Decarboxylative Photocyclization: Synthesis of Benzopyrrolizidines and Macrocyclic Lactones

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The benzopyrrolizidines **2**, **6a**, and **6b** were synthesized from the enantiomerically pure γ-amino acid derivatives **1**, **5a**, and **5b** by decarboxylative photocyclization of the corresponding potassium salts in aqueous acetone. The diastereoselectivity of the radical coupling step was low (dr = 60:40) for the *N*-phthaloylglutamic acid methyl ester **1**, whereas the α-benzyl- and the α-methyl-substituted γ-phthalimido butyric acid derivatives **5a**,**b** cyclized with high cis diastereoselectivity (dr = 91:9 and 97:3, respectively). Acid-catalyzed epimerization of the *cis*/*trans*-**2** mixture gave exclusively *cis*-**2**. The benzopyrrolizidines *cis*/*trans*-**2** mixture was transformed with high stereoselectivity (dr = 93:7, ee >98%) into the cis methyl ether **3** via the corresponding acyliminium cation and subsequently into the allyl derivative **4** (dr = 86:14) with trimethylallylsilane catalyzed by titanium tetrachloride. The structures of the benzopyrrolizidines *rac*-**3**, (+)-**3**, *rac*-**4**, and **6a** were determined by X-ray structure analyses. The macrocyclic lactones **8a**,**b** were formed in high yields from the precursors **7a**,**b**. The diastereoselectivity for the valine-derived substrate (in contrast to the reactions of **5a** and **5b**) was only moderate (dr = 64:36). The structure of the macrolide **9a** (from **8a**) was determined by X-ray structure analysis.

We have recently described the synthesis of medium- and large-sized heterocyclic compounds via decarboxylative intramolecular photocyclization of ω-phthalimido carboxylic acids.[2] An essential prerequisite for this reaction is the use of alkali metal carboxylates, which were prepared in situ or prior to the reaction. The in situ method uses heterogeneous conditions and is superior for base-labile substrates. Many starting materials could be deprotonated prior to photolysis and irradiated in homogeneous solvent mixtures of organic solvents and water.[3] Most probably, these reactions are of triplet-state origin; the use of a sensitizing solvent such as acetone or a triplet sensitizer, however, is not necessary. To evaluate this ring annulation methodology and to further widen the scope of the reaction, we have studied the synthesis of benzopyrrolizidines and macrocyclic lactones. Both groups of compounds originate retrosynthetically from α-amino acids as enantiomerically pure building blocks.

Benzopyrrolizidines of the type mentioned above have also been synthesized using the azomethine ylide route using *N*-trialkylsilylmethylimides or phthaloylglycine as 1,3-dipole precursors.[4] This highly useful route developed by Mariano, Yoon, and co-workers[5] has the disadvantage that the stereogenic α-center is epimerized during the course of the reaction, and consequently, only racemic products are obtained. By activation of remote carboxylate groups via photoinduced electron transfer this disadvantage can be overcome.

The photocyclization of the glutamic acid derivative **1** has been described previously.[2] After completion of the four-step synthesis, we isolated the methoxy-substituted compound **3** as a racemic mixture (space group $P2_1/n$).[6] Reexamination of the reaction protocol led to the conclusion that racemization had occurred at the (thermal) phthaloylation stage. Thus, we prepared enantiomerically pure (*S*)-**1** by an alternative route and converted it into the diastereoisomeric benzopyrrolizidines **2**. The in situ method gave approximately 20% of a simple decarboxylation product (i.e., the methyl ester of *N*-phthaloyl α-amino butyric acid) beside a 3:2 mixture of *cis*- and *trans*-**2**. When using the potassium salt of **1** in a 1:1 mixture of water directly and acetone as solvent, less than 5% of the decarboxylation product was observed after quantitative conversion. Treatment of the product mixture with catalytic trifluoroacetic acid or formic acid led to near-quantitative epimerization to give the *cis* diastereoisomer (Scheme 1).

Epimerization at the stereogenic center of hydroxy lactams resulting in a 1:1 equilibrium has already been reported by us for the product of the *N*-phthaloylvaline ester photolysis.[7] In the glutamic acid case reported herein, however, the epimerization equilibrium is >9:1 in favor of *cis*-**2**. Further treatment of *cis*-**2** with formic acid in methanol led to the methoxybenzopyrrolizidine **3** with high (93:7) diastereoselectivity.[6] This reaction

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(6) X-ray analyses of *rac*-**3**, *cis*-(+)-**3**, (+)-**4**, *cis*-**6a**, and **9a**. Data collection: Enraf-Nonius-CAD4 diffractometer, Mo Kα graphite monochromator, Wyckoff-scan, θ range (deg) 1.75−27.5. Structural analysis and refinement: solution by direct-phase determination, method of refinement full-matrix LSQ, hydrogen positions of riding model with fixed isotropic *U*, program used Siemens SHELXL-93.

