*R*)-*S*-isopropylcysteine (3.60 g, 22.1 mmol) thus obtained and phthalic anhydride (3.27 g, 22.1 mmol). The colorless oil was used for esterification without further purification. IR (CCl_4): $\tilde{\nu}$ = 2940 (w), 2900 (w), 1735 (s), 1710 (vs), 1375 (vs), 1350 (w), 1245 (m), 1230 (m), 1090 (m), 1010 (w) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 292.8 (1939), 217.7 (42332) nm; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.8 Hz, 3H, CH_3), 1.27 (d, J = 6.6 Hz, 3H, CH_3), 2.97 (sept, J = 6.7 Hz, 1H, $CHCH_3$), 3.39 (d, J = 9.7 Hz, 1H, CH_2S), 3.40 (d, J = 6.5 Hz, 1H, CH_2S), 5.03 (dd, J = 5.6, 10.5 Hz, 1H, NCH), 7.75 (m, 2H, Ar-H), 7.85 (m, 2H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.2 (q), 23.3 (q), 29.7 (t), 34.4 (d), 51.4 (d), 123.7 (d, 2C), 131.6 (s, 2C), 134.0 (s, 2C), 167.2 (s, 2C), 171.7 (s).

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(*R*)-*N*-Phthaloyl-*S*-isopropylcysteine methyl ester (4b): Ester **4b** (95%) was prepared from **4a** (3.00 g, 10.2 mmol) according to procedure C. The crude product was purified by Kugelrohr distillation. Pure **4b** (2.11 g, 67%) remained as the residue from distillation (colorless oil). R_f = 0.63 (PE/EA 1:1); IR (CCl_4): $\tilde{\nu}$ = 2920 (m), 2900 (w), 1790 (m), 1700 (vs), 1420 (m), 1370 (vs), 1280 (s), 1260 (s), 1240 (s), 700 (s) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 295.4 (1990), 218.8 (41047) nm; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.7 Hz, 3H, CH_3), 1.23 (d, J = 6.6 Hz, 3H, CH_3), 2.94 (sept, J = 6.7 Hz, 1H, $CHCH_3$), 3.31 (dd, J = 10.5, 14.2 Hz, 1H, CH_2S), 3.41 (dd, J = 5.6, 14.2 Hz, 1H, CH_2S), 3.73 (s, 3H, OCH_3), 4.96 (dd, J = 5.6, 10.5 Hz, 1H, NCH), 7.72 (m, 2H, Ar–H), 7.82 (m, 2H, Ar–H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.1 (q), 23.2 (q), 29.4 (t), 34.5 (d), 51.5 (q), 53.0 (d), 123.6 (d, 2C), 131.7 (s, 2C), 134.2 (s, 2C), 167.4 (s, 2C), 168.0 (s); $C_{15}H_{17}NO_4S$ (307.364): calcd. C 58.62, H 5.57, N 4.56; found C 58.34, H 5.55, N 4.45.

(*rac*)-*N*-Phthaloyl-*S*-methyl-β,β-dimethylcysteine (5a): A three-necked 2 L flask containing a N_2 atmosphere and fitted with a stirrer and a condenser was cooled with a dry ice/isopropanol bath (−78 °C). Ammonia (500 mL) was condensed in, and (*rac*)-penicillamine (10.0 g, 67.0 mmol) and subsequently sodium metal (3.80 g, 67.0 mmol) were added. To this deep blue solution methyl iodide (19.0 g, 0.13 mol) was added in one portion. After stirring (3 h at −78 °C) the solvent was evaporated and the residue was suspended in H_2O (50 mL). After crystallization in the refrigerator, (*rac*)-*S*-methylpenicillamine (10.2 g, 94%) was isolated as a colorless solid. M.p. 250 °C (254–256 °C [30]); ^1H NMR (200 MHz, D_2O): δ = 1.26 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.06 (s, 3H, SCH_3), 3.30 (s, 1H, NCH); ^{13}C NMR (50 MHz, D_2O): δ = 10.0 (q), 22.6 (q), 25.7 (q), 47.3 (s), 61.8 (d), 177.7 (s).

