Photochemistry of MTM- and MTE-Esters of ω-Phthalimido Carboxylic Acids: Macrocyclization versus Deprotection[1]

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The photochemistry of five linear methylthiomethyl (MTM)-esters of ω-phthalimido carboxylic acids Pht=N−$(CH_2)_n$$COOCH_2SCH_3$ **1a**−**e** (n = 1, 2 , 3, 5, and 10), of the two methylthioethyl (MTE)-esters Pht=N−$(CH_2)_n$$COOCH_2CH_2SCH_3$ **2a**,**b** (n = 1, 2), and of the two methyl-substituted MTM/MTE esters **3a** and **3b** was investigated. Two reaction channels were observed: (i) photocyclization to give medium-sized and macrocyclic rings, (ii) photochemical deprotection to give the free carboxylic acids. Photocyclization of **1b** and **1c** (n = 2, 3) resulted in **4b**,**c** in excellent yields whereas the substrates **1a** and **1d**,**e** with shorter as well as longer spacer groups (n = 1, 5, 10) gave preferentially the deprotected products **5a**,**d**,**e**. Subsequent photolysis afforded *N*-methylphthalimide (**6**) from **5a**. The MTE-esters **2a** and **2b** gave the macrocyclic lactones **7** and *E*-**8**. Thus, the competition between cyclization and deprotection strongly depended on the chain length of the hydrocarbon linker between phthalimido chromophore and ester group. To examine the influence of the position of the ester group in the linker chain the model substrates **3a** and **3b** with identical number of atoms separating electron donor and acceptor group were investigated. The more flexible MTE-derivative **3b** cyclized to give a 4:1 diastereoisomeric mixture of *cis*/*trans*-**9b**, whereas photolysis of the more reluctant MTM-ester **3a** resulted in *cis*-**9a** only after prolonged irradiation. These results show that MTM can function as a photolabile protecting group whereas MTE cannot be removed photochemically. The distance dependence of the secondary reaction steps indicates that the primary electron transfer is not necessarily induced starting from close contact geometries.

Introduction

The photochemical macrocyclization of N-alkylated phthalimides has been investigated by us in the last years for sulfur-,[2] carboxylate-,[3] and aryl-substituted derivatives.[4] Due to low-lying oxidation potentials thioethers are excellent substrates for electron transfer initiated cyclizations ($E_{ox.}$ of dialkylsulfides approximately 1.3 V vs SCE in MeCN[5]).[6] Especially interesting compounds in this context are the methylthiomethyl (MTM) and methylthioethyl (MTE) esters of phthaloyl amino acids which allow the investigation of conformational restricted linkers such as esters or amides. Although this concept has already been realized by Kanaoka and co-workers for macrocyclization reactions using ester[7] as well as peptide[8] linked substrates and the thiomethyl group as electron donor, little is known about the relationship between cyclization efficiency and the linker structure of the substrate, especially for precursors to medium-sized ring systems. In the context of decarboxylative cyclization of *N*-phthaloyl peptides[3,9] and esters,[10] we have recently found that rigid linker groups (with, as well as without, hydrogen bonding activity) strongly influence the efficiency of photochemical macrocyclizations.

The MTM- and MTE-protected phthalimides **1**, **2** of a series of amino acids, whose photochemical reactions are described in this publication, were expected to show preferentially oxidation at sulfur and subsequent radical combination reactions. To study the influence of the less conformationally flexible (in comparison with simple alkyl spacers) ester group on the cyclization selectivity, we focused on *N*-phthaloyl amino acid derivatives with relatively short hydrocarbon linker chains. For additional studies of the cyclization *diastereoselectivity*, we synthesized two model substrates **3a**,**b** with identical number of atoms separating electron donor and acceptor group differing only in the position of the ester group in the spacer chain.

Results and Discussion

All starting materials were easily available in moderate to good yields from the corresponding *N*-phthaloyl

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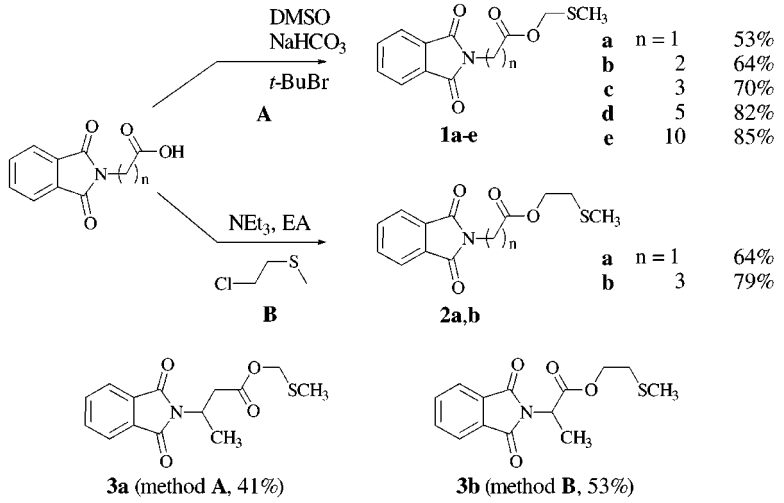
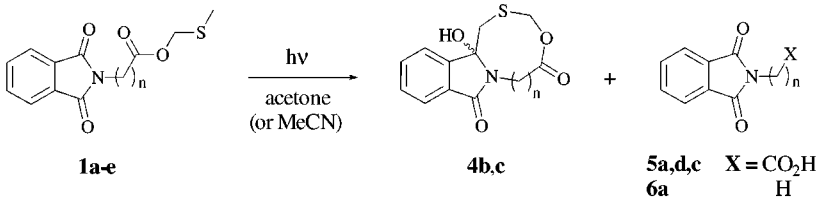
Scheme 1. Preparation of the Starting Materials