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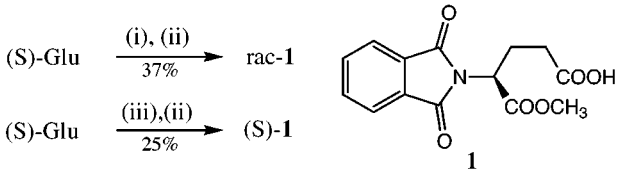
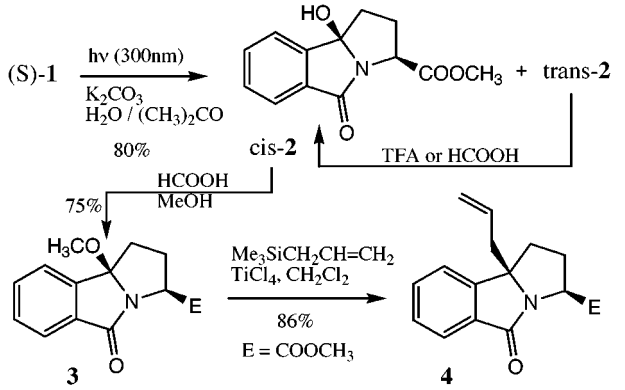
Published on Web 06/17/1999

Scheme 1. Synthesis of *N*-Phthaloylglutamic Acid α-Methyl Ester



(i) PHT_2O, 130°C; (ii) DMS, NEt_3; (iii) PHT=N-COOEt, Na_2CO_3

Scheme 2. Photocyclization of 1 and Transformations of 2



proceeds via an intermediary acyl iminium cation, which is known to be reactive with a multitude of nucleophiles.[8] The enantiomeric purity of (+)-**3** was determined by chiral HPLC to be >98%.[9] Allylation of the methoxy derivative (+)-**3** by $TiCl_4$-catalyzed reaction with trimethylsilylallylsilane[10] proceeded smoothly to give an 86:14 mixture of *cis* and *trans* diastereoisomers of **4** (Scheme 2). An X-ray structure of the major isomer *cis*-**4** was obtained as additional structural proof (from the racemic series).[6] The low diastereoselectivity of the C−C coupling step in the photodecarboxylation of **1** thus can be "repaired" by nucleophilic addition or substitution reactions involving acyliminium cations. In both cases, the asymmetric induction originates from the ester group, which probably directs the methanol addition (by hydrogen-bonding interaction) as well as the allylation (probably by complexation with the Lewis acid). Steric constraints seem not to determine the stereoselectivity of the nucleophilic addition since the intermediary acyliminium cation is essentially planar.

To investigate the stereoselectivity of the C−C coupling step in the presence of other directing groups, we synthesized the benzyl- and the methyl-substituted starting materials **5a** and **5b** from *N*-Boc-phenylalanine and *N*-Boc-alanine, respectively, by a literature-known six-step synthesis[11] involving chain-elongation by reaction with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) and subsequent reduction. Photocyclization of the benzyl derivative **5a** resulted in a 91:9 diastereomeric mixture of benzopyrrolizidinones **6a** in 74% yield (Figure 1). The major diastereomer could be crystallized and the *cis* configuration additionally proven by X-ray structure analysis.[6] Even higher was the stereoselectivity in the case of the α-methyl-GABA derivative **5b**: a 97:3 mixture of *cis*- and *trans*-**6b** was formed in 81% yield (Scheme 3). The preferred formation of the cis products might be due to a stereoelectronic effect that favors the axial position of the hydroxy group in the pyrrolizidine ring and leads to the thermodynamically favored *cis* products. Although total thermodynamic control did not seem to occur for the glutamic acid derivative **1**, it might for a yet unknown reason operate, however, for the starting materials **5a**,**b**.

