Photochemistry of *N*-Phthaloyl α-Amino Acid Esters: A New Approach to β,γ-Unsaturated α-Amino Acid, Dihydrobenzazepinedione, and Pyrrolizidinone Derivatives

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The *N*-phthaloyl-α-amino acid methyl esters of 2-aminobutyric acid (**2a**), valine (**2b**), norvaline (**2c**), *tert*-leucine (**2d**), isoleucine (**2e**), *allo*-isoleucine (**2f**), leucine (**2g**), methionine (**2h**), alanine (**2i**), and phenylalanine (**2k**) were synthesized in enantiomerically pure form via the *N*-phthaloyl-α-amino acids (**1a–k**), and their photochemistry was studied. Except **2i** and **2k**, which proved to be photostable, all compounds were converted into three types of products, depending on the substitution pattern: a) isomerization products (derivatives of β,γ-unsaturated α-amino acids) **3a**, **b**, **c**, and **e**, b) ring expansion products (benzazepinedione esters) **4a** and **c**, and c) cyclization products (**5d** from the *tert*-leucine derivative **2d**). High diastereoselectivities (d.r. >95:5) were observed for all reactions except the transformations of the 2-aminobutyric acid derivative **2a**. The absolute configuration of the α-stereogenic center was retained during photolysis, as proven for the isodehydrovaline (type a product) **3b**. PCC oxidation (to give **7b**) and hydrogenation afforded **2b** with an optical rotation comparable to the starting material. Treatment of **3b** with an acid or a base led to epimerization (**3b'**) or isomerization of the C=C bond (**6b**), respectively. The diastereomeric dihydrobenzazepinedione esters **4a**, **b** were formed with d.r. = 33:67 (*cis*:*trans*) and in 60% yield during photolysis of **2a**. The isoleucine derivative **2e**, however, was converted into the *cis* isomer **4a** with high diastereoselectivity (d.r. >95:5), whereas the corresponding *allo* substrate **2f** was only converted into the *trans*-isomer **4b**. Ethylene was extruded during irradiation of the latter substrates and during irradiation of the norvaline derivative **2c**, whereas propene extrusion from the leucine derivative **2g** led to the formation of the unsubstituted type b product **4c**. The methionine derivative **1h** was the only *N*-phthaloylamino acid which did not show photodecarboxylation, instead two ζ-hydrogen abstraction products were formed: the hydroxy acid **9h** and the tetracyclic lactone **10h**. The methionine ester **2h** was only converted into the ring expansion products **11h**, **h'** presumably by a photo electron transfer step. The chronology of the double hydrogen transfer reaction (γ- followed by δ-H abstraction, leading to type a products) was determined by using the deuterium labeled compound (±)[3-D_1]-**2b**.

The photochemistry of *N*-substituted phthalimides has been intensively investigated by several research groups in the last twenty years[2a–c]. The imido group displays high photochemical reactivity and versatility and most carbonyl-type reactions have been observed such as hydrogen abstraction[3], α-cleavage[4], [2 + 2] cycloaddition reaction (oxetane formation)[5], photoreduction[6], and electron-transfer reactions[7]. An efficient method for the decarboxylation of α-amino acids has been developed by Sato et al. in the irradiation of *N*-phthaloyl-α-amino acids[8]. The corresponding esters which cannot undergo decarboxylation during irradiation have, however, not been investigated yet. The only exception was *N*-phthaloylmethionine methyl ester, the rapid ring expansion reaction of which has been reported[9]. We have been interested in the photochemistry of these type of substrates, because it has been reported that the $^1(n\pi^*)$ state may be the reactive excited state[10]. This should lead to pronounced effects on the stereoselectivity of the photoreaction as already described for singlet-excited naphthyl aldehydes[11]. In this paper we describe full experimental details of our first investigations in this field[12].

Results

Starting Material

Most α-amino acids could be converted to their *N*-phthaloyl derivatives **1** by adding them directly to melted phthalic anhydride (140°C). This modification of a literature procedure[13] did not lead to detectable racemization as a comparison with literature data and NMR-spectroscopic analysis of the isoleucine and *allo*-isoleucine derivatives **1e** and **1f** revealed (for both compounds the diastereomerical purity was determined to be >98%). *N*-Phthaloyl-*tert*-leucine (**1d**), however, rapidly underwent ring opening during esterification. Compound **2d** was therefore synthesized via its methyl ester hydrochloride with *N*-(ethoxycarbonyl)phthalimide[14]. Esterification of the acids **1** with MeOH/HCl led to the methyl esters **2** in quantitative yields. Table 1 gives the relevant physical data for the substrates **2a–k**.

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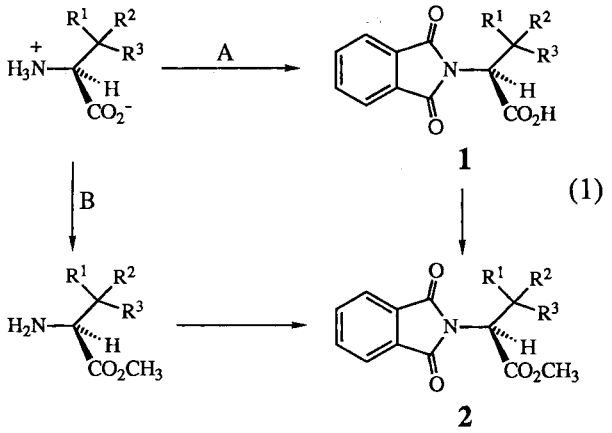
Table 1. Characteristic spectroscopic data of amino acid derivatives **1a–k** and **2a–k**

		^{1}H-NMR [a][b]	^{13}C-NMR [b][c]	Yield (%)	
		NCH (2)	NCH (2)	**1**	**2**
Abu	(**a**)	4.79 *(dd, 6.4, 9.4)*	53.9	97	92
Val	(**b**)	4.48 *(d, 8.3)*	57.5	98	94
Nva	(**c**)	4.79 *(dd, 5.0, 10.7)*	52.1	98	93
Tle	(**d**)	4.64 *(s)*	59.4		35 [d]
Ile	(**e**)	4.66 *(d, 8.3)*	57.0	99	99
allo-Ile	(**f**)	4.67 *(d, 7.3)*	55.7	98	98
Leu	(**g**)	4.97 *(dd, 4.2, 11.6)*	50.6	97	97
Met	(**h**)	5.07 *(dd, 5.5, 8.8)*	50.7	97	99
Ala	(**i**)	4.91 *(q, 7.3)*	47.3	98	93
Phe	(**k**)	5.08 *(dd, 5.7, 10.8)*	53.1	96	93

[a] 250 MHz. – [b] 63 MHz. – [c] $CDCl_3$. – [d] Method B.



A: 1) phthalic anhydride /135°C (100 %);
2) MeOH/HCl 10°C (98 %)

B: 1) MeOH/HCl, room temperature (>98 %);
2) N-(ethoxycarbonyl)-phthalimide /H_2O/Na_2CO_3 (45 - 55%)

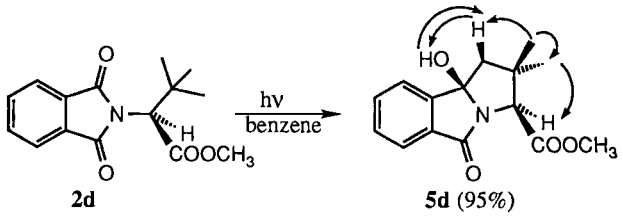
Photoreactions

All photoreactions were performed at 13°C in benzene (5 mmol) by using a Rayonet photoreactor equipped with 300-nm lamps. The *N*-phthaloyl methyl esters of alanine (**2i**) and phenylalanine (**2k**) showed no photoreaction even after irradiation for 100 h. For all other compounds quantitative conversion was observed after 36–48 h. All products were separated and purified by column chromatography and fully characterized. For the sake of simplification we will describe the results with respect to the existing abstractable hydrogens in the substrate. These are classified as β, γ, etc. with respect to the phthalimide nitrogen as the α position.