Scheme 2. Photochemistry of the MTM-Esters 1a-e



amino acids according to literature methods described for MTM ($m = 1$)[11,12] and MTE ($m = 2$) ester derivatives.[13]

The photolyses of the MTM substrates **1a**−**e** resulted in two groups of products: cyclization and "deprotection" products, respectively. The deprotection products, i.e., the free *N*-phthaloyl amino acids, were photostable under the reaction conditions; only the glycine derivative **5a** was rapidly photodecarboxylated to give *N*-methylphthalimide (**6**) in acetone whereas photolysis in acetonitrile resulted in a 2:1 mixture of **5a** and **6**. These were the only products formed from **1a** and no trace of photocyclization compound was detected in the NMR spectra of the crude material. Substrates **1b** and **1c** gave the corresponding macrocycles **4b** (also confirmed by X-ray structure analysis)[14] and **4c** in excellent yields of 84% (100% conversion) and 51% (after 61% conversion). The deprotection products were not detected from these substrates; thus, the cyclization/deprotection selectivity is >95:5 for nine- and ten-membered ring formation. Much to our surprise and in contrast to our results reported for the decarboxylative macrocyclization,[3] the MTM-esters **1d** and **1e** mainly gave the free *N*-phthaloyl amino acids **5d**,**e**. In the case of **1d**, the cyclization product **4d** was identified in minor amounts (<10%) by GC-MS from the crude product mixture after transformation into the corresponding TMS-ether, but could not be isolated. No such product could be detected from **1e**, i.e., the 17-membered lactone is formed in less than 2% relative yield.

Table 1. Photolysis of 1a-e. Product Composition[a]

1	solvent	conversion (%)	4 (%)	5 (%)	6 (%)
a	acetone	55	−	−	100
a	acetonitrile	100	−	66	34
b	acetone	100	100	−	−
c	acetone	61	100	−	−
d	acetone	100	<10	>80[c]	−
e	acetone	100	−	>90[c]	−

[a] Normalized to 100%. [b] 0.01−0.02 M solution of **1**/Pyrex/13 °C/24−48 h/RPR-208 Rayonet photoreactor. [c] Higher amounts of decomposition products (ca. 10%).

Only cyclization was observed when the more flexible MTE-esters **2a** and **2b** were irradiated. From **2a**, the nine-membered heterocycle **7** was produced in 82% yield whereas photolysis of **2b** resulted in the cyclization/dehydration product *E*-**8** in 72% yield. The *Z*-isomer of **8** was identified in minor amounts ($E:Z = 87:13$) in the proton NMR of the crude product mixture, but could not be isolated. Both structures were confirmed by X-ray structure analyses.[14]

Cyclization Efficiency versus Diastereoselectivity. To study the diastereoselectivity of the radical combination step, the two regioisomeric model systems **3a** and **3b** were examined. These two starting materials differ only in the relative position of the linking ester group. Irradiation of **3a** resulted in highly diastereoselective formation of *cis*-**9a** (61% yield). After transformation into the corresponding TMS-ether the *trans*-diastereoisomer could not even be detected in the crude product mixture by GC-MS analysis. Prolonged irradiation was necessary to run the reaction to 100% conversion. In contrast, the MTE-ester **3b** was readily transferred into the corresponding macrocyclic mixture **9b** after relatively short irradiation. After 18 h the two diastereoisomers *cis*- and *trans*-**9b** were isolated in a 79:21 ratio in 88% yield.