As another strategy for the use of α-amino acids as building blocks in decarboxylative photocyclization, we investigated ester-linked substrates with *N*-phthaloylglycine and *N*-phthaloylvaline as the carboxylic acid components. The substrates **7a**,**b** were easily available from the amino acids via three-step syntheses involving phthaloylation, esterification with benzyl 6-bromohexanoate, and hydrogenation. Using the homogeneous reaction conditions, photocyclization of these substrates afforded the macrocyclic lactones **8a**,**b** in excellent yields (77%, 81%) (Scheme 4). Asymmetric induction from the isopropyl group in **7a** was only marginal: a 60:40 cis,trans mixture resulted. To gain definitive structural proof for the macrolide structures, the hydroxy lactone **8a** was transformed via acid-catalyzed methanol addition into the methoxy compound **9a** from which an X-ray structure analysis was obtained (Figure 2, Table 1).[6]

As remarkable features of these photochemical transformations it should be noted that in no case did we observe the formation of either "simple" decarboxylation products or dimerization reactions when homogeneous photolysis conditions were used and the benzopyrrolizidines, as well as the macrocyclic lactones, were isolated in chemical yields >74%. Additionally, dilution conditions, which are often necessary for the synthesis of macrocyclic compounds, are not necessary, and substrate concentrations up to 0.1 M could be applied.

Experimental Section

General Methods. ^{1}H NMR: 300 and 500 MHz. ^{13}C NMR: 75 and 125 MHz, carbon multiplicities were determined by DEPT. IR: Perkin-Elmer 1605 FT-IR spectrophotometer. Column chromatography: silica gel (Merck) 60−230 mesh; petroleum ether (PE, 40−60 °C), ethyl acetate (EA). UV/vis: Perkin-Elmer Lambda 7 spectrophotometer. MS: Finnigan Incos 500. All melting points were determined with a Büchi melting point apparatus (type Nr. 535) and are uncorrected. Combustion analyses: Institut für Anorganische Chemie der Universität zu Köln and in-house. Rayonet chamber photoreactors RPR-208 (8 × 3000 Å lamps, ca. 800 W, $\lambda = 300 \pm 10$ nm) were used for irradiations.

(2*S*)-2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)pentanedioic Acid α-Methyl Ester (1). To a solution of (*S*)-*N*-phthaloylglutamic acid (27.72 g, 100 mmol) and triethylamine (14 mL, 100 mmol) in chloroform (150 mL) was added dimethyl sulfate (10.5 mL, 110 mmol) at rt. After the solution was stirred at rt for 40 h, the solvent was removed and the residue treated with water (150 mL) and extracted with ethyl acetate. The combined organic extracts were extracted with saturated $NaHCO_3$. The aqueous solutions were combined and acidified with concentrated HCl. The colorless precipitate was collected and, after drying ($MgSO_4$), dissolved in methanol and crystallized by adding hexane to give 17.4 g (60%) of the monoester

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(9) Nucleosil-Chiral 2 column, cyclohexane/1% propanol, $\Delta t_R = 1.2$ min.

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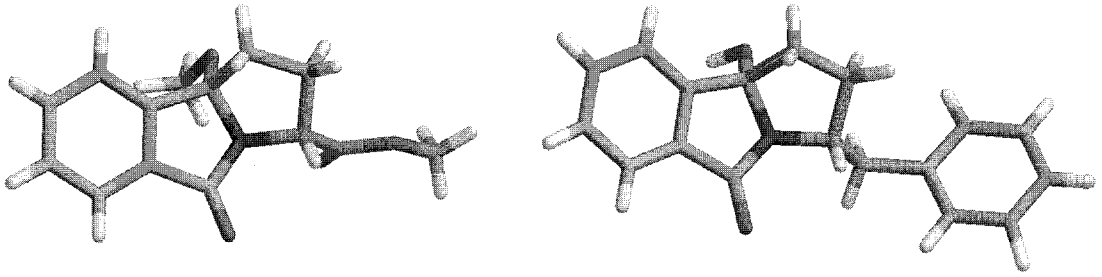
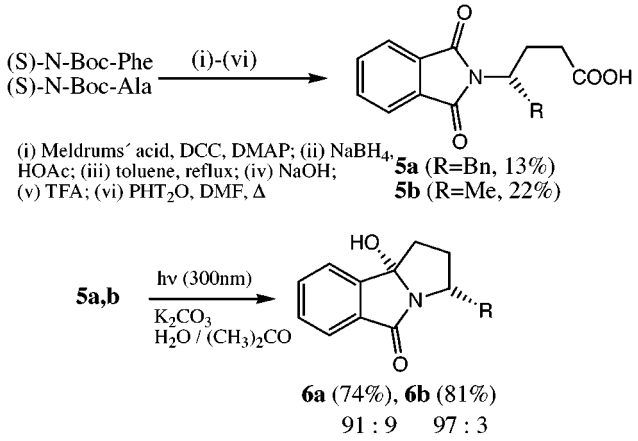
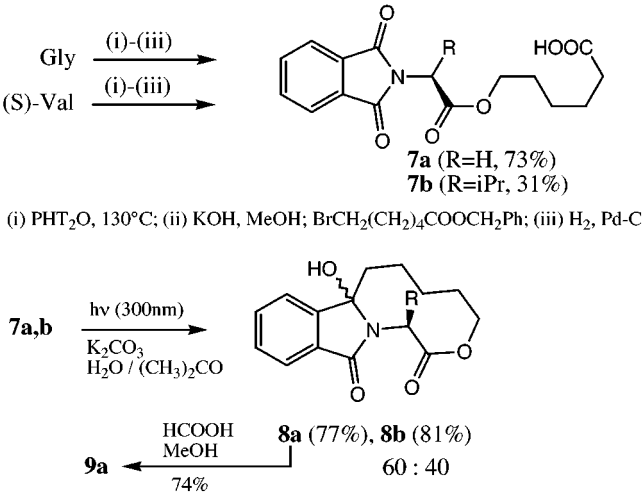