1) δ Hydrogens

In the *tert*-leucine compound **2d** only δ hydrogens are available for hydrogen abstraction. The benzoanellated pyrrolizidinone **5d** was isolated in 95% yield as the diradical cyclization product. ^{1}H- as well as ^{13}C-NMR analysis revealed that only one diastereomer was formed. From NOE difference spectroscopy a *cis* alignment of methyl ester and hydroxyl group of the aminoacetal functionality (3*S*,9b*R*) was verified. The relevant positive NOE's are shown in Scheme 1.

Scheme 1



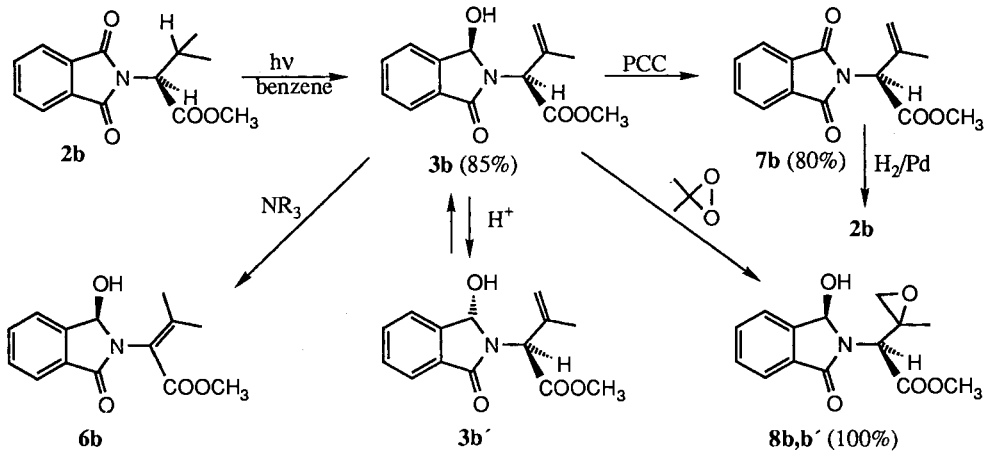
Saturation of the hydroxyl hydrogen leads to an enhancement of one of the two diastereotopic methylene hydrogens (2.1%). The relative configuration of this hydrogen was established by the NOE from saturation of one of the diastereotopic methyl groups (5.8%). This methyl group on saturation did not lead to a positive NOE on the α-methoxycarbonyl hydrogen, whereas the corresponding *gem*-methyl group showed an NOE of 10%.

2) γ and δ Hydrogens

The valine derivative **2b** was converted with high chemoselectivity into the substituted isoindolinone **3b**, again with a diastereoselectivity higher than 95:5. From the NMR data we assume that the relative configuration is equivalent to that of the pyrrolizidione **5d**, i.e. (1*S*,1′*R*). That **3b** is formed kinetically controlled could be shown by transformation to an equilibrium mixture of diastereomers **3b**, **b′** by acid catalysis. Treatment of **3b** in dichloromethane with catalytic amounts of HCl led to a 1:1 mixture of **3b**, **b′** after 24 h at room temperature. In contrast to acid catalysis, base catalysis (tertiary amines, e.g. tri-*n*-butylamine) caused rearrangement of the C=C bond to afford the α,β-unsaturated compound **6b**. A similar LiOH-catalyzed isomerization of a vinylglycine derivative has been reported[15].

Another question concerned the absolute configuration at the stereogenic center of the amino acid side chain. Oxidation of the hydroxyisoindolinone **3b** to the *N*-phthalimide-protected isodehydrovaline methyl ester **7b** was tried with serveral oxidants: neither oxalyl chloride/DMSO (Swern oxidation[16]) nor Ce(IV) ammonium nitrate[17] afforded more than 20% conversion. Dimethyldioxirane[18] quantitatively converted **3b** to a 1:1 mixture of diastereomeric epoxides **8b**, **b′**. Finally, the oxidation of **3b** could be successfully (95% conversion) accomplished with pyridinium chlorochromate adsorbed on alumina[19]. Hydrogenation (H_2/Pd-C) of **7b** gave **2b** with >96% retention of configuration, as

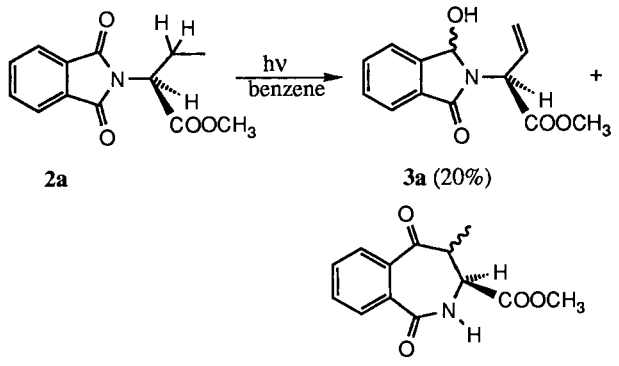
Scheme 2



the comparison of the optical rotation with the starting material **2b** revealed.

In contrast to the results with the valine derivative **2b**, the 2-aminobutyric acid analog **2a** did not show a high chemo- or stereoselectivity: the isomerization product **3a** was formed in 25% relative yield as a mixture of diastereomers. Additionally, the dihydrobenzazepinedione esters *cis*-**4a** and *trans*-**4a** were formed in 60% yield and in a ratio of 33:67. The relative configurations of these ring expansion products could be determined from the $^3J_{HH}$ coupling constants of the azepine α and β hydrogens. For *cis*-**4a** $^3J_{HH}$ is 2.7 and for *trans*-**4a** 8.4 Hz, in keeping with the calculated (force-field, MM2) values $^3J_{HH}$(*cis*-**4a**) = 0.9 and $^3J_{HH}$(*trans*-**4a**) = 7.8 Hz.

Scheme 3

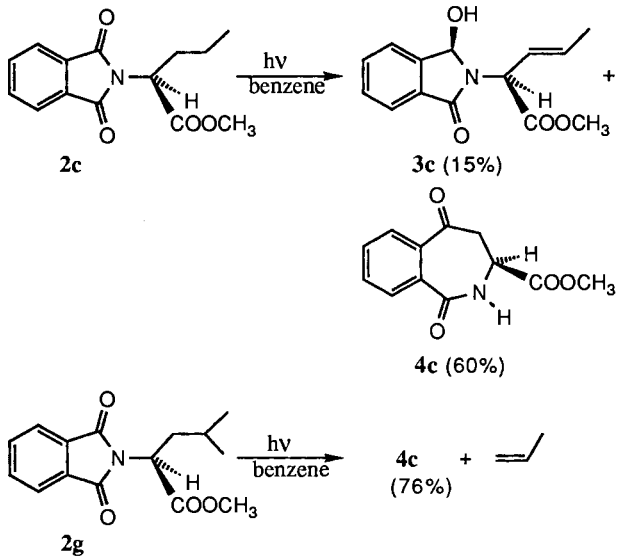


3) γ, δ, and ε Hydrogens

When these three types of abstractable hydrogens were present in the substrate, as in the norvaline (**2c**), leucine (**2g**), and both isoleucine derivatives (**2e**, **2f**), besides the isomerization products **3c** and **3e** the ring expansion products **4a** and **4c** were formed with concomitant extrusion of ethylene and propene, respectively.

