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Sceptrin – Enantioselective Synthesis of a Tetrasubstituted all-*trans* Cyclobutane Key Intermediate

Lena Barra[a] and Jeroen S. Dickschat*[a]

Abstract: The asymmetric synthesis of both enantiomers of tetrasubstituted all-*trans* dimethyl 3,4-diacetylcyclobutane-1,2-dicarboxylate with high enantiomeric purity (>98 % *ee*) using a valine-derived chiral auxiliary in a diastereoselective photodimerization is reported. The absolute configuration was assigned by single-crystal X-ray diffraction analysis. Because this cyclobutane is a key intermediate in the total synthesis of (–)-sceptrin and ageliferin, our findings strengthen the recently revised absolute configurations of these pyrrole-imidazole alkaloids.

Introduction

The cyclobutane ring is a widespread structural motif that occurs in all classes of natural products including terpenes, alkaloids, fatty acids, nucleosides and polyketides.[1] Particularly intriguing are cyclobutane-centred symmetric (or pseudo-symmetric) natural products that are presumably formed by an intermolecular [2+2] cycloaddition of two identical (or structurally related) monomers that can usually result in a variety of regio- and stereoisomers. Well-known examples are the pseudo-symmetric all-*trans* compound anisumic acid (**1**) from the Chinese medicinal plant *Clausena anisum-olens* (Rutaceae)[2] and sceptrin (**2**), which was isolated in 1981 by Faulkner and Clardy and co-workers from the marine sponge *Agelas sceptrum* (Figure 1).[3] This dimer of hymenidin (**3**) belongs to a large group of marine pyrrole-imidazole alkaloids that exhibit remarkable structural architectures and a broad spectrum of bioactivities,[4] including anti-microbial, anti-muscarinic and anti-histaminic activities, and inhibition of the cell motility of cancer cell lines without showing cytotoxicity at the effective concentrations.[5] Besides **2**, a series of related compounds can be isolated from different *Agelas* species, such as ageliferin (**4**),[6] which can be rationalized as the [4+2] cycloadduct of **3**, and nakamuric acid (**5**),[7] for which the absolute configuration was recently clarified.[8] From a synthetic point of view, these chiral natural products are challenging targets because methods for the asymmetric construction of cyclobutane scaffolds are limited.[9] The first total synthesis of (*rac*)-**2** was reported in 2004 and proceeded via the tetrasubstituted all-*trans* cyclobutane (*rac*)-**6** as a key intermediate that was transformed into (*rac*)-**2** in 12 linear steps.[10] A subsequent enantioselective synthesis of (+)-**6** gave access to natural (–)-**2** and confirmed the initially assigned absolute configuration,[11] but a more recent synthetic route starting from L-glutamic acid resulted in a revision of the absolute configuration for sceptrin and, consequently, for the key intermediate (+)-**6** of the first enantioselective approach towards sceptrin.[12] Here we describe an alternative procedure for the synthesis of both enantiomers of **6** from L- or D-valine that confirms the recently revised absolute configuration of sceptrin.