Figure 1. Structures of **3** and *cis*-**6a** in the crystal.

Scheme 3. Synthesis and Photocyclization of 5a and 5b



Scheme 4. Synthesis and Photocyclization of 7a and 7b



as colorless crystals: mp 134−136 °C (from acetone, lit.[12] mp 134−136 °C); IR (cm^{-1}) 2936, 2905, 1743, 1704, 1373, 710; ^1H NMR (methanol-d_4) δ 2.39−2.49 (m, 2H), 2.52−2.70 (m, 2H), 3.76 (s, 3H, OCH_3), 5.02 (dd, 1H, J = 4.9, 10.0 Hz), 7.85−8.05 (m, 4H, Ar-H); ^{13}C NMR (63 MHz, methanol-d_4) δ 25.2, 29.2, 50.3, 51.0, 122.3, 130.8, 133.6, 166.8, 168.9, 173.8.

General Procedure for Photodecarboxylation of *N*-Phthaloyl ω-Amino Carboxylic Acid Derivatives. A mixture of potassium carbonate (1 mmol) and the substrate (2 mmol) in water (1 mL) was heated to 60−70 °C for 1 min and dissolved in a 1:1 (vol) mixture of water and acetone (100−200 mL). A homogeneous solution resulted that was irradiated in a Pyrex tube for 6−16 h while being purged with a slow stream of nitrogen and cooled to ca. 15 °C. After evaporation of most of the acetone, the residual solution was extracted with $CHCl_3$ (3 × 100 mL). After drying ($MgSO_4$) and evaporation of the solvent, the resulting product was (if not indicated otherwise) crystallized from acetone.

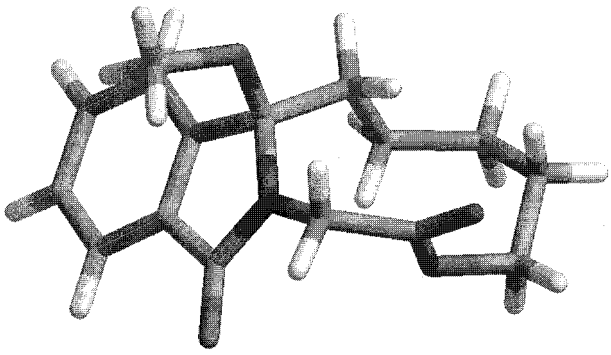


Figure 2. Structure of **9a** in the crystal.

(3*S*,9b*RS*)-Methyl 2,3,5,9b-Tetrahydro-9b-hydroxy-1*H*-pyrrolo[2,1-*a*]isoindol-5-one-3-carboxylate (2). Following the general reaction protocol, 1.46 g (5 mmol) of (*S*)-**1** was irradiated in a mixture of 100 mL of acetone and 100 mL of water for 6 h. After evaporation of the solvent and recrystallization of the residue from acetone, 982 mg (80%) of a 3:2 mixture of *cis*- and *trans*-**2**[3] resulted as a colorless powder.