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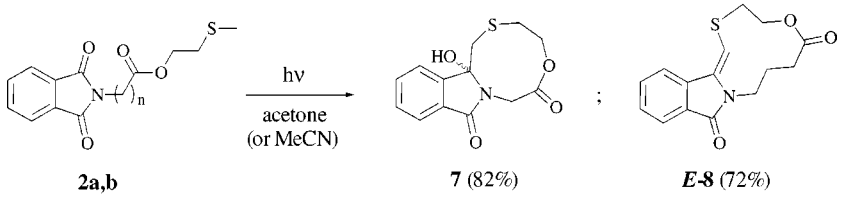
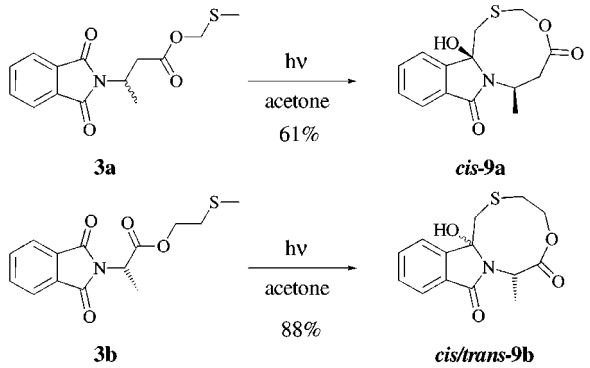
(14) X-ray data: Enraf-Nonius CAD4-diffractometer, Mo Kα, graphite monochromator. Crystallographic data available as Supporting Information.

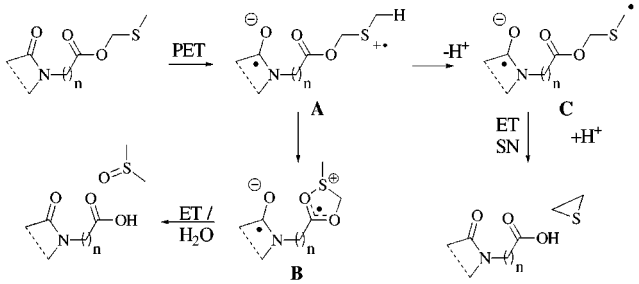
Scheme 3. Photochemistry of the MTE-Esters 2a and 2b



Scheme 4. Diastereoselectivity Studies with 3a and 3b



Scheme 5. Proposed Reaction Mechanism



After chromatography the pure *cis*-**9b** was obtained in 67% yield, and its structure was confirmed by X-ray analysis.[14]

Mechanistic Discussion. Both photocyclization and photodeprotection reactions of phthalimido-activated dialkyl sulfides are initiated via one-electron oxidation (PET) of the sulfur atom. The strongest evidence comes from the position of CH-activation: the homolytic Norrish bond cleavage should involve either adjacent (γ- or δ-)hydrogens or the weaker secondary α-thio CH bonds. In contrast to that, kinetic deprotonation of a thioether radical cation occurs preferentially from the thiomethyl group. This effect was observed in case of the MTM as well as the MTE substrates. When acetone is present as solvent (or alternatively other triplet sensitizers), *intermolecular* PET can generate the acetone radical anion in the first step.[15] Prior to formation of cyclization products, a second electron transfer which reduces the phthalimide electrophore has to occur in this case. A direct *intramolecular* PET can also be assumed for photoreactions in acetonitrile which, however, proceeds dramatically less efficient.[2] Kanaoka and co-workers have described a series of photocyclizations reactions involving long alkyl spacers separating the phthalimide electrophore and the thioether group.[6−8] In these cases, efficient radical combination was observed for nearly all spacer lengths (except for the shortest one: Pht=N−CH_2−S−CH_3). The same insensitivity was also observed for the PET-decarboxylation/cyclization sequence of ω-phthalimido alkylcarboxylates.[3b]

The MTM-substrates (**1a**−**e** and **3a**) investigated in this work were sensitive concerning the competition between photocyclization and photodeprotection with respect to the length of the hydrocarbon spacer. In contrast, irradiation of MTE esters (**2a**,**b** and **3b**) cleanly resulted in the corresponding macrocyclic products without loss of the MTE group. Consequently, the α-relationship between ester and thioether group makes the radical cation sensitive toward cleavage of the MTM protecting group.

At present, we can only speculate about the nature and the final product of the leaving group in the photodeprotection path of MTM esters. The cleavage can be initiated already at the stage of the radical cation **A** or after proton transfer from the highly acidic α-CH-position. In the former case, the formation of a cyclic distal radical cation **B** is energetically possible.[16] Further reduction and hydrolysis can lead to dimethyl sulfoxide and the protonated carboxylic acid—a *photochemical retro-Pummerer rearrangement*. Alternatively, back electron transfer can occur at the stage of the α-thioalkyl radical **C**. Intramolecular SN reaction can result in thiirane and the carboxylate anion. If the radical centers in **C** have optimal distances, C−C bond formation which results in the cyclization products **4** or **7** can efficiently compete. A further important aspect is the multiplicity of the biradical **C**: from time-resolved laser flash investigation it was deduced that triplet intermediates are formed in the PET reaction of phthalimidoalkyl-substituted thioethers.[15] Thus, spin inversion is necessary prior to bond formation, and this process competes also with the (spin-unrestricted) cleavage process. As already mentioned, the efficiency of the photocyclization reaction of phthalimidoalkyl-substituted carboxylates[3a,10] as well as the corresponding thioethers[7,8] does not depend on the spacer chain length. The distance dependence of the secondary reaction steps of the MTM substrates **1** indicates that the primary electron transfer is not necessarily induced starting from close contact geometries. In case of substrates with larger alkyl chains connecting the electron-donating thioether group with the electron-accepting phthalimide, long-range electron transfer can generate radical ion pairs separated in space. In these cases, the cleavage of the MTM group functions as a radical clock and competes with conformational dynamics necessary for the approach of the two radical centers in **C**. The reduced conformational flexibility due to the linking ester group in **1a** and the resulting low tendency for the approach of the two radical centers in substrates **1d** and **1e** favor cleavage reactions.[17] In these cases the MTM-protecting group acts as a **p**hoto**r**emovable **p**rotecting