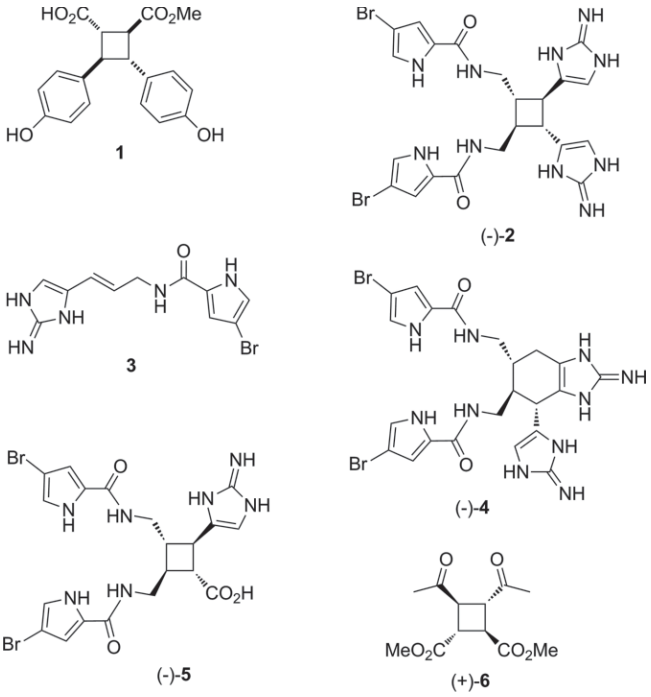


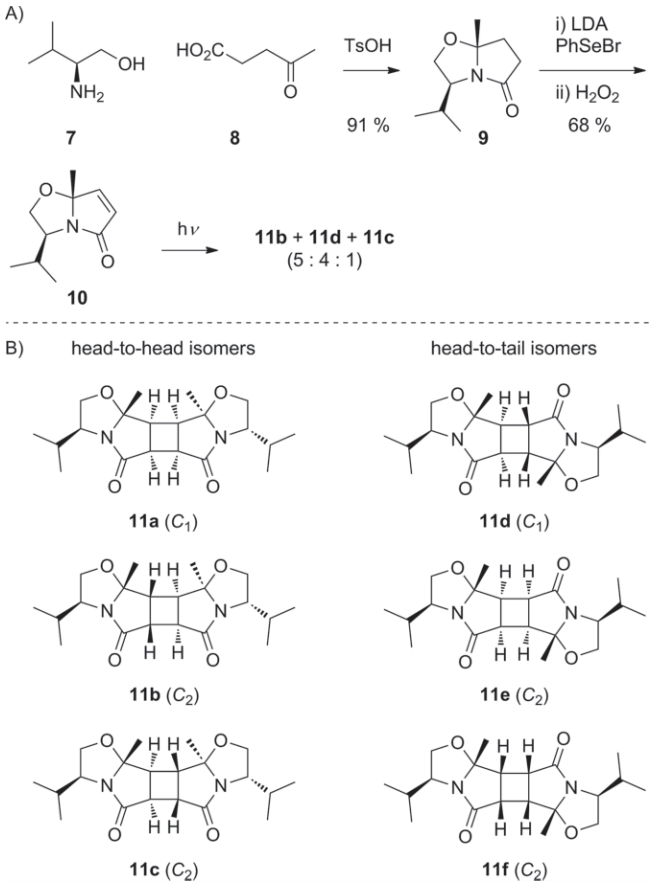
Figure 1. Structures of anisumic acid (**1**), sceptrin (**2**), hymenidin (**3**), ageliferin (**4**), nakamuric acid (**5**) and of the synthetic key intermediate (+)-**6** towards sceptrin and ageliferin.

Results and Discussion

For the enantioselective synthesis of **6**, L-valinol (**7**) and levulinic acid (**8**) were converted into the bicyclic lactam **9**, which is a

[a] *Kekulé-Institute of Organic Chemistry and Biochemistry, Rheinische Friedrich Wilhelms University of Bonn, Gerhard-Domagk-Straße 1, 53121 Bonn, Germany*
E-mail: dickschat@uni-bonn.de
https://www.chemie.uni-bonn.de/oc/forschung/arbeitsgruppen/ak_dickschat

known intermediate in the total synthesis of (–)-grandisol (Scheme 1A).[13] Introduction of an α,β-unsaturation by Grieco elimination yielded the enone **10**, a compound that was previously applied in face-selective cyclopropanation reactions.[14] UV irradiation of **10** at 250 nm in dichloromethane resulted in the formation of two products in yields of 15 % and 8 % that were tentatively identified as [2+2] dimerization products by GC–MS (Table 1).



Scheme 1. Synthesis of photodimers: A) synthesis of monomer **10** from valinol and subsequent irradiation to photodimers **11** and B) representation of all possible photodimers with their point groups given in parentheses.

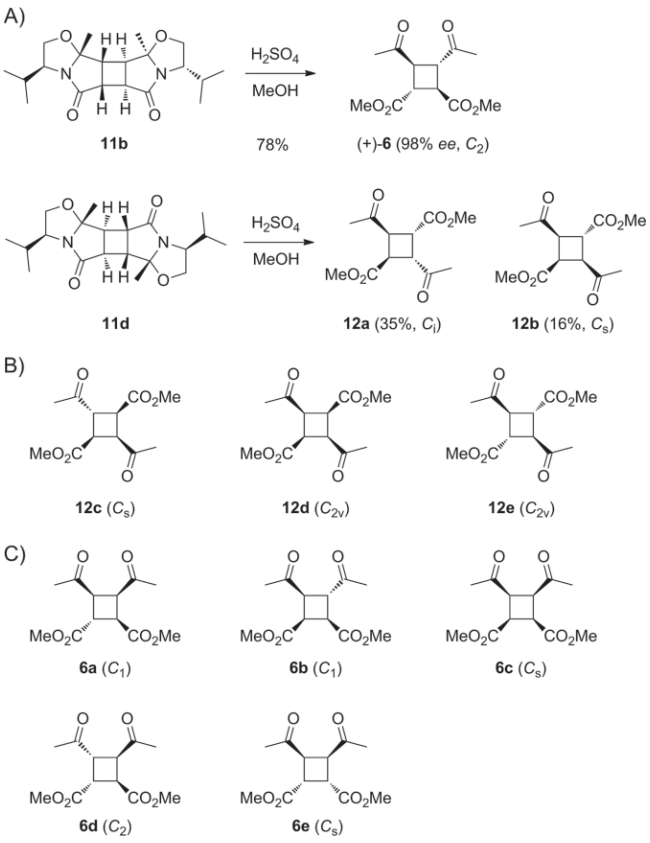
Table 1. Optimization of the reaction conditions for the photodimerization of **10**.[a]

λ [nm]	Solvent	Additive	Time [h]	Yield [%]		
				11b	**11c**	**11d**
250	DCM	–	24	15	n.d.	8
250	MeCN	–	24	19	n.d.	10
250	neat	–	48	0	0	0
350	MeCN	–	48	0	0	0
350	MeCN	acetophenone	12	37	5	32
350	MeCN	benzophenone	48	0	0	0
350	MeCN	acetone	48	0	0	0

[a] DCM = dichloromethane, MeCN = acetonitrile, n.d. = not determined.