(3*S*,9b*R*)-Methyl 2,3,5,9b-Tetrahydro-9b-methoxy-1*H*-pyrrolo[2,1-*a*]isoindol-5-one-3-carboxylate (3). A solution of 1.12 g (4.5 mmol) of a 3:2 cis/trans mixture of the 9b-hydroxybenzopyrrolizidines **2** in 50 mL of methanol was treated with 1 mL of formic acid. The solution was heated to reflux for 3 h, cooled to rt, and diluted with 10 mL of water. After extraction with CH_2Cl_2, the organic phase was dried over $MgSO_4$ and the solvent rota-evaporated. The crude solid material was recrystallized from acetone to give 882 mg (75%) of **3**: colorless needles; mp 121−122 °C; $[\alpha]^{20}_D$ = +55.8° (c = 1, MeOH); IR (cm^{-1}) 1759, 1752, 1716, 1712, 1708, 1365, 1202, 772; UV (CH_3CN) λ (log ϵ) = 229.6 (3.90), 222.2 (3.84), 209.2 (4.08); ^1H NMR ($CDCl_3$) δ 1.60 (ddd, 1H J = 8.8, 9.5, 14.1 Hz), 2.36 (ddd, 1H, J = 2.3, 9.5, 11.8 Hz), 2.66−2.75 (m, 2H), 3.03 (s, 3H, OMe), 3.78 (s, 3H, COOMe), 4.58 (dd, 1H, J = 8.8, 8.8 Hz, NCH), 7.44−7.62 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 32.7, 35.6, 50.5, 52.4, 55.6, 100.7, 122.7, 124.1, 130.1, 132.5, 133.0, 143.7, 170.1, 172.2. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.13; H, 5.78; N, 5.33.

(3*S*,9b*R*)-Methyl 2,3,5,9b-Tetrahydro-9b-2′-propenyl-1*H*-pyrrolo[2,1-*a*]isoindol-5-one-3-carboxylate (4). To a solution of 261 mg (1.0 mmol) of **3** in 6 mL of methylene chloride was added simultaneously 0.13 mL (1.2 mmol) of titanium tetrachloride and 0.24 mL (1.5 mmol) of trimethylallylsilane. The solution was stirred for 1 h at rt and quenched with 10 mL of water. After extraction of methylene chloride, the organic phase was dried over $MgSO_4$ and the solvent rota-evaporated. The crude solid material was purified by column chromatography (CH_2Cl_2/MeOH 20:1) and recrystallization from acetone to give 234 mg (75%) of *cis*-**4** as colorless needles: mp 68−69 °C; $[\alpha]^{20}_D$ = −94.0° (c = 1, MeOH); IR (cm^{-1}) 1751, 1746, 1702, 1698, 1687, 1373, 1360, 1201, 1187, 1173; UV (CH_3CN) λ (log ϵ) = 225.0 (4.0), 207.8 (3.80). Anal.

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Table 1. Crystallographic Data for Compounds *rac*-3, (+)-3, (+)-4, *cis*-8b, and 9a

no.	*rac*-**3**	(+)-**3**	*rac*-**4**	*cis*-**6a**	**9a**
emp formula	$C_{14}H_{15}NO_4$	$C_{14}H_{15}NO_4$	$C_{16}H_{17}NO_3$	$C_{18}H_{17}NO_2$	$C_{16}H_{19}NO_4$
molecular mass	261.27	261.27	271.30	279.33	289.32
cryst dimens (mm)	0.25 × 0.15 × 0.1	0.25 × 0.2 × 0.18	0.2 × 0.18 × 0.15	0.2 × 0.1 × 0.1	0.2 × 0.15 × 0.12
a (pm)	1068.4(3)	702.3(1)	689.4(2)	743.1(1)	1145.0(1)
b (pm)	1323.7(4)	1123.7(2)	1248.0(3)	790.3(1)	1117.7(1)
c (pm)	965.9(2)	1673.3(2)	1676.2(5)	1249(2)	1209.1(1)
α (deg)					
β (deg)	106.84(2)		90.68(2)	94.91(1)	108.26(1)
γ (deg)					
V (10^6pm^3)	1307.4(6)	1320.5(3)	1442.1(7)	730.9(2)	1469.4(2)
Z	4	4	2	2	4
ρ(calcd)	1.327	1.320	1.250	1.269	1.308
cryst syst	monoclinic	orthorhombic	monoclinic	monoclinic	monoclinic
space grp	$P2_1/n$	$P2_12_12_1$	Pc	$P2_1$	$P2_1/c$
no. reflns measd	2916	1664	3219	5170	5803
no. unique reflns	2844	1664	3135	2935	2983
no. obsd reflns[a])	2187	1146	2398	1361	2365
R	0.047	0.049	0.046	0.068	0.039
R_w[b]	0.117	0.104	0.094	0.080	0.098
largest diff peak/hole (e Å^{-3})	0.21/−0.21	0.13/−0.15	0.15/−0.17	0.12/-0.14	0.18/-0.16

[a] For $F > 2\sigma(F)$. [b] $R_w = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$ with $w = 1/\sigma^2(F)$.

Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.62; H, 6.48; N, 5.13.