For the leucine derivative **2g** this reaction mode was even the only detectable, i.e. the unsubstituted benzazepinedione **4c** was isolated in 76% yield. The same ring expansion product was formed as the main product in the photoreaction of the norvaline derivative **2c** (80% rel. yield), but additionally the unsaturated product **3c** was formed as minor component (20% rel. yield) with >95% *E* selectivity and also >95% diastereoselectivity with respect to the additionally formed stereogenic center in the isoindolinone skeleton. The configuration of the C=C bond is clearly *trans*, as the $^3J_{HH}$ constant of 6.3 Hz showed. For a corresponding *N*-Boc-protected *Z* isomer a *vic* coupling constant of $^3J_{HH}$ = 15.2 Hz has been reported[20].

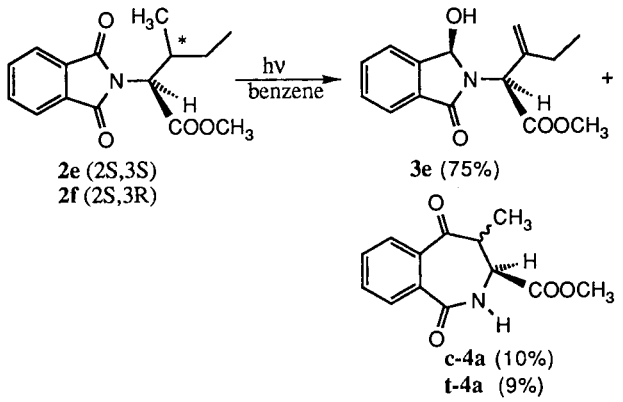
Scheme 4



The photoreaction of **2e** as well as of its *allo* isomer **2f** led to the same isomerization product **3e** in 75% relative yield and (for both substrates) with a diastereoselectivity >95%. As minor isomers (25%), the methyl-substituted dihydrobenzazepinediones *cis*-**4a** and *trans*-**4a**, as already described for the 2-aminobutyric derivative, were formed *stereospecifically*, i.e. *cis*-**4a** from the isoleucine precursor **2e** and *trans*-**4a** from the *allo*-isoleucine precursor **2f**.

This result was derived from a competition experiment by using a 55:45 mixture of **2e** and **2f**, corresponding to the ratio of commerically available isoleucine diastereomers. In this photoreaction, the diastereomeric dihydrobenzazepinediones *cis*-**4a** and *trans*-**4a** were formed in a 55:45 ratio and with 6 and 5% relative yield, respectively.

Scheme 5

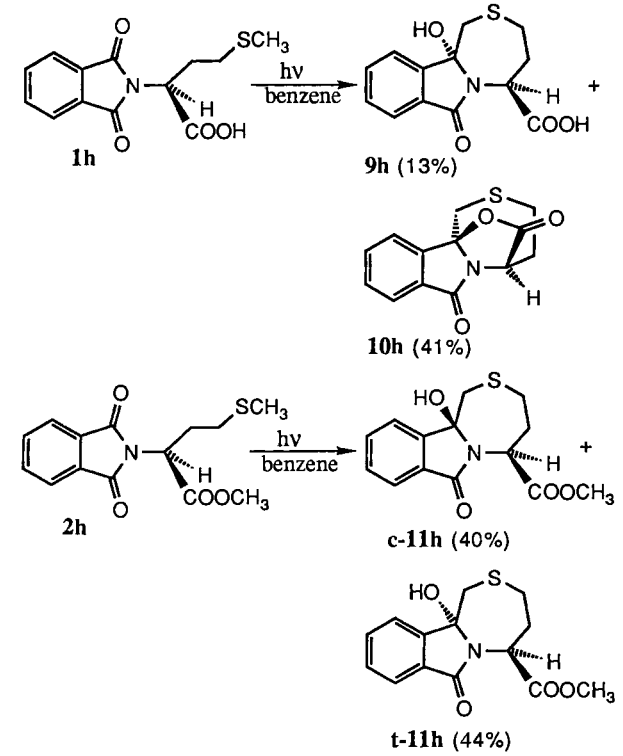


4) γ, δ, and ζ Hydrogens

The only compounds we investigated in this series were the methionine derivatives **1h** and **2h**. In contrast to the results published by Kanaoka et al.[9], photodecarboxylation was not observed in the case of the *C*-unprotected amino acid **1h**. After a pronounced shorter irradiation time than for the cases described before (less than 36 h for complete conversion) two main products were isolated with 13 and 14% yield, respectively, i.e. the *trans* hydroxy acid **9h** and the tetracyclic lactone **10h**. Apparently, the corresponding *cis* hydroxy acid which could never be detected in the crude reaction mixture immediately cyclizes to the lactone **10h** under the reaction conditions used. Especially the IR spectra and the similarity between the NMR spectra of **10h** and *cis*-**11h** reveal the proposed structures.

Analogously, the irradiation of the corresponding methyl ester **2h** afforded two diastereomeric products of ζ hydrogen abstraction and subsequent cyclization, namely *cis*-**11h** and *trans*-**11h** in a 48:52 ratio.

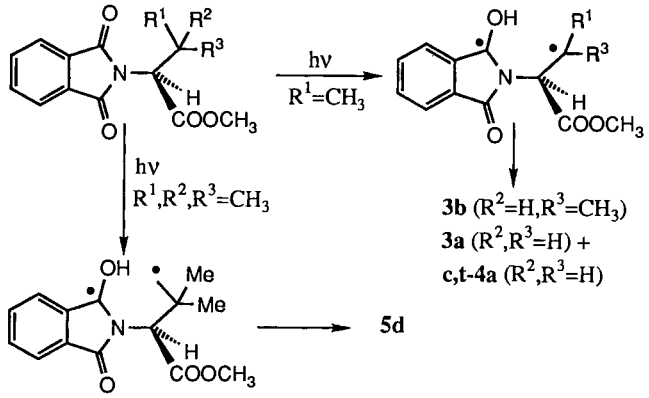
Scheme 6



Mechanistic Considerations

All photoreactions described here are initiated by hydrogen abstraction reactions. This initial step is also the elementary step of the Norrish-type II transformation, of which numerous mechanistic investigations are known. In this reaction, abstraction of a hydrogen from the γ position with respect to the electronically excited carbonyl group is favored. In open-chain systems the geometrical prerequisites are optimally fulfilled (six-membered transition state) as X-ray investigations of model compounds[21] and ab initio calculations[22] reveal. As our investigations clearly show, this situation must be different in the photochemistry of phthalimides. Because of the fact that the carbonyl group (which is photochemically excited), the phthalimide nitrogen, and the β carbon atom must be in one plane, the γ hydrogen cannot reach the optimal position for rapid C–H cleavage. This must be the reason for the drastically decreased reactivity of the alanine and phenylalanine compounds **2i** and **2k** which both possess only γ hydrogens. Especially hydrogen abstraction from a benzylic position (as possible for the phenylalanine derivative **2k**) should be thermodynamically favored.