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group (PRPG).[18] For the glycine compound **1a**, deprotection is followed by rapid photochemical α-decarboxylation, a process which has been described by us[19] and others[20,21] for *N*-phthaloyl α-amino acids.

The corresponding MTE esters did not show cleavage reactions which is probable due to higher conformational flexibility at the stage of the triplet biradicals and/or reduced tendency to undergo side-reactions such as the formation of intermediates such as **B**. Similar substrates to the MTE-esters (2-hydroxymethyl-1,3-dithiane esters) have been investigated by Kutateladze and co-workers and used for efficient electrochemical deprotection.[22]

Concerning the diastereoselectivity of the photocyclization of chiral substrates **3**, we have recently shown that α-alkyl substituents effect the diastereoselectivity in the cyclization step of the decarboxylative photocyclization.[10] The preferred formation of the cis product **9a** from **3a** might be due to a stereoelectronic effect that favors the axial position of the hydroxy group in the macrocyclic lactone ring and leads to the thermodynamically favored cis diastereoisomer. Compared to the result obtained for the compound **3a**, the additional methylene group in the thioalkyl fragment in **3b** increases the tendency for cyclization but on the other hand lowers the degree of stereoselectivity.

Experimental Section

The starting materials were synthesized from the *N*-phthaloyl amino acids according to literature procedures by Mora et al.,[11] Dossena at al.,[12] and Amaral and Rydon.[13] The photochemical reactions were performed in Pyrex vessels (100−250 mL) using a RPR-208 Rayonet photochemical reactor equipped with 3000 Å lamps (approximately 800 W) at 13 °C under a nitrogen atmosphere. All solvents used for photoreactions (acetone and acetonitrile) were puriss. p.a. (Fluka). Analyses of the crude product mixtures were performed using ^{1}H and ^{13}C NMR spectroscopy. Product mixtures were separated (when necessary) by means of silica gel column chromatography (Macherey & Nagel, 230−240 mesh). Analyses of the purified photoproducts were performed using ^{1}H and ^{13}C NMR (Bruker DPX 300, and Bruker AC 300 F) spectroscopy, IR (Perkin-Elmer FT-IR−S 1600), UV (Perkin-Elmer Lambda 7), mp (Büchi No. B-535; uncorrected), MS (Finnigan MAT 500) and HR-MS (Finnigan MAT H−SQ 30) spectroscopy, and combustion analyses (Elementar Vario EL). For GC-MS studies the products were transferred into the corresponding TMS-ethers and esters using *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA).[23]

Standard Procedure for the Synthesis of the MTM-Esters. *tert*-Butyl bromide (10.0 mmol) in 25 mL of DMSO was added slowly to a suspension of the *N*-phthaloylamino acid (1.0 mmol) and $NaHCO_3$ (10.0 mmol) in 50 mL of DMSO. After stirring overnight at rt, water (ca. 50 mL) was added. The reaction mixture was extracted with ether (3 × 100 mL); the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was dried in vacuo.

Phthalimidoacetic acid methylthio methyl ester (1a): mp: 67−69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3H), 4.47 (s, 2H), 5.20 (s, 2H), 7.74 (dd, J = 5.6, 3.1 Hz, 2H), 7.87 (dd, J = 5.6, 3.1 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.5 (q), 38.9 (t), 69.8 (t), 123.7 (d), 131.9 (s), 134.3 (d), 167.1 (s), 167.4 (s). Anal. Calcd for $C_{12}H_{11}NO_4S$ (268.06): C 54.33, H 4.18, N 5.28. Found: C 54.47, H 4.31, N 5.11.

Phthalimidopropionic acid methylthio methyl ester (1b): mp: 34−36 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3H), 2.76 (t, J = 7.2 Hz, 2H), 3.99 (t, J = 7.2 Hz, 2H), 5.11 (s, 2H), 7.70 (dd, J = 5.7, 3.1 Hz, 2H), 7.83 (dd, J = 5.7, 3.1 Hz, 2H, H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.4 (q), 33.0 (t), 33.6 (t), 68.7 (t), 123.3 (d), 132.0 (s), 134.0 (d), 167.9 (s), 170.5 (s). Anal. Calcd for $C_{13}H_{13}NO_4S$ (279.31): C 55.90, H 4.69, N 5.01. Found: C 56.12, H 4.77, N 5.30.