Major diastereoisomer (cis, from the crude 84:16 diastereoisomeric mixture): ^{1}H NMR ($CDCl_3$) δ 1.46 (ddd, 1H, J = 8.8, 12.0, 12.1 Hz), 2.11 (dd, 1H, J = 7.2, 12.2 Hz), 2.59 (mc, 2H), 2.66 (mc, 2H), 3.70 (s, 3H, COOMe), 4.63 (dd, 1H, J = 8.7, 8.8 Hz, NCH), 4.88−4.95 (m, 2H), 5.53 (dddd, 1H, J = 6.6, 7.6, 11.6, 17.7 Hz), 7.44−7.62 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$) δ 32.7, 33.9, 39.9, 52.2, 55.4, 73.6, 118.7, 121.8, 124.0, 128.2, 131.6,131.9, 132.1, 149.7, 171.5, 172.5.

Minor diastereoisomer (trans, from the crude 84:16 diastereoisomeric mixture): ^{1}H NMR ($CDCl_3$) δ 1.88 (ddd, 1H, J = 7.6, 12.3, 12.4 Hz), 2.07 (dd, 1H, J = 6.6, 12.2 Hz), 2.31 (dd, 1H, J = 8.1, 13.6 Hz), 2.45 (dd, 1H, J = 7.2, 13.9 Hz), 2.50 (dd, 1H, J = 7.2, 13.9 Hz), 2.55−2.77 (m, 1H), 3.63 (s, 3H, COOMe), 4.29 (dd, 1H, J = 9.0, 9.1 Hz, NCH), 4.80−4.88 (m, 2H), 5.33 (dddd, 1H, J = 7.2, 7.5, 9.8, 13.6 Hz), 7.29−7.35 (m, 2H, Ar-H), 7.45 (dd, 1H, J = 1.1, 7.5 Hz), 7.64−7.66 (m, 1H, Ar-H). ^{13}C NMR ($CDCl_3$) δ 31.2, 33.8, 42.1, 52.0, 55.8, 73.8, 119.2, 121.8, 123.9, 128.0, 131.6, 131.8, 132.9, 149.5, 169.9, 171.4.

(3*R*,9b*S*)-3-Benzyl-9b-hydroxy-1,2,3,9b-tetrahydropyrrolo[2,1-*a*]isoindol-5-one (6a). (*R*)-4-amino-5-phenylpentanoic acid[13] was synthesized in a five-step synthesis from (*S*)-phenylalanine[11] and condensed with phthalic anhydride to give **5a**. A 307 mg (0.95 mmol) portion of **5a** in 100 mL of acetone and 100 mL of water was converted into 285 mg of crude reaction product (diastereoisomeric mixture: 91:9) following the general reaction protocol (16 h irradiation time). After recrystallization from acetone, 196 mg (74%) of **6a** (pure cis isomer) resulted as colorless plates: mp 154−155 °C; IR (cm^{-1}) 3320, 1678, 1617, 1425, 764, 702; ^{1}H NMR (acetone-d_6) δ 1.49−1.60 (m, 1H), 2.23−2.46 (m, 3H), 2.86 (dd, 1H, J = 9.1, 13.2 Hz), 3.30 (dd, 1H, J = 5.5, 13.2 Hz), 4.10 (dddd, 1H, J = 1.3, 5.6, 8.1, 14.9 Hz), 7.17−7.64 (m, 9H, Ar-H); ^{13}C NMR (acetone-d_6) δ 34.9, 36.5, 44.6, 57.6, 97.1, 123.5, 123.7, 127.0, 129.0, 129.1, 130.1, 130.2, 133.3, 139.9, 170.4. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 76.40; H, 6.13; N, 5.01. Found: C, 76.48; H, 6.17; N, 5.00.

(3*S*,9b*S*)-9b-Hydroxy-3-methyl-1,2,3,9b-tetrahydropyrrolo[2,1-*a*]isoindol-5-one (6b). (*S*)-4-Aminopentanoic acid[14] was synthesized in a five-step synthesis from (*S*)-alanine[11] and condensed with phthalic anhydride to give **5b**. A 194 mg (0.79 mmol) portion of **5b** in 50 mL of acetone and 50 mL of water was converted into 154 mg of crude reaction product (diastereoisomeric mixture: 97:3) following the general reaction protocol (16 h irradiation time). After recrystallization from acetone, 129 mg (81%) of **6a** (pure cis isomer) resulted as a yellowish oil that could not be crystallized: ^{1}H NMR (acetone-d_6) δ 1.38 (d, 3H, J = 6.5 Hz), 1.45−1.57 (m, 1H), 2.19−2.33 (m, 2H), 2.50 (ddd, J = 4.4, 7.7, 15.9 Hz), 3.87 (ddd, 1H, J = 6.5, 7.8, 10.9 Hz), 5.38 (s, 1H, OH), 7.44−7.62 (m, 4H, Ar-H); ^{13}C NMR (acetone-d_6) δ 23.4, 36.5, 36.9, 51.9, 97.0, 123.3, 123.6, 130.0, 132.8, 133.2, 149.0, 170.5; HREIMS ($C_{12}H_{13}NO_3$) calcd 219.0895, found 219.0891.