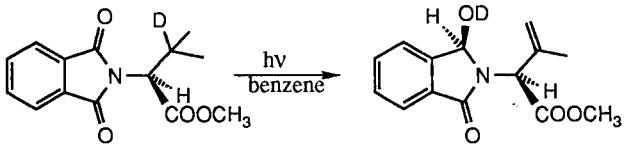
Scheme 7



In contrast, the *tert*-leucine derivative **2d**, which only bears δ hydrogens, rapidly undergoes hydrogen abstraction and radical recombination to give **5d**. This homologous Norrish-type II reaction is known for a series of organic substrates with hindered or nonexisting γ hydrogen positions[23]. A δ hydrogen abstraction must also be the initial step in the photodecarboxylation of *C*-unprotected *N*-phthaloylamino acids as described by Sato et al.[8], which is for all substrates **1a–g**, **1i** and **1k** by far the dominating reaction. An experiment with the specifically deuterium-labeled valine derivative [3-D_1]-**2b** (Scheme 8) showed, that the initial step in the photoreaction of *this* substrate is the abstraction of a hydrogen atom from the γ position. This change in reactivity is presumably due to a *gem*-dialkyl effect, which restricts the conformational flexibility of the amino acid side chain and activates the γ position.

The high stereoselectivity in the phototransformations of **2b**, **c**, **d**, **e**, and **2f** concerning the formation of the photoisomerization products **3b**, **c**, **e** can be directly correlated

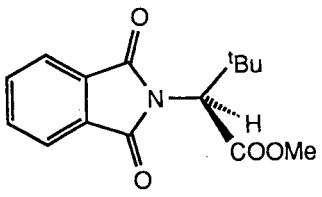
Scheme 8



[3-D_1]-**2b** [D_1]-**3b** (92%)

with the activation barrier to rotation around the N–C_α single bond, which was determined by ^{13}C-NMR spectroscopy.

In Figure 1 is given the ^{13}C-NMR spectrum for the *tert*-leucine derivative **2d** at different temperatures. Three coalescence temperatures were determined for the *ortho*, the *meta*, and the *ipso* carbon resonances, from which an activation barrier of 12.5 ± 0.5 kcal/mol was calculated. For the valine derivative **2b** a corresponding analysis gave 9.0 ± 0.5 kcal/mol. This method could not be applied to the 2-aminobutyric acid derivative **2a**, i.e. no coalescence was observed down to −100 °C. Therefore, an upper value of 5–6 kcal/mol for this rotation barrier could be estimated. Forcefield calculations indicate that in the conformational minimum the methoxycarbonyl as well as the alkyl substituent are located in a dihedral angle of approximately 55° with respect to the plane of the phthalimide ring. Therefore, the primary hydrogen abstraction (γ or δ) occurs from the *Si* side of one of the phthalimide carbonyl groups. The 1,4- or 1,5-diradical formed (which should be a singlet diradical because of the reactive ^{1}[nπ*] state of the electronically excited phthalimide[10]) should exhibit a pronounced shorter lifetime than that of the initial conformer and therefore the second step (diradical cyclization as in the *tert*-leucine (**2d**) derivative or transfer of a second hydrogen as in the case of valine (**2b**), norvaline (**2c**), and isoleucine (**2e**, **f**) also has to occur from the *Si* side (*lk* topicity). Apparently, this relationship is different for the 2-aminobutyric derivative (**2a**). Because of the increased flexibility of the N–C_α single bond, the second hydrogen transfer (leading to the vinylglycine derivative **3a**) or the radical recombination reaction (leading to intermediary diastereomeric hydroxyazetines) occurs non-selectiv from both the *Si* and the *Re* side of the hydroxybenzyl radical. Transannular ring opening of the hydroxyazetines (which were never detected in the reaction mixture) leads to the diastereomeric benzazepinediones *cis*-**4a** and *trans*-**4a**.



2d

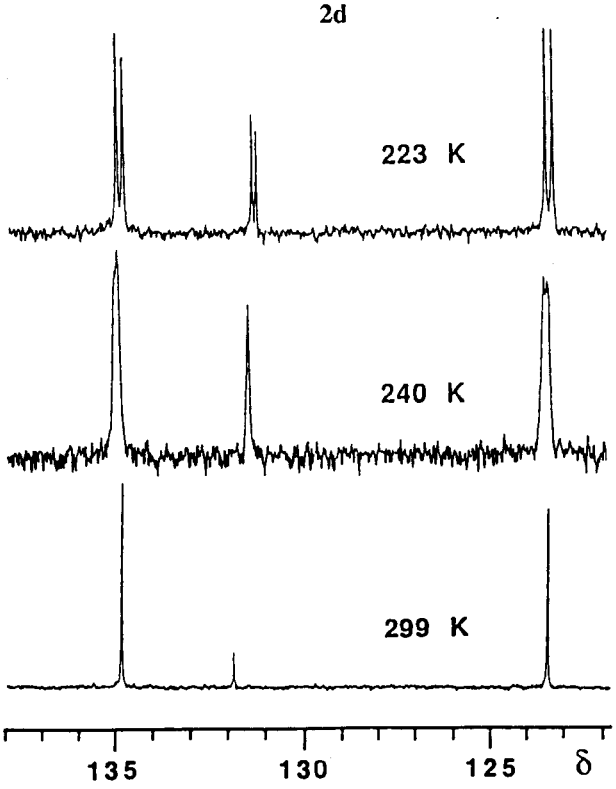
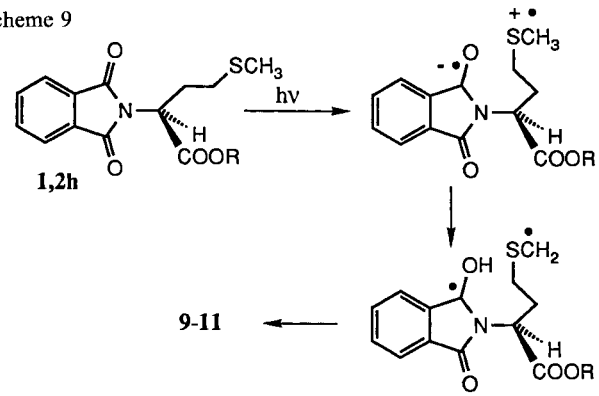


Figure 1. ^{13}C-NMR spectra ($CDCl_3$, 100.6 MHz) of **2d**

Scheme 9



A completely different situation is evident for the methionine substrates **1h** and **2h**. In both the acid and the methyl ester only a ζ hydrogen atom is abstracted. Because no isomerization product could be formed in the subsequent reaction step, the radical recombination products **9h**, **10h**, and **11h** are the only detectable products. This remarkable change in reactivity could be due to a primary electron transfer from the excited phthalimide carbonyl group to the methionine sulfur atom with concomitant proton transfer as already postulated by Kanaoka et al.[24] Even the *C*-unprotected amino acid which normally undergoes rapid decarboxylation is only converted to the anellation products **9h** and **10h** with intact carboxyl group in the methionine derivative **1h**. We therefore conclude that in nonpolar solvents such as benzene intramolecular electron transfer from appropriate electron donor heteroatoms must be at least 50 times faster than hydrogen abstraction from the hydroxyl group of the *C*-unprotected amino acid. In the absence of such donor atoms, the δ hydrogen transfer and decarboxylation is again ca. 50–100 times faster than any competing reaction, which accounts for hydrogen bonding interaction already in the ground state of the substrate.

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Experimental

IR: Perkin-Elmer 1420 spectrometer. – ^{1}H NMR: Hitachi-Perkin-Elmer R-24 B (60 MHz), Bruker AW 80 (80 MHz), Bruker AC 200 (200 MHz), Bruker AC 250 (250 MHz), Bruker WM 400 (400 MHz). – ^{13}C NMR: Bruker AC 200 (50.3 MHz), Bruker AC 250 (63.4 MHz), Bruker WM 400 (100.6 MHz), TMS as internal standard. – MS: Varian MAT CH 7 and Finnigan MAT 8200. – 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. – Combustion analyses: Institut für Anorganische Chemie der Universität Würzburg.