4-Phthalimidobutyric acid methylthio methyl ester (1c): mp: 63−65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (quin, J = 7.2 Hz, 2H), 2.22 (s, 3H), 2.41 (t, J = 7.2 Hz, 2H), 3.75 (t, J = 7.2 Hz, 2H), 5.10 (s, 2 H), 7.70 (dd, J = 5.6, 3.1 Hz, 2H), 7.83 (dd, J = 5.6, 3.1 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.3 (q), 23.7 (t), 31.5 (t), 37.0 (t), 68.2 (t), 123.2 (d), 131.9 (s), 133.9 (d), 168.3 (s), 172.2 (s). Anal. Calcd for $C_{14}H_{15}NO_4S$ (293.34): C 57.32, H 5.15, N 4.77. Found: C 57.22, H 5.34, N 5.00.

6-Phthalimidohexanoic acid methylthio methyl ester (1d): oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (m, 2H), 1.62 (m, 4H), 2.14 (s, 3H), 2.28 (t, J = 7.4 Hz, 2H), 3.60 (t, J = 7.1 Hz, 2H), 5.04 (s, 2H), 7.64 (dd, J = 5.4, 3.0 Hz, 2H), 7.76 (dd, J = 5.4, 3.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.2 (q), 24.2 (t), 26.1 (t), 27.6 (t), 28.1 (t), 33.9 (t), 37.5 (t), 67.8 (t), 123.0 (d), 131.9 (s), 133.7 (d), 168.2 (s), 172.9 (s). MS (EI, 70 eV): m/z (%) = 274 ($M^+ - SCH_3$, 1), 260 (1), 245 (1), 217 (12), 160 (100), 130 (18), 77 (17), 69 (5), 61 (40), 55 (12), 50 (4). HR-MS (PI−FAB): 321.1042 (calcd 321.1035).

11-Phthalimidoundecanoic acid methylthio methyl ester (1e): mp: 47−48 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (m, 12H), 1.62 (m, 4H), 2.21 (s, 3H), 2.31 (t, J = 7.4 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 5.10 (s, 2H), 7.68 (dd, J = 5.4, 3.2 Hz, 2H), 7.82 (dd, J = 5.4, 3.2 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.3 (q), 24.8 (t), 26.8 (t), 28.5 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 29.3 (t), 34.3 (t), 38.0 (t), 67.8 (t), 123.1 (d), 132.1 (s), 133.8 (d), 168.4 (s), 173.4 (s). MS (EI, 70 eV): m/z (%) = 391 (M^+, 1), 377 (1), 331 (1), 315 (21), 287 (30), 244 (1), 188 (2), 160 (100), 130 (13), 77 (11), 69 (4), 61 (38), 55 (17), 50 (2). HR-MS (PI−FAB): 391.1809 (calcd 391.1817).

***rac*-3-Phthalimidobutyric acid methylthio methyl ester (3a):** mp: 73−75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, J = 6.9 Hz, 3H), 2.11 (s, 3H), 2.83 (dd, J = 16.0, 5.9 Hz, 1H), 3.22 (dd, J = 16.0, 9.2 Hz, 1H), 4.80 (ddd, J = 5.9, 6.9, 9.2 Hz, 1H), 5.05 (s, 2H), 7.69 (dd, J = 5.6, 3.1 Hz, 2H), 7.81 (dd, J = 5.6, 3.1 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.4 (q), 18.8 (q), 38.1 (d), 43.5 (t), 68.5 (t), 123.2 (d), 131.9 (s), 133.9 (d), 168.0 (s), 170.5 (s). IR (CsI): $\bar{\nu}$ (cm^{-1}) = 1742, 1703, 1698, 1694, 1393, 1375, 1169, 1024, 718. MS (EI, 70 eV): m/z (%) = 293 (M^+, 3), 265 (1), 247 (2), 232 (5), 217 (27), 189 (3), 174 (100), 147 (10), 130 (27), 104 (9), 76 (17), 69 (17), 61 (30), 50 (5). UV (MeCN): λ (nm, ϵ) = 218.4 (18950), 239.8 (4702), 291.4 (803). HR-MS (PI−FAB): 293.0726 (calcd 293.0722).

Standard Procedure for the Synthesis of the MTE-Esters. *N*-Phthalimidocarboxylic acid (10 mmol), 2.0 mL (14.3 mmol) of triethylamine, and 2.0 mL (20.3 mmol) of methyl-2-chloroethyl sulfide in 50 mL of ethyl acetate were heated to reflux for 3 days. After cooling to rt, ethyl acetate (50 mL) was added, and the reaction mixture was filtered. The filtrate was washed with sat. $NaHCO_3$, water, and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was dried in vacuo.