4b-Hydroxy-4b,5,6,7,8,9-hexahydro-10-oxa-12a-azacyclodeca[*a*]indene-11,13-dione (8a). A solution of 4.1 g (20 mmol) of *N*-phthaloylglycine potassium salt and 5.7 g (20 mmol) of benzyl 6-bromohexanoate in 100 mL of DMF was treated with 21 mmol of K_2CO_3 and stirred for 16 h at r.t. After filtration, the solvent was rota-evaporated and the residue dissolved in diethyl ether and washed with saturated aqueous $NaHCO_3$. After drying over $MgSO_4$ and evaporation of the solvent, 2.53 g (31%) of the coupled benzyl ester resulted as a colorless oil. This compound was dissolved in 200 mL of methanol, treated with 250 mg of Pd on charcoal, and hydrogenated for 16 h in a Parr apparatus (3 bar hydrogen pressure). After evaporation of the solvent under reduced pressure, the residue was dissolved in 100 mL of ether, washed with 50 mL of 1 N HCl, and extracted into 100 mL of saturated aqueous $NaHCO_3$. After acidification to pH = 1, 2.11 g (73%) of the free acid **7a** resulted as colorless needles: mp 94−95 °C; IR (cm^{-1}) 1745, 1740, 1731, 1221; UV (CH_3CN) λ (log ϵ) = 293.0 (1.3), 217.0 (4.0); ^{1}H NMR ($CDCl_3$) δ 1.38 (mc, 2H), 1.60−1.71 (m, 4H), 2.33 (t, 2H, J = 7.4 Hz), 4.15 (t, 2H, J = 6.6 Hz), 4,42 (s, 2H), 7.72−7.88 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 24.1, 25.2, 28.1, 33.6, 38.9, 65.5, 123.6, 132.0, 134.3, 167.3, 167.5, 178.7. Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.05; H, 5.32; N, 4.29.

A 319 mg (1 mmol) portion of **7a** in 50 mL of acetone and 50 mL of water was converted into 260 mg of crude reaction product following the general reaction protocol (12 h irradiation time). After recrystallization from acetone, 213 mg (77%) of **8a** resulted as colorless needles: mp 174−175 °C; IR (cm^{-1}) 3297, 1741, 1736, 704; UV (CH_3CN) λ (log ϵ) = 244.4 (3.68), 228.0 (3.87); ^{1}H NMR ($CDCl_3$) δ 0. 80−0.87 (m, 2H), 1.26−1.48 (m, 3H), 1.75 (ddd, 1H, J = 4.4, 7.0, 14.6 Hz), 1.83−1.87 (m, 1H), 2.08 (ddd, 1H, J = 9.7, 10.0, 14.8 Hz), 3.59 (d, 1H, J = 17.1 Hz), 3.64 (t, 1H, J = 11.2 Hz), 4.15 (d, 1H, J = 17.1 Hz), 4.21 (s, 1H, OH), 4.73 (dt, 1H, J = 0.7, 11.2 Hz), 7.40−7.59 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.5, 25.2, 31.2, 39.6, 66.9, 91.7, 121.9, 123.4, 129.6, 130.3, 132.8, 146.1, 167.2, 168.9. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.26; H, 6.21; N, 5.00.

4b-Hydroxy-4b,5,6,7,8,9-hexahydro-10-oxa-11-(1′-methylethyl)-12a-azacyclodeca[*a*]indene-11,13-dione (8b). A solution of 12.4 g (50 mmol) of (*S*)-*N*-phthaloylvaline potassium