During optimization of the reaction conditions, moderately increased yields were obtained in acetonitrile, whereas neat conditions did not give any [2+2] cycloadducts, even after prolonged reaction times. Changing to a wavelength of 350 nm did not yield any photodimerization products, but with the addition of acetophenone as photosensitizer significantly improved yields could be obtained, even with reduced reaction times, and also minor quantities (5 %) of a third product were obtained. When applied under the same conditions, benzophenone and acetone proved to be ineffective as photosensitizers.

The structures of the three compounds obtained under the optimized reaction conditions were elucidated by the following rationale. In theory, the photodimerization of **10** can lead to six isomers, namely three head-to-head connected isomers **11a**–**c** and three head-to-tail cycloadducts **11d**–**f** (Scheme 1B, the symmetry properties of the molecules discussed in the following section are summarized in Tables S1 and S2 in the Supporting Information). Among the head-to-head compounds the *cis-syn-cis* stereoisomer **11a** exhibits C_1 symmetry, whereas the two *cis-anti-cis* stereoisomers **11b** and **11c** both represent the point group C_2. Analogously, the head-to-tail isomer **11d** is of C_1 symmetry, whereas **11e** and **11f** belong to the C_2 point group. The main product of the photodimerization shows 10 signals in its ^{13}C NMR spectrum, in agreement with one of the C_2-symmetric structures. The acid-catalysed cleavage of this product in methanol resulted in (+)-**6** (Scheme 2A), the reported intermediate in the synthesis of sceptrin, which can only be formed from **11b** with epimerization of both methyl ketones or from **11c** with epimerization of both methyl ester groups to yield the



Scheme 2. Methanolysis of photodimers: A) acid-catalyzed cleavage of photodimers **11b** and **11d**, B) further possible methanolysis products from head-to-tail photodimers and C) from head-to-head photodimers with their point groups given in parentheses.

thermodynamically most stable all-*trans* cyclobutane. Epimerization of the methyl ketones was assumed to be faster than epimerization of the methyl esters, thereby favouring the structure of **11b** for the main product. Indeed, the cleavage in ($^2H_4$)methanol with $^2H_2SO_4$ proceeded with H/D exchange of only the cyclobutane hydrogens at the α positions with respect to the methyl ketones and not the methyl esters (Figure 2, for incorporation rates, ^{13}C NMR and HSQC spectra see Table S3 and Figures S1–S3 in the Supporting Information). The structure of **11b** is further supported by X-ray diffraction analysis, with the crystallographic data of its lysis product pointing to a (1*R*,2*R*,3*S*,4*S*) configuration for (+)-**6** (Figure 3).

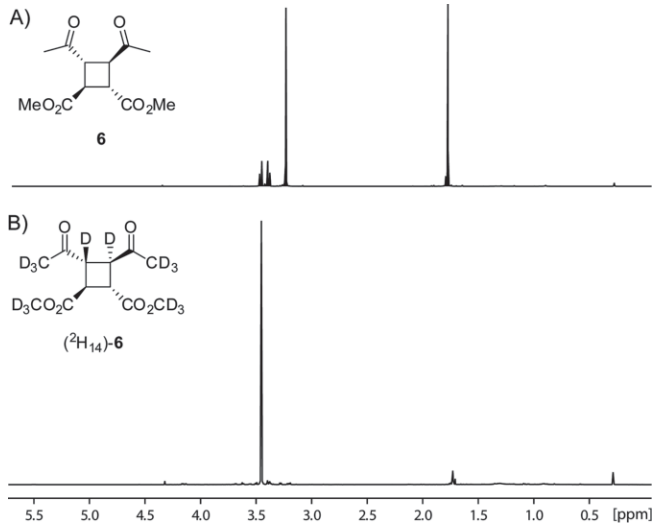


Figure 2. Result of the H/D exchange experiment. A) ^1H NMR spectrum of **6** (700 MHz, C_6D_6) and B) ^1H NMR spectrum of ($^2H_{14}$)-**6** (700 MHz, C_6D_6).