General Procedure for the Synthesis of N-Phthaloyl α-Amino Acids **1**: 10.0 mmol of phthalic anhydride was melted in a stoppered flask preheated to 140–145°C. During vigorous stirring 10.0 mmol of α-amino acid was added within 5 min. This mixture was kept at 140°C for about 10 min. During the last 5 min the flask was opened in order to evaporate the reaction water. After cooling the crystalline residue was recrystallized from MeOH or used for esterification without further purification.

General Procedure for the Synthesis of N-Phthaloyl α-Amino Acid Esters **2**: A stream of gaseous HCl was bubbled through a cooled (0°C) solution of 15.0 mmol of *N*-phthaloyl-α-amino acid (**1**) in 50 ml of methanol for 2 min. After cooling again to 0°C the solution was again saturated with gaseous HCl for 2 min. The solution was stirred for complete conversion (about 4 h) and the methanol removed at reduced pressure. Product formation was monitored by TLC. Yields for both steps and characteristic spectroscopical data of the *N*-phthaloyl-α-amino acid esters **2** are given in Table 1.

Irradiation of N-Phthaloyl α-Amino Acid Esters **2**

1. *(S)-N-phthaloyl-tert-leucine Methyl Ester* (**2d**): A solution of 200 mg (0.727 mmol) of **2d** in 100 ml of benzene was irradiated (λ = 300 nm) for 10 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 2:1) to give 189 mg (95%) of methyl *(3S,9bR)-2,3,5-9b-tetrahydro-9b-hydroxy-2,2-dimethyl-5-oxo-1H-pyrrolo[2,1-a]isoindol-3-carboxylate* (**5d**) as a colorless oil. – IR (CCl_4): $\tilde{\nu}$ = 3350 cm^{-1} (br w), 2880 (w), 1670 (vs), 1520 (vs), 1350 (m), 1230 (s), 1190 (s), 990 (s), 980 (s), 950 (m), 620 (w). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.88 (d, *J* = 13.6 Hz, 1H, CH_2), 2.24 (d, *J* = 13.6 Hz, 1H, CH_2), 3.72 (s, 3H, OCH_3), 4.30 (s, 1H, CH), 4.58 (br s, 1H, OH), 7.36–7.65 (m, 4H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 24.1 (q), 29.0 (q), 47.6 (s), 49.0 (t), 51.3 (q), 66.6 (d), 95.7 (s), 121.6 (d), 123.0 (d), 128.6 (d), 129.4 (s), 132.4 (s), 147.5 (s), 169.9 (s), 171.7 (s). – MS (70 eV): *m/z* (%) = 258 (1) [M^+ – OH], 257 (4), 242 (5), 219 (32), 216 (11) [M^+ – CO_2CH_3], 198 (36), 154 (57), 132 (14), 86 (100), 84 (100). – $[\alpha]_D$ = –39.1 (*c* = 1.0, MeOH).

$C_{15}H_{17}NO_4$ (275.3) Calcd. C 65.44 H 6.22 N 5.09
Found C 65.81 H 6.38 N 5.07

2. *(S)-N-Phthaloylvaline Methyl Ester* (**2b**): A solution of 500 mg (1.91 mmol) of **2b** in 100 ml of benzene was irradiated (λ = 300 nm) for 24 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 4:1 to 1:1) to give 425 mg (85%) of *methyl (1'R,2S)-2-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-2-yl)-3-methyl-3-butenoate* (**3b**) (R_f = 0.43, PE/EA, 1:1) as a colorless oil. – IR (CCl_4): $\tilde{\nu}$ = 3350 cm^{-1} (br. s), 3010 (w), 2900 (s), 2860 (m), 1670 (vs), 1520 (vs), 1415 (s), 1340 (s), 1200 (m), 1050 (s), 900 (m). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.79 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.72 (s, 1H, OH), 5.03 (s, 1H, $=CH_2$), 5.25 (s, 1H, $=CH_2$), 5.59 (s, 1H, NC*H*CO_2Me), 5.82 (s, 1H, NC*H*OH), 7.55 (dd, *J* = 7.6/4.1 Hz, 1H, Ar-H), 7.59 (d, *J* = 3.9 Hz, 2H, Ar-H), 7.78 (d, *J* = 7.1 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.4 (q), 52.9 (q), 59.2 (d), 80.3 (d), 117.4 (t), 123.3 (d), 123.6 (d), 129.5 (d), 129.9 (s), 132.8 (d), 137.5 (s), 144.5 (s), 168.1 (s), 172.8 (s). – MS (70 eV): *m/z* (%) = 261 (<1) [M^+], 202 (1), 148 (<1), 88 (10), 86 (64), 84 (100), 51 (3), 49 (15), 47 (19). – $[\alpha]_D$ = –21.1(*c* = 1.0, MeOH).

$C_{14}H_{15}NO_4$ (261.3) Calcd. C 64.35 H 5.79 N 5.36
Found C 64.74 H 5.77 N 5.73

3. *Methyl (RS)-2-(Phthaloylamino)butyrate* (**2a**): A solution of 500 mg (2.02 mmol) of **2a** in 100 ml of benzene was irradiated (λ = 300 nm) for 75 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1 to 1:1) to give 97 mg of **3a**, 99 mg of *cis*-**4a** and 201 mg of *trans*-**4a** in a total yield of 80%. The ^{1}H-NMR analysis of the crude reaction mixture indicated a ratio of **3a**:*cis*-**4a**:*trans*-**4a** of 25:25:50.

Methyl (1'R,2S*)-2-(2,3-Dihydro-1-hydroxy-3-oxo-1H-isoindol-2-yl)-3-butenoate* (**3a**): Colorless oil, R_f = 0.30. – IR (CCl_4): $\tilde{\nu}$ = 3440 cm^{-1} (m), 2980 (m), 2950 (m), 1740 (vs), 1480 (m), 1445 (m), 1400 (s), 1225 (s), 1060 (m), 920 (m). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.65–3.73 (br s, 1H, OH), 3.73 (s, 3H, OCH_3), 5.40 (d, *J* = 17.2, 1H, $=CH_2$), 5.44 (d, *J* = 10.2 Hz 1H, $=CH_2$), 5.45 (d, *J* = 7.2 Hz, 1H, NCH), 5.87 (s, 1H, CHOH), 6.17 (ddd, *J* = 7.2/10.2/17.2 Hz, 1H, =CH), 7.46 (dd, *J* = 4.3/7.4 Hz, 1H, Ar-H), 7.54 (dd, *J* = 0.9/4.3 Hz, 2H, Ar-H), 7.74 (d, *J* = 7.4 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.9 (q), 56.4 (d), 80.8 (d), 121.9 (d), 123.2 (t), 123.5 (d), 129.6 (d, 2 C), 130.5 (s), 132.5 (d), 144.3 (s), 167.1 (s), 171.8 (s). – MS (70 eV): *m/z* (%) = 247 (3) [M^+], 202 (28), 188 (100), 160 (29), 148 (17), 133 (100), 114 (11), 105 (26), 91 (18), 77 (27).