The (*rac*)-*S*-methylpenicillamine thus obtained (1.00 g, 6.13 mmol) treated with phthalic anhydride (0.91 g, 6.13 mmol) according to procedure B yielded **5a** (1.76 g, 98%) as colorless crystals. M.p. 172 °C (from acetone/H_2O); IR (CCl_4): $\tilde{\nu}$ = 2905 (w), 1765 (w), 1715 (s), 1460 (w), 1375 (m), 1095 (w), 715 (w) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 291.9 (2875), 218.3 (47180) nm; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.11 (s, 3H, SCH_3), 4.95 (s, 1H, NCH), 7.75 (m, 2H, Ar–H), 7.89 (m, 2H, Ar–H), 9.13 (br s, 1H, CO_2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.9 (q), 25.4 (q), 26.9 (q), 47.4 (s), 57.5 (d), 123.7 (d, 2C), 131.4 (s, 2C), 134.3 (d, 2C), 167.7 (s, 2C), 171.3 (s); $C_{14}H_{15}NO_4S$ (293.3): calcd. C 57.32, H 5.15, N 4.77, S 10.93; found C 57.77, H 5.18, N 4.65, S 10.57.

(*rac*)-*N*-Phthaloyl-*S*-methyl-β,β-dimethylcysteine methyl ester (5b): A solution of KOH (0.82 g, 14.6 mmol) in H_2O (1.40 mL), 2-hydroxyethyl methyl ether (4.8 mL) and diethyl ether (1.4 mL) was heated in a distillation apparatus to 70 °C. A solution of *N*-methyl-*N*-nitroso-4-toluenesulfonamide (2.93 g, 13.7 mmol) in ether (20 mL) was dropped into this reaction mixture over 15 min. The resulting etheric diazomethane solution was distilled into a solution of **5a** (2.00 g, 6.82 mmol) in ether (30 mL). After distillation (ca. 30 min) the yellow reaction mixture was stirred at room temperature for 4 h. The excess diazomethane was quenched by addition of formic acid. After evaporation of the solvent at 20 °C/18 Torr the crystalline residue was dried at reduced pressure to yield **5b** (1.86 g, 89%). M.p. 138 °C; IR (CCl_4): $\tilde{\nu}$ = 2950 (w), 2930 (w), 2900 (w), 1760 (m), 1740 (m), 1710 (s), 1455 (w), 1420 (w), 1370 (s), 1090 (m), 905 (w), 710 (m) cm^{-1}; UV (CH_3CN): λ_{max} (ε) = 293.6 (2002), 218.5 (41056) nm; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.11 (s, 3H, SCH_3), 3.67 (s, 3H, OCH_3), 4.87 (s, 1H, NCH), 7.75 (m, 2H, Ar–H), 7.88 (m, 2H, Ar–H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.0 (q), 25.2 (q), 26.8 (q), 47.8 (s), 52.4 (q), 57.2 (d), 123.7 (d, 2C), 131.1 (s, 2C), 134.2 (d, 2C), 167.5 (s, 2C), 167.7 (s); $C_{15}H_{17}NO_4S$ (307.4): calcd. C 58.62, H 5.57, N 4.56, S 10.43; found C 58.89, H 5.79, N 4.38, S 10.00.

General procedure for the irradiation of *N*-phthaloyl α-amino acid methyl esters: A solution of the methyl ester (1.00 mmol) in the corresponding solvent (100 mL) was irradiated (λ = 300 nm) for 24 h under a N_2 atmosphere. After removal of the solvent (rotary evaporator), the crude product was dried at reduced pressure. Subsequently the conversion rate and product ratio was determined by ^1H NMR analysis.