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salt and 14.2 g (50 mmol) of benzyl 6-bromohexanoate in 400 mL of DMF was treated with 51 mmol of K_2CO_3 and stirred for 16 h at rt. After filtration, the solvent was rota-evaporated, the residue dissolved in diethyl ether and washed with saturated aqueous $NaHCO_3$. After drying over $MgSO_4$ and evaporation of the solvent, 17.9 g (79%) of the coupled benzyl ester resulted as a colorless oil. A 5.0 g (11 mmol) portion of this compound was dissolved in 200 mL of methanol, treated with 250 mg of Pd on charcoal, and hydrogenated for 16 h in a Parr apparatus (3 bar hydrogen pressure). After evaporation of the solvent under reduced pressure, the residue was dissolved in 100 mL of ether, washed with 50 mL of 1 N HCl, and extracted into 100 mL of saturated aqueous $NaHCO_3$. After acidification to pH = 1, 1.26 g (31%) of the free acid **7b** resulted as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 6.8 Hz), 1.12 (d, 3H, J = 6.7 Hz), 1,27 (m, 2H), 1.54 (mc, 4H), 2.21 (t, 2H, J = 7.4 Hz), 2.67−2.78 (m, 1H), 4.03−4.17 (m, 2H), 4.53 (d, 1H, J = 8.2 Hz), 7.71−7.86 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 19.4, 20.9, 24.0, 25.2, 28.0, 28.5, 33.7, 57.7, 65.1, 123.5, 131.6, 134.2, 167.8, 168.8, 179.3. Following the general irradiation procedure, 1.13 g (3.1 mmol) of **7b** in 100 mL of acetone and 100 mL of water were converted into 980 mg of crude reaction product (16 h irradiation time). After recrystallization from acetone, 807 mg (81%) of a 3:2 cis/trans mixture of **8b** resulted as a colorless powder: mp 184−186 °C; IR (cm^{-1}) 1735, 1722, 1668, 1468, 1211, 1200, 1127, 1066, 700; UV (CH_3CN) λ (log ϵ) = 244.8 (3.7). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.83; H, 7.32; N, 4.34.

Major diastereoisomer (cis, from the crude 60:40 diastereoisomeric mixture): ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 3H, J = 2.3 Hz), 1.07 (d, 3H, J = 2.2 Hz), 1.28−1.61 (m, 6H), 2.09−2.14 (m, 2H), 2.62−2.75 (m, 1H), 3.86 (ddd, 1H, J = 2.1, 11.0, 11.2 Hz), 4.70−4.74 (m, 1H), 4.79 (d, 1H, J = 11.3 Hz), 5.50 (s, 1H, OH), 7.45−7.71 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 19.8, 21.1, 22.1, 24.7, 25.1, 28.7, 32.6, 58.4, 67.3, 93.6, 121.0, 123.9, 129.7, 131.7, 132.8, 146.1, 167.5, 170.2.

Minor diastereoisomer (trans, from the crude 60:40 diastereoisomeric mixture): ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3H, J = 2.2 Hz), 1.00 (d, 3H, J = 2.3 Hz), 1.28.1.61 (m, 6H), 2.09−2.14 (m, 2H), 2.29−2.37 (m, 1H), 3.71 (d, 1H, J = 11.0 Hz), 4.16−4.21 (m, 1H), 4.29 (ddd, 1H, J = 1.6, 10.7, 11.2 Hz), 5.43 (s, 1H, OH), 7.45−7.71 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 20.0, 20.3, 21.6, 24.5, 25.3, 29.7, 33.3, 62.1, 65.7, 92.2, 121.4, 123.6, 129.8, 132.2, 132.5, 145.4, 167.5, 169.7.

4b-Methoxy-4b,5,6,7,8,9-hexahydro-10-oxa-12a-azacyclodeca[*a*]indene-11,13-dione (9a). To a solution of 100 mg (0.36 mmol) of **8a** in 25 mL of methanol was added 0.1 mL of trifluoroacetic acid. The resulting solution was heated to reflux for 3 h. After addition of 3 mL of water and drying over $MgSO_4$, the solvent was rota-evaporated and recrystallized from acetone to give 77 mg (74%) of **9a** as colorless needles: mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 0.82−0.94 (m, 1H), 0.95−1.08 (m, 1H), 1.28−1.49 (m, 3H), 1.76 (ddd, 1H, J = 0.9, 10.4, 12.6 Hz), 1.83−1.96 (m, 1H), 2.07 (ddd, 1H, J = 1.4, 11.8, 11.9 Hz), 2.71 (s, 3H, OMe), 3.55 (d, 1H, J = 17.0 Hz), 3.72 (ddd, 1H, J = 1.8, 5.6, 9.2 Hz), 4.79−4.82 (m, 1H), 4.84 (d, 1H, J = 17.0 Hz), 7.38−7.83 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 21.8, 23.5, 25.3, 31.4, 39.9, 49.9, 67.1, 95.9, 122.1, 123.7, 129.7, 132.4, 132.5, 142.5, 167.4, 169.0. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.32; H, 6.80; N, 5.05.

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Supporting Information Available: ^{1}H- and ^{13}C NMR data of compounds **3**, **4**, **6a**,**b**, **8a**,**b**, and **9a** and X-ray data of compounds *rac*-**3**, (+)-**3**, (+)-**4**, *cis*-**6a**, and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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