$C_{13}H_{13}NO_4$ (247.2) Calcd. C 63.15 H 5.30 N 5.67
Found C 63.07 H 5.48 N 5.80

Methyl (3S,4S*)-2,3,4,5-Tetrahydro-4-methyl-1,5-dioxo-1H-benz[c]azepine-3-carboxylate* (*cis*-**4a**): Colorless oil, R_f = 0.24. – IR (CCl_4): $\tilde{\nu}$ = 3385 cm^{-1} (m), 2955 (w), 1750 (vs), 1678 (vs), 1600 (w), 1370 (m), 1270 (s), 1218 (s), 1180 (m), 1005 (m), 920 (w). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 7.2 Hz, 3H, CH_3), 3.15 (dd, *J* = 2.7/7.2 Hz, 1H, C*H*–CH_3), 3.78 (s, 3H, OCH_3), 4.78 (dd, *J* = 2.7/5.0 Hz, 1H, C*H*–CO_2CH_3), 6.86 (d, *J* = 5.0 Hz, 1H, NH), 7.53–7.64 (m, 3H, Ar-H), 7.86 (dd, *J* = 2.3/5.5 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 10.2 (q), 51.4 (d), 53.3 (q), 55.0 (d), 128.6 (d), 129.9 (d), 131.6 (s), 132.3 (d), 132.7 (d), 136.5 (s), 168.1 (s), 169.3 (s), 202.5 (s). – MS (70 eV): *m/z* (%) = 247 (<1) [M^+], 182 (2), 171 (5), 154 (8), 127 (11), 113 (10), 99 (21), 85 (43), 71 (63), 57 (100).

$C_{13}H_{13}NO_4$ (247.2) Calcd. C 63.15 H 5.30 N 5.67
Found C 63.12 H 5.40 N 5.66

Methyl (3S,4R*)-2,3,4,5-Tetrahydro-4-methyl-1,5-dioxo-1H-benz[c]azepine-3-carboxylate* (*trans*-**4a**): Colorless oil, R_f = 0.16. – IR (CCl_4): $\tilde{\nu}$ = 3450 cm^{-1} (m), 2960 (m), 1750 (vs), 1680 (vs), 1432 (w), 1365 (m), 1255 (s), 1230 (m), 1015 (m), 912 (m). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 7.4 Hz, 3H, CH_3), 3.28 (dq,

J = 7.4/8.4 Hz, 1H, $CH-CH_3$), 3.61 (s, 3H, OCH_3), 4.13 (dd, J = 6.3/8.4 Hz, 1H, $CH-CO_2CH_3$), 7.15 (d, J = 6.3 Hz, 1H, NH), 7.46–7.61 (m, 3H, Ar-H), 7.82 (dd, J = 2.0/7.0 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.0 (q), 53.4 (d), 53.5 (q), 57.3 (d), 128.8 (d), 130.1 (d), 131.8 (s), 132.7 (d), 132.9 (d), 136.6 (s), 169.7 (s), 170.2 (s), 204.4 (s). – MS (70 eV): m/z (%) = 247 (<1) [M^+], 183 (2), 171 (5), 125 (7), 113 (11), 97 (17), 85 (39), 71 (67), 69 (25), 57 (100). $C_{13}H_{13}NO_4$ (247.2) Calcd. C 63.15 H 5.30 N 5.67 Found C 63.40 H 5.43 N 5.76

4. *(S)-N-Phthaloylleucine Methyl Ester* (**2g**): A solution of 500 mg (1.82 mmol) of **2g** in 100 ml of benzene was irradiated (λ = 300 nm) for 24 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1 to 1:1) to give 321 mg (76%) of *methyl (3S)-2,3,4,5-tetrahydro-1,5-dioxo-1H-benz[c]azepine-3-carboxylate* (**4c**) as a colorless oil, R_f = 0.16. – IR (Film): $\tilde{\nu}$ = 3480 cm^{-1} (m), 2950 (w), 1745 (s), 1670 (vs), 1590 (w), 1425 (m), 1360 (m), 1265 (s), 1215 (w), 905 (m). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.20 (dd, J = 10.2/18.9 Hz, 1H, CH_2), 3.31 (dd, J = 18.9/4.0 Hz, 1H, CH_2), 3.80 (s, 3H, OCH_3), 4.62 (ddd, J = 4.0/5.5/10.1 Hz, 1H, CH), 7.25 (br d, J = 5.5 Hz, 1H, NH), 7.60–7.74 (m, 3H, Ar-H), 7.95 (dd, J = 1.8/6.9 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 49.4 (t), 51.1 (d), 53.9 (q), 129.1 (d), 130.8 (d), 132.6 (s), 132.7 (d), 133.5 (d), 136.1 (s), 168.8 (s), 170.0 (s), 199.6 (s). – MS (70 eV): m/z (%) = 233 (10) [M^+], 221 (2), 202 (1), 174 (100) [$M^+ - CO_2CH_3$], 147 (70), 129 (29), 104 (13), 86 (40), 84 (57). – $[\alpha]_D$ = –11.6 (c = 0.5, MeOH).

$C_{12}H_{11}NO_4$ (233.2) Calcd. C 61.80 H 4.75 N 6.01 Found C 61.90 H 4.76 N 6.04

5. *(S)-N-Phthaloylnorvaline Methyl Ester* (**2c**): A solution of 1.40 g (5.70 mmol) of **2c** in 100 ml of benzene was irradiated (λ = 300 nm) for 50 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1 to 1:1) to give 796 mg of **4c** and 210 mg of **3c** (total yield of 75%). ^{1}H-NMR analysis of the crude reaction mixture revealed a **4c**:**3c** ratio of 80:20.

Methyl cis-(1'R,2S)-2-(2,3-Dihydro-1-hydroxy-3-oxo-1H-isoindol-2-yl)-3-pentenoate (**3c**): Colorless oil, R_f = 0.35. – IR (CCl_4): $\tilde{\nu}$ = 3420 cm^{-1} (s), 2940 (s), 2915 (m), 1740 (vs), 1670 (vs), 1505 (w), 1385 (s), 1200 (m), 1040 (s), 965 (m). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.71 (d, J = 5.0 Hz, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.88 (br s, 1H, OH), 5.35 (d, J = 6.3 Hz, 1H, NCH), 5.79 (dd, J = 6.3/15.2 Hz, 1H, $HC-CH=$), 5.83 (s, 1H, $CH-OH$), 5.87 (dd, J = 5.0/15.2 Hz, 1H, $CH_3CH=$), 7.37–7.52 (m, 3H, Ar-H), 7.69 (d, J = 7.3 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.9 (q), 52.9 (q), 56.1 (d), 80.7 (d), 122.3 (d), 123.2 (d), 123.4 (d), 129.6 (d), 130.6 (s), 132.5 (d), 134.3 (d), 144.4 (s), 167.1 (s), 172.6 (s). – MS (70 eV): m/z (%) = 247 (<1) [M^+], 239 (3), 202 (21), 154 (14), 141 (12), 133 (28), 111 (13), 97 (19), 71 (64), 57 (100).

Methyl (3S)-2,3,4,5-Tetrahydro-1,5-dioxo-1H-benz[c]azepine-3-carboxyate (**4c**) (R_f = 0.16). On the basis of the spectral data the separated isomer was identical in every respect with **4c** isolated after irradiation of **2g**.

6. *(S)-N-Phthaloylisoleucine Methyl Ester* (**2e**): A solution of 500 mg (1.81 mmol) of **2e** in 100 ml of benzene was irradiated (λ = 300 nm) for 50 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1 to 1:1) to give 371 mg of **3e** and 41 mg of *cis*-**4a** in a total yield of 84%. The ^{1}H-NMR analysis of the crude reaction mixture revealed a **3e**:*cis*-**4a** ratio of 89:11.