Irradiation of (*R*)-*N*-phthaloyl-*S*-methylcysteine methyl ester (1b): The crude product from the photolysis of **1b** in acetone (entry 2) was purified by column chromatography (PE:EA 1:1) to give **6** (20 mg, 6%), **7** (250 mg, 63%), and **12** (40 mg, 10%).

Methyl (3*S*)-2,3,4,5-tetrahydro-1,5-dioxo-1*H*-benz[c]azepine-3-carboxylate (6) [6b]: Colorless oil, R_f = 0.20 (PE:EA 1:1); ^1H NMR (250 MHz, $CDCl_3$): δ = 3.18 (dd, J = 10.7, 18.7 Hz, 1H, CH_2), 3.29 (dd, J = 3.6, 18.8 Hz, 1H, CH_2), 3.80 (s, 3H, OCH_3), 4.61 (ddd, J = 3.7, 5.4, 10.6 Hz, 1H, NCH), 7.08 (br d, J = 4.8 Hz, 1H, NH), 7.66 (m, 3H, Ar–H), 7.94 (m, 1H, Ar–H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 49.1 (t), 50.7 (q), 53.5 (d), 128.7 (d), 130.4 (d), 132.1 (s), 132.3 (d), 133.1 (d), 135.7 (s), 168.4 (s), 169.5 (s), 199.1 (s).

Methyl (4*R*)-1,3,4,10b-tetrahydro-10b-hydroxy-6*H*-[1,4]thiazino[3,4a]-isoindol-6-one-4-carboxylate (7): Colorless oil, R_f = 0.38 (PE:EA 1:1); IR (CCl_4): $\tilde{\nu}$ = 3350 (w), 3000 (w), 2910 (w), 2870 (w), 1710 (s), 1680 (vs), 1440 (m), 1305 (m), 1200 (s), 1190 (s), 1150 (m) cm^{-1}; $C_{13}H_{13}NO_4S$ (279.31): calcd. C 55.96, H 4.69, N 5.01; found C 56.07, H 4.82, N 4.82. **Major diastereoisomer**: ^1H NMR (250 MHz, $CDCl_3$): δ = 2.62 (d, J = 13.6 Hz, 1H, CH_2S), 2.76 (dd, J = 4.6, 14.2 Hz, 1H, CH_2), 3.06 (d, J = 13.6 Hz, 1H, CH_2S), 3.06 (dd, J = 2.0, 14.0 Hz, 1H, CH_2), 3.72 (s, 3H, OCH_3), 5.15 (s, 1H, OH), 5.44 (dd, J = 2.0, 4.8 Hz, 1H, NCH), 7.47 (m, 3H, Ar–H), 7.68 (m, 1H, Ar–H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.2 (t), 37.8 (t), 50.6 (d), 52.9 (q), 83.1 (s), 121.3 (d), 123.6 (d), 128.9 (s), 129.6 (d), 132.8 (d), 147.0 (s), 165.8 (s), 168.3 (s). **Minor diastereoisomer**: ^1H NMR (250 MHz, $CDCl_3$): δ = 2.81 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.52 (dd, J = 3.1, 8.2 Hz, 1H, NCH), 5.14 (s, 1H, OH), 7.47 (m, 3H, Ar–H), 7.68 (m, 1H, Ar–H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 26.9 (t), 35.4 (t), 52.3 (q), 53.9 (d), 84.8 (s), 121.3 (d), 123.3 (d), 128.9 (s), 129.8 (d), 132.4 (d), 146.7 (s), 165.3 (s), 170.0 (s).