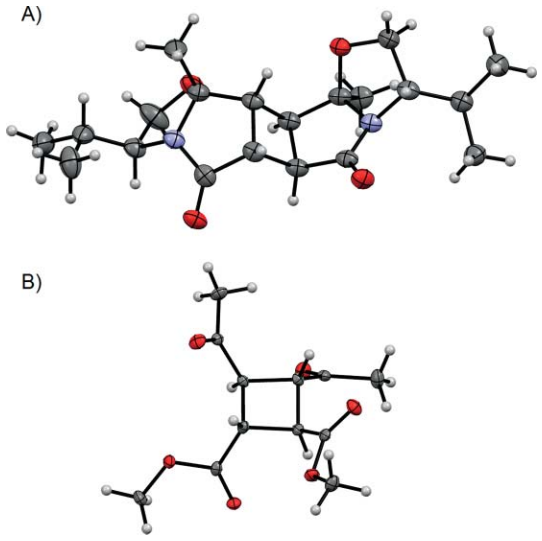


Figure 3. X-ray structures of **11b** and its cleavage product (+)-**6**. ORTEP representations of A) **11b** and B) (1*R*,2*R*,3*S*,4*S*)-**6** (crystallographic data are given in Tables S4 and S5 in the Supporting Information).

Starting from D-valinol, *ent*-(–)-**6** was obtained by the same route. Both enantiomers were isolated with high enantiomeric purity (>98 % *ee*), as revealed by HPLC analysis on a homochiral stationary phase (Figure 4). The delineated structure of **11b** is also supported by 2D NMR spectroscopy, including $^1H,^1H$ COSY, HSQC, HMBC and NOESY, but many of the observed correlations are also in line with the other C_2-symmetric isomers. This was also a major problem in the identification of the other two photodimers.

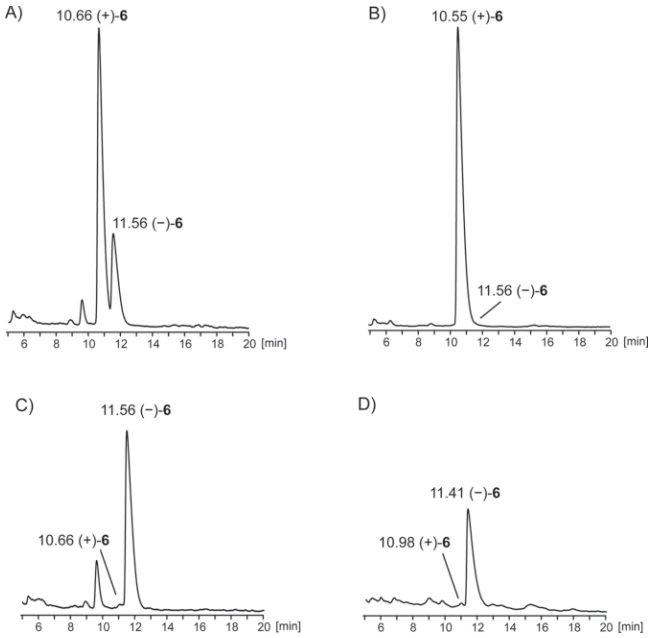


Figure 4. Analysis of the enantiomeric excess of **6** by HPLC on a chiral stationary phase. A) Mixture of (+)- and (–)-**6**, B) (+)-**6** obtained from the cleavage of (+)-**11b**, C) (–)-**6** obtained from the cleavage of (–)-**11b** and D) (–)-**6** obtained from the cleavage of (+)-**11c**.

The second most abundant photodimerization product from **10** exhibits 20 signals in its ^{13}C NMR spectrum, which points to one of the two possible structures of C_1 symmetry (**11a** or **11d**). Methanolysis of this product yielded two achiral or chiral racemic products, as indicated by a missing optical rotation. One of these products reveals six and the other one nine signals in their ^{13}C NMR spectra, requiring the presence of symmetric elements in both cases. Taking epimerizations (preferably at the methyl ketones) into account, the only possible structures for the minor product with nine ^{13}C NMR signals are the achiral compounds **12b** or **12c** (see Table S2 in the Supporting Information). For all the other stereoisomers of **12** with either C_i or C_{2v} symmetry, six carbon signals are expected, whereas none of the stereoisomers of **6** that could potentially arise from a head-to-head isomer such as **11a** has the correct symmetry properties to explain the observed ^{13}C NMR spectrum. The product **12b** was finally identified, because two sets of signals for the diastereotopic methyl ester functions and coinciding signals for the enantiotopic methyl ketones are observed, whereas **12c** would require two sets of signals for the methyl ketones and just one for the methyl esters. The major product of this methanolysis is likely to be **12a**, and the initial mixture of these two products pointed to the structure of **11d** for the second photodimer of **10**. The formation of **12b** shows again the preferential epimerization of the methyl ketone functions, whereas the hypothetical isomerization of one methyl ester group would

produce **12c**. No formation of the all-*trans* cyclobutane **12e** was observed, which also demonstrates the difficulties associated with the epimerization of the methyl ester groups under the applied reaction conditions.

The third minor product of the photodimerization of **10** exhibits 10 signals in the ^{13}C NMR spectrum, in agreement with the structures of **11c**, **11e** or **11f**. Methanolysis resulted in (–)-**6**, which is only explainable from the second C_2-symmetric head-to-head dimer **11c**, again requiring epimerization of both methyl ketones.