Methyl (1'R,2S)-2-(2,3-Dihydro-1-hydroxy-3-oxo-1H-isoindol-2-yl)-3-ethyl-3-butenoate (**3e**): Colorless oil, R_f = 0.42. – IR (CCl_4): $\tilde{\nu}$ = 3450 cm^{-1} (br m), 2960 (w), 2930 (w), 1715 (vs), 1440 (m), 1385 (m), 1360 (m), 1215 (s), 1180 (m), 1060 (m). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.4 Hz, 3H, CH_3), 1.97 (q, J = 7.4 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.80 (br s, 1H, OH), 5.04 (d, J = 0.9 Hz, 1H, CH), 5.21 (dd, J = 1.6/1.6 Hz, 1H, CH), 5.58 (s, 1H, NCH), 5.70 (br s, 1H, CH), 7.41 (dd, J = 3.6/4.0 Hz, 1H, Ar-H), 7.51 (dd, J = 1.0/3.6 Hz, 2H, Ar-H), 7.70 (dd, J = 1.0/7.4 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.8 (q), 27.7 (t), 52.9 (q), 58.1 (d), 80.2 (d), 115.1 (t), 123.3 (d), 123.6 (d), 128.6 (s), 130.1 (d), 132.8 (d), 143.0 (s), 144.7 (s), 168.0 (s), 173.3 (s). – MS (70 eV): m/z (%) = 275 (1) [M^+], 216 (17), 198 (11), 154 (23), 147 (11), 141 (10), 133 (29), 85 (38), 71 (66), 57 (100). – $[\alpha]_D$ = +50.3 (c = 1.0, MeOH).

cis-**4a**: R_f = 0.24. On the basis of the spectral data the separated isomer was identical in every respect with **4a** isolated after irradiation of **2a**.

7. *(RS)-N-Phthaloylalloisoleucine Methyl Ester* (**2f**): A solution of 500 mg (1.81 mmol) of a 45:55 mixture of **2e** and **2f** in 100 ml of benzene was irradiated (λ = 300 nm) for 50 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1 to 1:1) to give a mixture of **3e**, *cis*-**4a** and *trans*-**4a** in a total yield of 81%. The ^{1}H-NMR analysis of the crude reaction mixture indicated a **3e**:*cis*-**4a**:*trans*-**4a** ratio of 89:6:5.

8. *(S)-N-Phthaloylmethionine* (**1h**): A solution of 500 mg (1.79 mmol) **1h** in 80 ml of benzene was irradiated (λ = 300 nm) for 36 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1 to 1:1) to give 65 mg (13%) of **9h** and 205 mg (41%) of **10h** in a total yield of 51%. The ^{1}H-NMR analysis of the crude reaction mixture revealed a **9h**:**10h** ratio of 25:75.

10h: Colorless crystals, m.p. 188–189°C, R_f = 0.21. – IR (CCl_4): $\tilde{\nu}$ = 2930 cm^{-1} (s), 2880 (m), 1810 (m), 1740 (s), 1470 (w), 1390 (w), 1310 (s), 1090 (vs), 1030 (vs), 920 (m). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41–2.70 (m, 4H), 2.98 (d, J = 15.0 Hz, 1H), 3.42 (d, J = 15.0 Hz, 1H), 4.70 (d, J = 6.9 Hz, 1H, NCH), 7.72 (m, 3H, Ar-H), 7.90 (d, J = 6.9 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 29.6 (t), 33.2 (t), 42.1 (t), 55.4 (d), 97.6 (s), 123.4 (d), 123.7 (s), 125.0 (d), 131.8 (d), 134.0 (d), 134.5 (s), 171.7 (s), 174.6 (s).

$C_{13}H_{11}NO_3S$ (261.3) Calcd. C 59.75 H 4.24 N 5.36 Found C 59.70 H 4.76 N 5.35

9h: Colorless oil, R_f = 0.73. – IR (CCl_4): $\tilde{\nu}$ = 3400 cm^{-1} (s), 2900 (s), 2680 (m), 1970 (m), 1720 (s), 1620 (m), 1460 (s), 1060 (s), 930 (s). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.22–2.68 (m, 4H), 2.88 (s, 1H), 4.84 (dd, J = 5.6/8.8 Hz, 1H), 7.31–7.71 (m, 4H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.6 (t), 32.8 (t), 42.4 (t), 52.9 (d), 90.7 (s), 120.8 (d), 122.3 (d), 128.8 (d), 130.0 (s), 131.9 (d), 145.2 (s), 167.2 (s), 171.9 (s).

$C_{13}H_{13}NO_4S$ (279.3) Calcd. C 55.90 H 4.69 N 5.02 Found C 56.12 H 4.84 N 5.32

9. *(S)-N-Phthaloylmethionine Methyl Ester* (**2h**): A solution of 500 mg (1.71 mmol) of **2h** in 80 ml of benzene was irradiated (λ = 300 nm) for 30 h under nitrogen. After removal of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1) to give 420 mg (84%) of a 48:52 mixture of *cis*-**11h** and *trans*-**11h** (ref.[8] 27.5:38.2).

10. *Epimerization of* **3b** *with HCl:* To a stirred solution of 3 ml of HCl-saturated $CDCl_3$ under nitrogen 100 mg (0.38 mmol) of **3b**

in 2 ml of $CDCl_3$ was added. After 24 h at room temp. (TLC control) a 1:1 mixture of epimers was observed: **3b'**: ^1H NMR (250 MHz, $CDCl_3$): δ = 1.86 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.72 (s, 1H, OH), 4.98 (s, 1H, CH_2), 5.09 (s, 1H, CH_2), 5.20 (s, 1H, NC*H*CO_2Me), 6.16 (s, 1H, NC*H*OH), 7.44 (m, 1H, Ar-H), 7.52 (d, *J* = 4.1 Hz, 2H, Ar-H), 7.72 (d, *J* = 7.4 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.1 (q), 52.7 (q), 58.6 (d), 81.1 (d), 116.2 (t), 123.3 (d), 123.6 (d), 129.4 (d), 129.9 (s), 132.7 (d), 139.9 (s), 143.7 (s), 167.9 (s), 170.5 (s).

11. *Isomerization of* **3b** *with Tri-n-butylamine:* To a stirred solution of 240 mg (0.92 mmol) of **3b** in 30 ml of EtOH under nitrogen 340 mg (1.80 mmol) of tri-*n*-butylamine was added, and the mixture was refluxed for 15 h. After evaporation of the solvent (rotary evaporator), the crude product was purified by column chromatography (PE/EA, 3:1 to 1:1) to give 160 mg (67%) of **6b**. – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.84 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 5.87 (s, 1H, NC*H*OH), 7.45 (dd, *J* = 7.4/3.7 Hz, 1H, Ar-H), 7.53 (d, *J* = 3.7 Hz, 2H, Ar-H), 7.72 (d, *J* = 7.4 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.8 (q), 23.4 (q), 51.8 (q), 83.2 (d), 120.1 (s), 123.3 (d), 123.7 (d), 129.7 (d), 130.8 (s), 132.5 (d), 144.3 (s), 156.0 (s), 165.2 (s), 166.9 (s).

$C_{14}H_{15}NO_4$ (261.3) Calcd. C 64.35 H 5.79 N 5.36
Found C 64.21 H 6.03 N 5.87

12. *PCC Oxidation of* **3b**: To a stirred solution of 100 mg (0.38 mmol) of **3b** in 5 ml of CH_2Cl_2 was added 0.50 g of pyridinium chlorochromate (PCC)/aluminium oxide (6.1 mmol (PCC)/7.5 g Al_2O_3). The reaction mixture darkened from orange to black, and after 24 h again 0.5 g of PCC/aluminium oxide was added. After completion of the reaction (62 h, TLC) the mixture was filtered through a small column, washed with 50 ml of CH_2Cl_2, and the solvent was removed at reduced pressure to yield 79 mg (80%) of **7b**.