Methyl (4*R*)-3,4-dihydro-6*H*-[1,4]thiazino[3,4a]isoindol-6-one-4-carboxylate (12): R_f = 0.50 (PE:EA 1:1); m.p. 128 °C (from acetone/H_2O, colorless crystals); IR (CCl_4): $\tilde{\nu}$ = 3020 (w), 2930 (w), 2910 (w), 1725 (vs), 1710 (vs), 1455 (m), 1425 (m), 1375 (s), 1300 (m), 1230 (m), 1195 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.27 (dd, J = 3.6, 13.1 Hz, 1H, CH_2), 3.52 (ddd, J = 1.9, 3.1, 13.1 Hz, 1H, CH_2), 3.75 (s, 3H, OCH_3), 5.51 (dd, J = 3.1, 3.6 Hz, 1H, NCH), 6.26 (d, J = 1.9 Hz, 1H, =CH), 7.46 (m, 1H, Ar–H), 7.57 (m, 2H, Ar–H), 7.84 (m, 1H, Ar–H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 27.9 (t), 50.7 (q), 53.1 (d), 99.0 (d), 119.0 (d), 123.5 (d), 127.3 (s), 128.5 (d), 130.2 (s), 132.2 (d), 134.9 (s), 165.8 (s), 168.3 (s); $C_{13}H_{11}NO_3S$ (261.30): calcd. C 59.76, H 4.24, N 5.36; found C 60.03, H 4.39, N 5.27.

Irradiation of (*R*)-*N*-phthaloyl-*S*-benzylcysteine methyl ester (2b): The crude product from the photolysis of **2b** in acetone (entry 8) was purified by column chromatography (PE:EA 1:1) to give **6** (20 mg, 8%), **8** (155 mg, 40%), and **13** (130 mg, 35%).

Methyl (4*R*)-1,3,4,10b-tetrahydro-10b-hydroxy-1-phenyl-6*H*-[1,4]thiazino[3,4a]isoindol-6-one-4-carboxylate (8): Colorless oil, R_f = 0.35 (PE/EA 1:1); IR (CCl_4): $\tilde{\nu}$ = 3540 (w), 3300 (w), 3020 (w), 2920 (w), 1725 (s), 1690 (vs), 1360 (m), 1190 (m), 1160 (w), 680 (s) cm^{-1}; $C_{19}H_{17}NO_4S$ (355.412): calcd. C 64.21, H 4.82, N 3.94; found C 64.07, H 5.02, N 3.63. **Major diastereoisomer**: ^1H NMR (250 MHz, $CDCl_3$): δ = 3.12 (dd, J = 6.6, 13.1 Hz, 1H, CH_2S), 3.59 (dd, J = 3.4, 13.1 Hz, 1H, CH_2S), 3.80 (s, 3H, OCH_3), 4.16 (d, J = 1.4 Hz, 1H, CHPh), 4.67 (dd, J = 3.4, 6.6 Hz, 1H, NCH), 4.73 (s, 1H, OH), 6.20 (d, J = 7.6 Hz, 1H, Ar–H), 7.16–7.49 (m, 7H, Ar–H), 7.54 (d, J = 7.6 Hz, 1H, Ar–H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 29.3 (t), 52.8 (d), 53.0 (q), 54.1 (d), 88.0 (s), 123.4 (d), 124.0 (d), 128.1 (d), 128.7 (d), 129.6 (s), 129.7 (d), 130.3 (d), 130.7 (d), 131.9 (d), 136.2 (s), 145.3 (s), 167.4 (s), 169.5 (s). **Minor diastereoisomer**: ^1H NMR (250 MHz, $CDCl_3$): δ = 3.02 (dd, J = 5.5, 13.0 Hz, 1H, CH_2S), 3.28 (dd, J = 2.1, 13.0 Hz, 1H, CH_2S), 3.72 (s, 3H, OCH_3), 4.20 (d, J = 1.6 Hz, 1H, CHPh), 5.13 (s, 1H, OH), 5.54 (dd, J = 2.1, 5.5 Hz, 1H, NCH), 6.21 (d, J = 7.6 Hz, 1H, Ar–H), 7.16–7.49 (m, 7H, Ar–H), 7.55 (d, J = 7.6 Hz, 1H, Ar–H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 35.6 (t), 51.9 (d), 52.8 (q), 53.4 (d), 89.7 (s), 123.7 (d), 124.2 (d), 128.0 (d), 128.5 (d), 129.7 (s), 129.9 (d), 130.1 (d), 130.7 (d), 132.0 (d), 136.5 (s), 144.5 (s), 166.0 (s), 169.6 (s).