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Phthalimidoacetic acid methylthioethyl ester (2a): mp: 71−73 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.71 (t, J = 6.9 Hz, 2H), 4.30 (t, J = 6.9 Hz, 2H), 4.44 (s, 2H), 7.72 (dd, J = 5.4, 3.0 Hz, 2H), 7.86 (dd, J = 5.4, 3.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.7 (q), 32.2 (t), 38.8 (t), 64.3 (t), 123.6 (d), 132.0 (s), 134.2 (d), 167.1 (s), 167.4 (s). Anal. Calcd for $C_{13}H_{13}NO_4S$ (279.31): C 55.90, H 4.69, N 5.01. Found: C 55.78, H 5.01, N 4.89.

4-Phthalimidobutyric acid methylthioethyl ester (2b): oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (quin, J = 7.2 Hz, 2H), 2.06 (s, 3H), 2.33 (t, J = 7.4 Hz, 2H), 2.63 (t, J = 6.9 Hz, 2H), 3.68 (t, J = 6.8 Hz, 2H), 4.15 (t, J = 6.9 Hz, 2H), 7.65 (dd, J = 5.7, 3.1 Hz, 2H), 7.77 (dd, J = 5.7, 3.1 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.5 (q), 23.6 (t), 31.3 (t), 32.3 (t), 37.0 (t), 62.8 (t), 123.1 (d), 131.9 (s), 133.8 (d), 168.1 (s), 172.2 (s). Anal. Calcd for $C_{15}H_{17}NO_4S$ (307.36): C 58.62, H 5.57, N 4.56. Found: C 58.38, H 5.71, N 4.44.

***R*-2-Phthalimidopropionic acid methylthioethyl ester (3b):** oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67 (d, J = 7.4 Hz, 3H), 2.06 (s, 3H), 2.66 (m, 2H), 4.28 (m, 2H), 4.96 (q, J = 7.4 Hz, 1H), 7.71 (dd, J = 5.4, 3.1 Hz, 2H), 7.84 (dd, J = 5.4, 3.1 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.2 (q), 15.7 (q), 32.1 (t), 47.4 (d), 64.3 (t), 123.5 (d), 131.9 (s), 134.1 (d), 167.3 (s), 169.5 (s). HR-MS (PI-FAB): 293.0731 (calcd 293.0722).

Standard Irradiation Procedure. A solution of 2.0 mmol of the substrate in 200 mL of the appropriate solvent in a Pyrex vessel purged with a constant stream of dry nitrogen was irradiated for 24 h. After evaporation of the solvent, the pure products were obtained by column chromatography or recrystallization. Compounds **5a**,**d**,**e** and **6** are described in ref 3 and 19.

4b-Hydroxy-4b,5,10,11-tetrahydro-8-oxa-6-thia-11a-azacyclonona[*a*]indene-9,12-dione (4b): mp: 163−165 °C. ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6 (ca. 10%)): δ = 3.17 (d, J = 15.3 Hz, 1H), 3.31 (ddd, J = 13.0, 5.6 Hz, 1H), 3.52 (d, J = 15.3 Hz, 1H), 3.53−3.74 (m, 3H), 4.86 (d, J = 10.3 Hz, 1H), 5.25 (d, J = 10.3 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.41 (ddd, J = 7.5, 1.1 Hz, 1H), 7.53 (ddd, J = 7.5, 1.1 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$/DMSO-d_6 (ca. 10%)): δ = 34.1 (t), 36.0 (t), 38.0 (t), 64.2 (t), 91.2 (s), 121.4 (d), 122.7 (d), 129.4 (d), 131.7 (s, d), 132.2 (d), 146.6 (s), 169.6 (s), 172.5 (s). IR (CsI): $\bar{\nu}$ (cm^{-1}) = 3211, 1751, 1676, 1670, 1420, 1328, 1203, 1078, 764, 703. MS (EI, 70 eV): m/z (%) = 261 ($M^+ - H_2O$, 1), 217 (2), 203 (12), 188 (1), 160 (17), 104 (7), 77 (13), 61 (100), 46 (8). UV (MeCN): λ (nm, ϵ) = 215.6 (10194), 209.6 (4187), 206.6 (4240). Anal. Calcd for $C_{13}H_{13}NO_4S$ (279.31): C 55.90, H 4.69, N 5.01. Found: C 55.39, H 4.83, N 4.82.