Conclusions

An alternative approach to the synthesis of both pure enantiomers of the tetrasubstituted all-*trans* cyclobutane **6** in five steps and 19 % overall yield has been developed. The stereoinformation is transferred from valinol, guiding a diastereoselective photodimerization that yields three products with interesting stereochemical properties. Also, their methanolysis with potential epimerization of the methyl ketones is a peculiar and intellectually challenging stereochemical problem. As outlined, the cyclobutane (+)-**6** is a key intermediate in the total synthesis of the pyrrole-imidazole alkaloid sceptrin (**2**) that serves itself as a precursor for the synthesis of the related natural products ageliferin (**4**) and nakamuric acid (**5**).[15] In the work presented here, the absolute configuration of (+)-**6** was re-examined, including by X-ray diffraction analysis, which confirmed the recently revised absolute configurations of this compound and all the natural products that were synthetically obtained from it. The efficient enantioselective approach to both enantiomers of **6** from cheap L- and D-valinol may be of use for the total synthesis of other cyclobutane natural products.

Experimental Section

General Synthetic Methods: All chemicals were obtained from Acros Organics (Geel, Belgium), Sigma Aldrich Chemie GmbH (Steinheim, Germany) or TCI Deutschland GmbH (Eschborn, Germany). All solvents were purified by distillation. Whenever necessary, reactions were carried out under inert atmosphere (Ar) using vacuum-heated flasks and dried solvents (dried according to standard protocols). TLC was performed on 0.20 mm silica plates (Polygram SIL G/UV254) obtained from Macherey–Nagel (Düren, Germany). Column chromatography was performed on Merck silica gel (0.040–0.063 Mesh). NMR spectra were recorded with Bruker AV I (400 MHz), AV III HD Prodigy (500 MHz) and AV III HD Cryo (700 MHz) spectrometers, and were referenced against $CDCl_3$ (δ = 7.26 ppm), C_6D_6 (δ = 7.16 ppm) and [D_3]DMSO (δ = 2.50 ppm) for ^1H NMR, and $CDCl_3$ (δ = 77.01 ppm), C_6D_6 (δ = 128.06 ppm) and [D_6]DMSO (δ = 39.52 ppm) for ^{13}C NMR spectroscopy. The multiplicities are specified as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept.), multiplet (m). GC–MS analyses were carried out with an Agilent HP7890B gas chromatograph connected to a HP5977A mass detector fitted with a HP-5MS silica capillary column (30 m, 0.25 mm i.d., 0.50 µm film). The GC–MS conditions were as follows: 1) inlet pressure: 77.1 kPa, He flow 23.3 mL/min; 2) injection volume: 1 µL; 3) injection mode: split 50:1, valve time 60 s; 4) oven temperature ramp: 5 min at 50 °C increasing at 10 °C/min to 320 °C; 5) carrier gas He at 1 mL/min; 6) transfer line: 250 °C; 7) electron energy: 70 eV. Retention indices (*I*) were determined from a homologous series of *n*-alkanes (C_8–C_{40}). Optical rotary powers were recorded with a P8000 Polarimeter (Krüss). UV/Vis spectra were recorded with a Cary 100 UV/Vis spectrometer (Agilent). IR spectra were recorded with an Alpha FT-IR spectrometer from Bruker. The intensities of the signals are specified as follows: strong (s), medium (m), weak (w), broad (br).

(3*S*,7a*R*)-3-Isopropyl-7a-methyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one [(+)-9]: L-Valinol (7.20 g, 69.8 mmol, 1.0 equiv.) and levulinic acid (8.11 g, 69.8 mmol, 1.0 equiv.) were dissolved in toluene (400 mL) and *p*-toluenesulfonic acid (0.60 g, 3.49 mmol, 0.05 equiv.) was added. The reaction mixture was heated at reflux for 16 h using a Dean–Stark trap. After completion of the reaction the mixture was concentrated and washed with $NaHCO_3$ (sat. aqueous solution). The organic phase was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 3:1) and (+)-**9** (12.0 g, 65.6 mmol, 94 %) was isolated as a colourless oil. $[\alpha]_D^{21}$ = +84.2 (*c* = 1, acetone). R_f = 0.2. GC (HP-5MS): *I* = 1379. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.14 (dd, $^2J_{H,H}$ = 8.7, $^3J_{H,H}$ = 7.3 Hz, 1 H, C*H*H), 3.85 (dd, $^2J_{H,H}$ = 8.7, $^3J_{H,H}$ = 6.1 Hz, 1 H, C*H*H), 3.59 (ddd, $^3J_{H,H}$ = 6.3, $^3J_{H,H}$ = 7.3, $^3J_{H,H}$ = 10.4 Hz, 1 H, CH), 2.73 (ddd, $^2J_{H,H}$ = 17.0, $^3J_{H,H}$ = 9.8, $^3J_{H,H}$ = 9.8 Hz, 1 H, CHH), 2.46 (ddd, $^2J_{H,H}$ = 17.0, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 5.6 Hz, 1 H, CHH), 2.20–2.12 (m, 2 H, CH_2), 1.73–1.61 (m, 1 H, CH), 1.47 (s, 3 H, CH_3), 1.03 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH_3), 0.88 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0 (C_q), 100.0 (C_q), 71.1 (CH_2), 61.8 (CH), 34.2 (CH_2), 33.6 (CH), 33.1 (CH_2), 25.1 (CH_3), 20.6 (CH_3), 19.2 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 2959 (w), 2931 (w), 2872 (w), 1704 (s), 1466 (w), 1347 (s), 1247 (w), 1190 (w), 1020 (m), 879 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 183 (32), 168 (87), 154 (18), 140 (100), 126 (19), 112 (32), 100 (46), 82 (55), 69 (23), 55 (24), 43 (30). HRMS (ESI): calcd. for $C_{10}H_{17}NNaO_2^+$ 206.1151; found 206.1151 $[M + Na]^+$.