Methyl (4*R*)-3,4-dihydro-1-phenyl-6*H*-[1,4]thiazino[3,4a]isoindol-6-one-4-carboxylate (13): R_f = 0.45 (PE:EA 1:1); m.p. 155–157 °C (from MeOH/H_2O); IR (CCl_4): $\tilde{\nu}$ = 3040 (w), 2930 (w), 1750 (s), 1730 (s), 1690 (vs), 1460 (m), 1370 (m), 1300 (m), 1225 (m), 1160 (m), 1040 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.43 (dd, J = 3.6, 13.0 Hz, 1H, CH_2), 3.52 (dd, J = 3.1, 13.1 Hz, 1H, CH_2), 3.79 (s, 3H, OCH_3), 5.63 (dd, J = 3.3, 3.3 Hz, 1H, NCH), 6.55 (d, J = 7.9 Hz, 1H, Ar–H), 7.21 (td, J = 1.0, 7.4 Hz, 1H, Ar–H), 7.32 (td, J = 0.8, 7.4 Hz, 1H, Ar–H), 7.44 (m, 5H, Ar–H), 7.83 (d, J = 1.0, 7.4 Hz, 1H, Ar–H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 29.2 (t), 50.5 (d), 53.0 (q), 118.5 (s), 121.9 (d), 123.1 (d), 125.9 (s), 127.7 (s), 127.8 (s), 128.6 (d), 129.1 (d), 129.4 (d), 129.9 (d), 130.4 (d), 131.6 (d), 134.7 (s), 135.6 (s), 165.6 (s), 168.2 (s) cm^{-1}; $C_{19}H_{15}NO_3S$ (337.39): calcd. C 67.64, H 4.48, N 4.15; found C 67.98, H 4.60, N 3.97.

Irradiation of (*R*)-*N*-phthaloyl-*S*-methoxycarbonylmethylcysteine methyl ester (3b): The crude product from the photolysis of **3b** in acetone (entry 2) was purified by column chromatography (PE:EA 1:1) to give **9** (100 mg, 53%).

Methyl (4*R*)-1-methoxycarbonyl-1,3,4,10b-tetrahydro-10b-hydroxy-6*H*-[1,4]thiazino[3,4a]isoindol-6-one-4-carboxylate (9): Significant signals for the four isomers: diastereoisomer 1: ^1H NMR (200 MHz, $CDCl_3$): δ = 2.97 (dd, J = 2.0, 14.1 Hz, 1H, CH_2S), 3.32 (s, 1H, $CHCO_2Me$), 3.46 (dd, J = 5.0, 14.1 Hz, 1H, CH_2S), 3.83 (s, 3H, OCH_3), 5.58 (dd, J = 2.0, 5.0 Hz, 1H, NCH), 7.53 (m, 3H, Ar–H), 7.80 (m, 1H, Ar–H); diastereoisomer 2: ^1H NMR (200 MHz, $CDCl_3$): δ = 3.72 (s, 1H, $CHCO_2Me$), 3.87 (s, 3H, OCH_3), 5.45 (dd, J = 2.4, 4.8 Hz, 1H, NCH), 7.53 (m, 3H, Ar–H), 7.80 (m, 1H, Ar–H); diastereoisomer 3: ^1H NMR (200 MHz, $CDCl_3$): δ = 3.69 (s, 1H, $CHCO_2Me$), 3.86 (s, 3H, OCH_3), 4.82 (dd, J = 3.4, 6.0 Hz, 1H, NCH), 7.53 (m, 3H, Ar–H), 7.80 (m, 1H, Ar–H); diastereoisomer 4: ^1H NMR (200 MHz, $CDCl_3$): δ = 2.56 (dd, J = 2.6, 13.2 Hz, 1H, CH_2S), 3.25 (s, 1H, $CHCO_2Me$), 3.82 (s, 3H, OCH_3), 4.49 (dd, J = 2.6, 11.8 Hz, 1H, NCH), 7.53 (m, 3H, Ar–H), 7.80 (m, 1H, Ar–H). Mixture of the four diastereoisomers as colorless oil: R_f = 0.28 (EA/PE 1:1); $C_{15}H_{15}NO_4S$ (337.3): calcd. C 53.4, H 4.48, N 4.15, S 9.50; found C 53.19, H 4.54, N 4.33, S 9.29.