4b-Hydroxy-4b,10,11,12-tetrahydro-5*H*-8-oxa-6-thia-12a-azacyclodeca[*a*]indene-9,13-dione (4c): mp: 175−178 °C. ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6 (ca.10%)): δ = 2.11−2.20 (m, 2H), 2.31 (m, 1H), 2.46 (m, 1H), 3.07 (d, J = 14.3 Hz, 1H), 3.28 (d, J = 14.3 Hz, 1H), 3.29 (m, 1H), 3.55 (m, 1H), 4.71 (d, J = 10.4 Hz, 1H), 4.89 (d, J = 10.4 Hz, 1H), 6.22 (s, 1H, OH), 7.23 (dd, J = 7.5, 1.0 Hz, 1H), 7.27 (ddd, J = 7.4, 7.5, 1.0 Hz, 1H), 7.36 (ddd, J = 7.4, 7.5, 1.0 Hz, 1H), 7.54 (dd, J = 7.4, 1.0 Hz, 1H). ^{13}C NMR (75.5 MHz, acetone-d_6/DMSO-d_6 (ca.10%)): δ = 24.1 (t), 32.9 (t), 36.1 (t), 38.4 (t), 62.9 (t), 90.6 (s), 121.0 (d), 122.4 (d), 129.0 (d), 131.8 (s, d), 147.1 (s), 170.7 (s), 171.3 (s). IR (CsI): $\bar{\nu}$ (cm^{-1}) = 3294, 1728, 1674, 1481, 1424, 1345, 1156, 1066, 779, 703. UV (MeCN): λ (nm, ϵ) = 239.6 (3555), 271.6 (1591), 281.2 (1027). Anal. Calcd for $C_{14}H_{15}NO_4S$ (293.33): C 57.32, H 5.15, N 4.77. Found: C 57.28, H 5.24, N 4.70.

***cis*-4b-Hydroxy-11-methyl-4b,5,10,11-tetrahydro-8-oxa-6-thia-11a-azacyclonona[*a*]indene-9,12-dione (*cis*-9a):** mp: 152−154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, J = 6.8 Hz, 3H), 2.63 (dd, J = 13.5, 5.2 Hz, 1H), 3.22 (d, J = 14.9 Hz, 1H), 3.46 (d, J = 14.9 Hz, 1H), 3.57 (dd, J = 13.5, 12.0 Hz, 1H), 4.13 (qdd, J = 5.2, 6.8, 12.0 Hz, 1H), 4.90 (d, J = 10.1 Hz, 1H), 5.06 (d, J = 10.1 Hz, 1H), 6.25 (s, 1H, OH), 7.31 (d, J = 7.1 Hz, 1H), 7.41−7.48 (m, 2H), 7.69 (dd, J = 6.8, 0.7 Hz, 1H). ^{13}C NMR (75.5 MHz, acetone-d_6/DMSO-d_6 (ca. 10%)): δ = 18.8 (q), 35.5 (t), 40.1 (t), 47.6 (d), 64.0 (t), 91.5 (s), 121.3 (d), 122.5 (d), 129.2 (d), 131.9 (d), 132.7 (s), 146.1 (s), 168.2 (s), 170.7 (s). IR (CsI): $\bar{\nu}$ (cm^{-1}) = 3324, 1763, 1708, 1692, 1684, 1672, 1469, 1437, 1364, 1202, 989, 707. MS (EI, 70 eV): m/z (%) = 275 (M^+-H_2O, 7), 245 (50), 230 (2), 202 (20), 188 (85), 161 (12), 147 (3), 76 (10), 69 (100), 51 (7). MS (EI, 70 eV, TMS-derivative): m/z (%) = 365 (M^+, 12), 350 (2), 335 (1), 319 (20), 276 (2), 261 (48), 160 (12), 73 (100). UV (MeCN): λ (nm, ϵ) = 230.8 (6324), 246.2 (3382). Anal. Calcd for $C_{14}H_{15}NO_4S$ (293.33): C 57.32, H 5.15, N 4.77. Found: C 56.89, H 5.08, N 4.32.

4b-Hydroxy-4b,5,7,8-tetrahydro-10-oxa-6-thia-11a-azacyclonona[*a*]indene-9,12-dione (7): mp: 186−188 °C (decomp.). ^{1}H NMR (300 MHz, acetone-d_6/DMSO-d_6 (ca. 10%)): δ = 2.72 (ddd, J = 15.3, 2.9, 5.1 Hz, 1H), 2.88 (ddd, J = 15.3, 5.4, 10.1 Hz, 1H), 2.93 (br. d, J = 13.8 Hz, 1H), 3.53 (br. d, J = 13.8 Hz, 1H), 3.77 (m, 1H), 3.78 (d, J = 16.0 Hz, 1H), 4.59 (ddd, J = 10.9, 2.9, 5.4 Hz, 1H), 4.77 (d, J = 16.0 Hz, 1H), 6.70 (s, 1H, OH), 7.50 (ddd, J = 7.3, 1.3 Hz, 1H), 7.55 (dd, J = 7.3, 1.0 Hz, 1H), 7.61 (ddd, J = 7.3, 1.2 Hz, 1H), 7.68 (dd, J = 7.3, 1.0 Hz, 1H). ^{13}C NMR (75.5 MHz, acetone-d_6/DMSO-d_6 (ca. 10%)): δ = 29.4 (t), 36.8 (t), 40.6 (t), 63.4 (t), 90.2 (s), 122.3 (d), 122.9 (d), 129.7 (d), 131.3 (s), 132.7 (d), 147.3 (s), 166.4 (s), 170.8 (s). IR (CsI): $\bar{\nu}$ (cm^{-1}) = 3376, 1746, 1700, 1682, 1419, 1245, 1059, 961, 699, 577. UV (MeCN): λ (nm, ϵ) = 222.2 (10833), 230.8 (7833), 253.2 (4000). Anal. Calcd for $C_{13}H_{13}NO_4S$ (279.31): C 55.90, H 4.69, N 5.01. Found: C 55.78, H 4.52, N 4.91.