(3*R*,7a*S*)-3-Isopropyl-7a-methyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one [(–)-9]: Lactam (–)-**9** was synthesized analogously from D-valinol (5.00 g, 48.5 mmol). Yield: 8.08 g (44.1 mmol, 91 %). All recorded spectroscopic data, with the exception of the optical rotary power, were identical to those for (+)-**9**. $[\alpha]_D^{21}$ = –81.9 (*c* = 1, acetone).

(3*S*,7a*R*)-3-Isopropyl-7a-methyl-2,3-dihydropyrrolo[2,1-*b*]oxazol-5(7a*H*)-one [(+)-10]: Diisopropylamine (0.61 g, 6.00 mmol, 2.2 equiv.) was dissolved in dry THF (15 mL) under Ar and cooled to 0 °C. A solution of *n*-butyllithium (1.6 M in hexane, 3.80 mL, 6.00 mmol, 2.2 equiv.) was added dropwise and the mixture was stirred for 30 min and afterwards cooled to –78 °C. A solution of (+)-**9** (0.50 g, 2.73 mmol, 1.0 equiv.) in dry THF (1 mL) was added dropwise and the mixture was stirred for 2 h, followed by dropwise addition of a cooled solution (–78 °C) of PhSeBr (0.77 g, 3.28 mmol, 1.2 equiv.) in dry THF (10 mL). The mixture was warmed to room temperature and stirred overnight, quenched with water and extracted with EtOAc. The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude selenylation product and pyridine (0.54 g, 6.82 mmol, 2.5 equiv.) were dissolved in DCM (15 mL) and cooled to 0 °C. A 35 % aqueous H_2O_2 solution (0.80 mL, 8.18 mmol, 3.0 equiv.) was added dropwise and the mixture was stirred for 3 h. After completion of the reaction the mixture was quenched with 1 M HCl solution. The organic phase was washed with water and brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 3:1) and (+)-**10** was obtained as a pale-yellow solid, which was repeatedly washed with cold pentane until a colourless product was obtained (0.34 g, 1.86 mmol,

68 %). $[\alpha]_D^{21}$ = +48.6 (*c* = 1, acetone). R_f = 0.2. GC (HP-5MS): *I* = 1320. M.p. 49–51 °C. ^{1}H NMR (500 MHz, C_6D_6): δ = 6.37 (d, $^3J_{H,H}$ = 5.8 Hz, 1 H, CH), 5.64 (d, $^3J_{H,H}$ = 5.8 Hz, 1 H, CH), 3.88 (dd, $^2J_{H,H}$ = 8.8, $^3J_{H,H}$ = 7.3 Hz, 1 H, C*H*H), 3.64 (dd, $^2J_{H,H}$ = 8.8, $^3J_{H,H}$ = 6.0 Hz, 1 H, C*H*H), 3.44 (ddd, $^3J_{H,H}$ = 10.1, $^3J_{H,H}$ = 7.2, $^3J_{H,H}$ = 6.3 Hz, 1 H, CH), 1.45 (dsept., $^3J_{H,H}$ = 10.1, $^3J_{H,H}$ = 6.6 Hz, 1 H, CH), 1.17 (s, 3 H, CH_3), 1.10 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3), 0.58 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 177.6 (C_q), 150.6 (CH), 127.9 (CH), 100.4 (C_q), 73.7 (CH_2), 62.7 (CH), 33.2 (CH), 22.3 (CH_3), 20.8 (CH_3), 19.2 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3089 (w), 2959 (w), 2930 (w), 2875 (w), 1708 (s), 1671 (m), 1320 (s), 1105 (s), 1011 (m), 892 (s), 833 (m) cm^{-1}. UV/Vis (MeCN): λ_{max} [log (ε/M^{-1} cm^{-1})] = 245 [3.187] nm. MS (EI, 70 eV): *m/z* (%) = 181 (6), 166 (49), 151 (60), 138 (100), 124 (11), 110 (54), 96 (27), 80 (11), 59 (17), 53 (11), 41 (16). HRMS (ESI): calcd. for $C_{10}H_{15}NNaO_2^+$ 204.0995; found 204.0999 [M + Na]$^+$.