Methyl (4*R*)-1-methoxycarbonyl-3,4-dihydro-6*H*-[1,4]thiazino[3,4a]isoindol-6-one-4-carboxylate (14): Colorless oil, R_f = 0.43 (EA/PE 1:2); IR (CCl_4): $\tilde{\nu}$ = 2930 (m), 2900 (m), 1725 (s), 1700 (vs), 1375 (m), 1250 (s), 1210 (m), 1120 (s), 1090 (m) cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.20 (dd, J = 3.5, 13.2 Hz, 1H, CH_2S), 3.53 (dd, J = 3.1, 13.2 Hz, 1H, CH_2S), 3.70 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.60 (dd, J = 3.1, 3.5 Hz, 1H, NCH), 7.59 (m, 3H, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 27.4 (t), 51.1 (q), 52.9 (q), 53.3 (d), 107.6 (s), 123.4 (d), 126.1 (d), 128.0 (s), 133.2 (d), 133.9 (s), 134.3 (d), 136.1 (s), 164.2 (s), 166.0 (s), 168.0 (s).

Irradiation of (*R*)-*N*-phthaloyl-*S*-isopropylcysteine methyl ester (4b): The crude product from the photolysis of **4b** in acetone (entry 18) was purified by column chromatography (PE:EA 1:1) to give **6** (50 mg, 15%) and **10** (110 mg, 24%).

Methyl (4*R*)-1,3,4,10b-tetrahydro-10b-hydroxy-1,1'-dimethyl-6*H*-[1,4]thiazino-[3,4a]isoindol-6-one-4-carboxylate (10): Colorless oil, R_f = 0.35 (EA:PE 1:1); IR (CCl_4): $\tilde{\nu}$ = 2920 cm^{-1} (m), 2900 (m), 1730 (m), 1690 (vs), 1450 (m), 1390 (vs), 1320 (m), 1200 (m), 1130 (m), 1070 (w); $C_{15}H_{17}NO_4S$ (307.4): calcd. C 58.62, H 5.57, N 4.56; found C 58.33, H 5.52, N 4.36. **Major diastereoisomer**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.63 (dd, J = 3.0, 14.0 Hz, 1H, CH_2S), 3.27 (dd, J = 11.6, 14.0 Hz, 1H, CH_2S), 3.81 (s, 3H, OCH_3), 4.32 (dd, J = 3.0, 11.6 Hz, 1H, NCH), 4.57 (s, 1H, OH), 7.53 (m, 3H, Ar-H), 7.73 (m, 2H, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.1 (q), 23.9 (q), 26.9 (t), 48.3 (s), 49.0 (d), 52.9 (q), 90.6 (s), 122.7 (d), 123.5 (d), 131.5 (s), 131.7 (d), 143.8 (s), 168.9 (s, 2C), 171.6 (s). **Minor diastereoisomer**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 3.08 (dd, J = 2.1, 14.3 Hz, 1H, CH_2S), 3.20 (dd, J = 4.9, 14.3 Hz, 1H, CH_2S), 3.76 (s, 3H, OCH_3), 4.79 (s, 1H, OH), 5.45 (dd, J = 2.1, 4.9 Hz, 1H, NCH), 7.53 (m, 3H, Ar-H), 7.82 (m, 2H, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.1 (q), 23.8 (q), 25.1 (t), 48.3 (s), 49.2 (d), 53.0 (q), 89.8 (s), 122.5 (d), 123.9 (d), 131.4 (s), 132.3 (d), 145.5 (s), 164.3 (s, 2C), 166.5 (s).