(S)-N-Phthaloylisodehydrovaline Methyl Ester (**7b**): Colorless oil. – IR (CCl_4): ṽ = 2980 cm^{-1} (m), 2950 (w), 1790 (s), 1730 (s), 1480 (m), 1445 (m), 1400 (s), 1300 (m), 1252 (m), 1120 (s), 1050 (m), 925 (s). – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.84 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.03 (s, 1H, =CH_2), 5.06 (s, 1H, =CH_2), 5.30 (s, 1H, CH), 7.69 (dd, *J* = 3.1/5.5 Hz, 2H, Ar-H), 7.81 (dd, *J* = 3.1/5.5 Hz, 2H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.4 (q), 52.8 (q), 57.0 (d), 117.3 (t), 124.5 (d, 2 C), 131.7 (s, 2 C), 134.2 (d, 2 C), 138.2 (s), 167.1 (s, 2 C), 168.0 (s). – $[\alpha]_D$ = −95.8 (*c* = 1.0, acetone).

$C_{14}H_{13}NO_4$ (259.25) Calcd. C 64.86 H 5.05 N 5.40
Found C 65.02 H 5.23 N 5.23

13. *Hydrogenation of* **7b**: A mixture of 100 mg of **7b** and 40 mg of Pd/C in 20 ml of ethyl acetate was stirred at room temp. under hydrogen for 24 h. After removal of the solvent (rotary evaporator), 93 mg (94%) of **2b** could be isolated as a colorless oil. On the basis of the spectral data this compound was identical with **2b** obtained from phthaloylation and esterification of (*S*)-valine. $[\alpha]_D$ = −62.4 (*c* = 1.5, MeOH), starting material: $[\alpha]_D$ = −66.7 (*c* = 1.2, MeOH).

14. *Epoxidation of* **3b** *with Dimethyldioxirane:* To a stirred solution of 138 mg (0.53 mmol) of **3b** in 5 ml of CH_2Cl_2 under nitrogen 15 ml of dimethyldioxirane in acetone (5.23 mg/ml) was added. After complete consumption of the starting olefin (4 h, TLC), the solvent and excess dimethyldioxirane were removed (rotary evaporator) to yield 145 mg (100%) of a 50:50 mixture of the diastereomeric epoxides **8b** and **8b'** as a pale yellow oil. – IR (CCl_4): ṽ = 3500 cm^{-1} (w), 3050 (w), 1790 (m), 1755 (vs), 1570 (m), 1270 (m), 1232 (m), 1015 (m), 990 (w), 928 (s). – Diastereomer A: ^1H NMR (250 MHz, $CDCl_3$): δ = 1.46 (s, 3H, CH_3), 2.80 (AB, *J* = 4.1 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.79 (s, 1H, NCH), 5.10 (br s, 1H, OH), 6.05 (s, 1H, CH), 7.44–7.62 (m, 3H, Ar-H), 7.74 (d, *J* = 7.1 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.1 (q), 52.2 (q), 53.1 (t), 56.2 (s), 58.9 (q), 82.4 (d), 123.3 (d), 123.5 (d), 129.6 (d), 132.8 (d), 134.7 (s), 144.1 (s), 167.6 (s), 169.3 (s). – Diastereomer B: ^1H NMR (250 MHz, $CDCl_3$): δ = 1.46 (s, 3H, CH_3), 2.76 (AB, *J* = 4.1 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.79 (s, 1H, NCH), 5.10 (br s, 1H, OH), 6.05 (s, 1H, CH), 7.44–7.62 (m, 3H, Ar-H), 7.74 (d, *J* = 7.1 Hz, 1H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.3 (q), 52.6 (q), 52.7 (t), 56.0 (s), 59.0 (q), 82.0 (d), 123.3 (d), 123.5 (d), 129.6 (d), 132.8 (d), 134.3 (s), 144.1 (s), 167.6 (s), 169.7 (s).

15. *Synthesis and Photoreaction of (RS)-[3-D_1]-N-Phthaloylvaline Methyl Ester* ([3-D_1]-**2b**). (RS)-[3-D_1]-valine was obtained in 41% yield from sodium α-ketoisovalerate according to a literature procedure[25]. Following the standard procedures, [3-D_1]-**2b** was synthesized in 94% total yield and with 95% deuterium content: colorless oil. – IR (CCl_4): ṽ = 2960 cm^{-1} (m), 2880 (w), 1720 (vs), 1470 (m), 1385 (s), 1225 (m), 1225 (m), 1110 (m), 980 (w), 720 (m). – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.86 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.72 [m, 0.05H, C*H*$(CH_3)_2$], 3.67 (s, 3H, OCH_3), 4.53 (s, 1H, CHN), 7.72 (dd, *J* = 3.0/5.5 Hz, 2H, Ar-H), 7.84 (dd, *J* = 3.0/5.5 Hz, 2H, Ar-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.1 (q), 20.7 (q), 28.0 (t, J_{CD} = 20.1 Hz), 52.3 (q), 57.3 (d), 123.4 (d, 2 C), 131.6 (s, 2 C), 134.1 (d, 2 C), 167.6 (s, 2 C), 169.2 (s).

$C_{14}H_{14}DNO_4$ (262.3) Calcd. C 64.11 H 6.15 N 5.34
Found C 64.35 H 5.98 N 5.21

A solution of 700 mg (2.67 mmol) of [3-D_1]-**2b** in 100 ml of benzene was irradiated (λ = 300 nm) for 40 h under nitrogen. After removal of the solvent (rotary evaporator), 642 mg (92%) of crude product resulted. On the basis of the spectral data the product was identical with **3b** [^{13}C NMR (63 MHz, $CDCl_3$): δ = 80.3 (d)] besides the missing OH signal in the ^1H-NMR spectrum.

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1a: 5203-11-2 / **1b**: 6306-54-3 / **1c**: 58073-26-0 / **1d**: 142765-23-9 / **1e**: 29588-88-3 / **1f**: 114926-62-4 / **1g**: 2419-38-7 / **1h**: 29588-91-8 / **1i**: 4192-28-3 / **1k**: 5123-55-7 / **2a**: 69043-98-7 / **2b**: 124729-87-9 / [3-D_1]-**2b**: 142781-54-2 / **2c**: 137649-34-4 / **2d**: 137649-36-6 / **2e**: 137649-35-5 / **2f**: 142765-24-0 / **2g**: 132785-19-4 / **2h**: 39739-05-4 / **2i**: 75082-78-9 / **2k**: 14380-85-9 / **3a** (isomer 1): 137649-37-7 / **3a** (isomer 2): 137649-45-7 / **3b**: 137649-38-8 / [D_1]-**3b**: 142765-29-5 / **3b′**: 142765-26-2 / **3c**: 142796-79-0 / **3e**: 137649-40-2 / (*c*)-**4a**: 137649-42-4 / (*t*)-**4a**: 137764-48-8 / **4c**: 137649-41-3 / **5d**: 137649-43-5 / **6b**: 142765-27-3 / **7b**: 137649-44-6 / **8b**: 142765-28-4 / **8b′**: 142796-81-4 / **9h**: 142796-00-3 / **10h**: 142765-25-1 / (*c*)-**11h**: 82796-85-8 / (*t*)-**11h**: 82796-84-7 / Abu: 1492-24-6 / Val: 72-18-4 / Nva: 6600-40-4 / Ile: 73-32-5 / (*allo*)-Ile: 1509-34-8 / Leu: 61-90-5 / Met: 63-68-3 / Ala: 56-41-7 / Phe: 63-91-2 / (*RS*)-[3-D_1]-valine: 79168-24-4 / propene: 115-07-1 / dimethyldioxirane: 74087-85-7 / phthalic anhydride: 85-44-9