(3*R*,7a*S*)-3-Isopropyl-7a-methyl-2,3-dihydropyrrolo[2,1-*b*]-oxazol-5(7a*H*)-one [(–)-10]: Compound (–)-**10** was synthesized analogously from (–)-**9** (5.00 g, 27.3 mmol). Yield: 3.26 g (18.0 mmol, 66 %). All recorded spectroscopic data, with the exception of the optical rotary power, were identical to those for (+)-**10**. $[\alpha]_D^{21}$ = –49.3 (*c* = 1, acetone).

General procedure for the photochemical dimerization of 10: Enone **10** was dissolved at a concentration of 0.1 M in freshly degassed solvent according to Table 1 and irradiated by use of a Rayonet RPR-200 photoreactor. When utilized, photosensitizers were added (5 equiv.) directly to **10**. When irradiation with λ = 250 nm was conducted, reaction vessels made of fused silica glass were used. The reaction progress was monitored by GC and carried out until all starting material was consumed or after no product formation was detected after 48 h. The solvent was removed under reduced pressure and the crude products were directly subjected to HPLC separation [system: Fa. KNAUER GmbH (Berlin, Germany), two pumps S-1800, assistant 6000 with feedpump S-100 (10 mL pumphead) and electronic injection valve (6 port), UV/Vis detector S-2550 (190–900 nm); column: KNAUER Eurospher II 100-5 C18P, 5 µm, 250 × 20 mm; solvent: MeCN/H_2O (45:55); flow rate: 24.0 mL/min]. Fractions containing the target compound were pooled and the solvent was removed by lyophilization. For the different tested reaction conditions, see Table 1.

Photodimers (+)-11b, (+)-11d and (+)-11c: Enone (+)-**10** (0.20 g, 1.10 mmol, 1.0 equiv.) was dissolved in freshly degassed dry MeCN (10 mL) and acetophenone (0.66 g, 5.52 mmol, 5.0 equiv.) was added. The solution was irradiated with λ = 350 nm until all starting material was consumed (12 h). The solvent was removed under reduced pressure and the crude product mixture was purified by HPLC. After lyophilization (+)-**11b** (74.0 mg, 0.20 mmol, 37 %), (+)-**11d** (64 mg, 0.18 mmol, 32 %) and (+)-**11c** (10 mg, 0.03 mmol, 5 %) were isolated as colourless solids.

Analytical data for (+)-**11b**: $[\alpha]_D^{21}$ = +193.6 (*c* = 1, MeOH). GC (HP-5MS): *I* = 2642. M.p. 196–198 °C. ^{1}H NMR (400 MHz, C_6D_6): δ = 3.99–3.89 (m, 2 H, 2 C*H*H), 3.58–3.51 (m, 4 H, 2 C*H*H, 2 CH), 3.57–3.48 (m, 2 H, 2 CH), 3.31 (m, 2 H, 2 CH), 2.99 (m, 2 H, 2 CH), 1.39–1.27 (m, 2 H, 2 CH), 1.08 (s, 6 H, 2 CH_3), 1.07 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, 2 CH_3), 0.57 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 176.9 (2 C_q), 97.8 (2 C_q), 73.0 (2 CH_2), 61.0 (2 CH), 46.1 (2 CH), 42.2 (2 CH), 34.5 (2 CH), 25.5 (2 CH_3), 20.9 (2 CH_3), 19.0 (2 CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 2957 (w), 2940 (w), 2875 (w), 1703 (s), 1466 (w), 1352 (s), 1227 (w) 1148 (w), 1047 (w), 1007 (m), 899 (w), 769 (m), 609 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 362 (7), 347 (100), 319 (25), 291 (4), 279 (8), 261 (3), 236 (3), 219 (2), 207 (9), 193 (8), 182 (12), 166 (17), 151 (46), 138 (33), 128 (54), 108 (44), 96 (32), 80 (20), 69 (45), 55 (16), 43 (52). HRMS (ESI): calcd. for $C_{20}H_{31}N_2O_4^+$ 363.2278; found 363.2278 [M + H]$^+$. Optical rotary power of (–)-**11b**: $[\alpha]_D^{21}$ = –184.2 (*c* = 1, MeOH).