***E*-8,11,12,13-Tetrahydro-7*H*-9-oxa-6-thia-13a-azacycloundeca[*a*]indene-10,14-dione (8).** This compound was detected in the proton NMR spectrum of the crude reaction product in mixture of the two isomers *E*-/*Z*-**8** (ca. 87:13). After purification, only *E*-**8** was isolated. *E*-**8**: mp: 166−170 °C. ^{1}H NMR (300 MHz, acetone-d_6/DMSO-d_6 (ca. 10%)): δ = 2.12 (m, 4H), 3.25 (t, J = 5.2 Hz, 2H), 3.87 (t, J = 5.7 Hz, 2H), 4.35 (t, J = 5.3 Hz, 1H), 6.14 (s, 1H), 7.54 (ddd, J = 7.5, 0.8 Hz, 1H, 7.67 (ddd, J = 7.8, 1.1 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75.5 MHz, acetone-d_6/DMSO-d_6 (ca. 10%)): δ = 23.9 (t), 31.7 (t), 34.6 (t), 37.8 (t), 65.4 (t), 107.5 (d), 123.5 (d), 125.3 (d), 129.9 (d), 132.1 (s), 132.8 (d), 135.6 (s), 137.3 (s), 173.5 (s).

(4b*R*,11*S*)-4b-Hydroxy-11-methyl-4b,5,7,8-tetrahydro-10-oxa-6-thia-11a-azacyclonona[*a*]indene-9,12-dione (9b). This compound was detected in the proton NMR spectrum of the crude reaction product in mixture of the two diastereoisomers *cis*-/*trans*-**9b** (ca. 80:20). After purification, only *cis*-**9b** was isolated. *cis*-**9b**: mp: 145−148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (d, J = 7.5 Hz, 3H), 2.71 (ddd, J = 15.6, 0.9, 5.1 Hz, 1H), 2.89 (d, J = 15.4 Hz, 1H), 3.07 (ddd, J = 15.6, 5.7, 12.1 Hz, 1H), 3.59 (ddd, J = 11.0, 5.1, 12.1 Hz, 1H), 3.83 (d, J = 15.4 Hz, 1H), 4.65 (ddd, J = 11.0, 0.9, 5.7 Hz, 1H), 5.46 (q, J = 7.5 Hz, 1H), 5.59 (s, 1H, OH), 7.48−7.65 (m, 3H), 7.69 (m, 1H). ^{13}C NMR (75.5 MHz, acetone-d_6): δ = 15.4 (q), 33.2 (t), 41.8 (d), 48.2 (t), 63.2 (t), 93.2 (s), 122.2 (d), 123.6 (d), 130.2 (d), 133.0 (s), 133.3 (d), 148.2 (s), 167.5 (s), 174.1 (s). IR (CsI): $\bar{\nu}$ (cm^{-1}) = 3412, 1743, 1696, 1472, 1388, 1170, 1073, 776, 703. UV (MeCN): λ (nm, ϵ) = 220.4 (16104), 226.8 (12593), 244.8 (6156), 282.8 (2575), 306.4 (2224). Anal. Calcd for $C_{14}H_{15}NO_4S$ (293.33): C 57.32, H 5.15, N 4.77. Found: C 57.35, H 5.18, N 4.62.

***trans*-9b**: ^{1}H NMR (300 MHz, acetone-d_6, in mixture with *cis*-**9b**): δ = 1.81 (d, J = 7.2 Hz, 3H), 2.57 (ddd, J = 15.1, 1.3, 3.6 Hz, 1H), 2.96 (m, 1H), 3.30 (d, J = 13.9 Hz, 1H), 3.72 (d, J = 13.9 Hz, 1H), 4.23 (ddd, J = 11.0, 3.6, 11.9 Hz, 1H), 4.33 (ddd, J = 11.0, 0.8, 5.3 Hz, 1H), 5.39 (q, J = 7.2 Hz, 1H), 5.79 (s, 1 H, OH), 7.46−7.65 (m, 4H).

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Supporting Information Available: Tables of crystallographic data of compounds **4b**, **7**, *E*-**8**, and *cis*-**9b**; ^{1}H and ^{13}C NMR spectra of compounds **4b**, **7**, *E*-**8**, *cis*-**9a**, and *cis*-**9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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