Irradiation of (*rac*)-*N*-phthaloyl-*S*-methyl-β,β-dimethylcysteine methyl ester (5b): The crude product from the photolysis of **5b** in acetone (entry 24) was purified by column chromatography (PE:EA 1:1) to give **11** (160 mg, 80%).

Methyl(*rac*)-(4,10b-*trans*)-1,3,4,10b-tetrahydro-10b-hydroxy-3,3-dimethyl-6*H*-[1,4]-thiazino[3,4a]isoindol-6-one-4-carboxylate (*trans*-11): M.p.: 200 °C (from MeOH/H_2O); IR (CCl_4): $\tilde{\nu}$ = 3550 (w), 2930 (w), 2910 (w), 1740 (s), 1700 (s), 1455 (m), 1390 (m), 1325 (w), 1300 (w), 1200 (m), 1110 (m), 1075 (m), 935 (w), 925 (w), 690 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.92 (d, J = 14.0 Hz, 1H, CH_2), 3.00 (d, J = 14.0 Hz, 1H, CH_2), 3.73 (s, 3H, OCH_3), 4.38 (s, 1H, NCH), 7.57 (m, 3H, Ar-H), 7.78 (m, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.1 (q), 24.5 (q), 36.3 (t), 43.6 (s), 52.1 (q), 61.2 (d), 84.3 (s), 121.6 (d), 124.0 (d), 130.2 (s), 130.3 (s), 132.6 (d), 145.8 (s), 166.6 (s), 167.2 (s); $C_{15}H_{17}NO_4S$ (307.4): calcd. C 58.62, H 5.57, N 4.56, S 10.43; found C 58.86, H 5.80, N 4.79, S 10.53.

Methyl (*rac*)-(4,10b-*cis*)-1,3,4,10b-tetrahydro-10b-hydroxy-3,3-dimethyl-6*H*-[1,4]-thiazino[3,4a]isoindol-6-one-4-carboxylate (*cis*-11): Colorless oil, R_f = 0.40 (PE/EA 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.06 (d, J = 14.0 Hz, 1H, CH_2), 3.16 (d, J = 14.0 Hz, 1H, CH_2), 3.81 (s, 3H, OCH_3), 5.16 (s, 1H, NCH), 7.59 (m, 3H, Ar-H), 7.73 (m, 1H, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.9 (q), 27.4 (q), 36.1 (t), 40.4 (s), 52.7 (q), 60.8 (d), 82.3 (s), 121.5 (d), 124.2 (d), 128.9 (d), 129.8 (s), 131.1 (d), 133.1 (s), 167.1 (s), 172.0 (s).

Methyl (*rac*)-3,4-dihydro-3,3-dimethyl-6*H*-[1,4]thiazino[3,4a]isoindol-6-one-4-carboxylate (15): colorless oil, R_f = 0.50 (PE/EA 1:1); IR (CCl_4): $\tilde{\nu}$ = 2935 (w), 1765 (w), 1730 (s), 1710 (s), 1695 (s), 1610 (w), 1460 (w), 1425 (w), 1380 (m), 1300 (w), 1110 (w), 1025 (w); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.97 (s, 1H, NCH), 6.53 (s, 1H, =CH), 7.44 (m, 1H, Ar-H), 7.58 (m, 2H, Ar-H), 7.86 (d, J = 9.7 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.4 (q), 30.9 (q), 43.9 (s), 53.4 (q), 60.5 (d), 104.9 (d), 107.8 (s), 111.5 (s), 117.2 (s), 119.4 (d), 123.8 (d), 128.9 (d), 133.3 (d), 159.1 (s), 160.8 (s).

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