Analytical data for (+)-**11d**: $[\alpha]_D^{21}$ = +89.0 (*c* = 1, acetone). GC (HP-5MS): *I* = 2690. M.p. 189–192 °C. ^{1}H NMR (500 MHz, C_6D_6): δ = 3.87 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 7.6 Hz, 1 H, C*H*H), 3.79 (dd, $^2J_{H,H}$ = 8.2, $^3J_{H,H}$ = 8.2 Hz, 1 H, C*H*H), 3.67 (ddd, $^3J_{H,H}$ = 10.8, $^3J_{H,H}$ = 7.2, $^3J_{H,H}$ = 7.0 Hz, 1 H, CH), 3.56 (m, 1 H, CH), 3.53 (m, 1 H, C*H*H), 3.46 (ddd, $^3J_{H,H}$ = 10.2, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 7.1 Hz, 1 H, CH), 3.36 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 6.9 Hz, 1 H, C*H*H), 3.00 (m, 1 H, CH), 2.99 (m, 1 H, CH), 2.63 (m, 1 H, CH), 1.43–1.30 (m, 2 H, 2 CH), 1.23 (s, 3 H, CH_3), 1.15 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3), 1.07 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 0.57 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3), 0.56 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 182.0 (C_q), 178.2 (C_q), 100.8 (C_q), 97.9 (C_q), 72.6 (CH_2), 69.0 (CH_2), 64.0 (CH), 61.9 (CH), 45.7 (CH), 44.9 (CH), 44.1 (CH), 41.4 (CH), 34.4 (CH), 34.1 (CH), 25.9 (CH_3), 21.2 (CH_3), 20.9 (CH_3), 20.4 (CH_3), 19.0 (CH_3), 18.9 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 2924 (w), 2903 (w), 2868 (w), 1694 (s), 1463 (w), 1329 (m), 1138 (w), 1030 (w), 873 (w), 751 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 362 (23), 347 (100), 319 (60), 279 (11), 236 (21), 220 (3), 207 (7), 182 (20), 166 (7), 151 (72), 138 (21), 128 (45), 126 (44), 108 (21), 96 (23), 84 (12), 69 (21), 56 (7), 43 (21). HRMS (ESI): calcd. for $C_{20}H_{30}N_2NaO_4^+$ 385.2098; found 385.2098 [M + Na]$^+$. Optical rotary power of (–)-**11d**: $[\alpha]_D^{21}$ = –91.5 (*c* = 0.6, acetone).

Analytical data for (+)-**11c**: $[\alpha]_D^{21}$ = +5.2 (*c* = 1, acetone). GC (HP-5MS): *I* = 2738. M.p. 192–193 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 4.10 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2 C*H*H), 3.76 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.9 Hz, 2 H, 2 C*H*H), 3.50 (ddd, $^3J_{H,H}$ = 10.7, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 7.5 Hz, 2 H, 2 CH), 3.04 (m, 2 H, 2 CH), 2.98 (m, 2 H, 2 CH), 1.76–1.64 (m, 2 H, 2 CH), 1.50 (s, 6 H, 2 CH_3), 0.98 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H, 2 CH_3), 0.85 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 181.2 (2 C_q), 100.3 (2 C_q), 68.0 (2 CH_2), 63.8 (2 CH), 42.6 (2 CH), 42.1 (2 CH), 32.8 (2 CH), 20.9 (2 CH_3), 19.3 (2 CH_3), 18.8 (2 CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 2963 (w), 2951 (w), 2872 (w), 1718 (s), 1459 (w), 1296 (m), 1280 (m), 1181 (m), 1071 (w), 999 (w), 986 (w), 863 (s), 695 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 362 (21), 347 (27), 319 (40), 295 (5), 279 (5), 235 (13), 182 (9), 151 (100), 138 (19), 128 (60), 108 (60), 96 (20), 84 (10), 69 (16), 56 (6), 43 (20). HRMS (ESI): calcd. for $C_{20}H_{30}N_2NaO_4^+$ 385.2098; found 385.2098 [M + Na]$^+$.

Dimethyl (1*R*,2*R*,3*S*,4*S*)-3,4-Diacetylcyclobutane-1,2-dicarboxylate [(+)-6]: Photodimerization product (+)-**11b** (62.0 mg, 0.17 mmol, 1.0 equiv.) was dissolved in MeOH (10 mL) and conc. H_2SO_4 (1 mL) was added carefully. The reaction mixture was heated at 70 °C for 6 h. After completion of the reaction, the mixture was diluted with EtOAc and washed with water. The organic phase was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 1:1) and (+)-**6** (34.0 mg, 0.13 mmol, 78 %, 98 % *ee*, Figure 4) was isolated as a colourless solid. $[\alpha]_D^{21}$ = +30.3 (*c* = 1, $CHCl_3$). R_f = 0.3. GC (HP-5MS): *I* = 1663. M.p. 76–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (s, 6 H, 2 CH_3), 3.51 (dd, *J* = 9.5, 2.4 Hz, 2 H, 2 CH), 3.40 (dd, *J* = 9.5, 2.4 Hz, 2 H, 2 CH), 2.20 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.0 (C_q), 171.8 (C_q), 52.7 (CH_3), 46.6 (CH), 39.1 (CH), 27.9 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 2964 (w), 2922 (w), 2903 (w), 2865 (w), 1695 (s), 1461 (w), 1347 (m), 1168 (m), 1114 (m), 874 (w), 773 (w), 683 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 256 (3), 241 (7), 224 (33), 213 (19), 196 (1), 182 (21), 171 (10), 164 (5), 153 (25), 140 (22), 123 (12), 111 (26), 95 (14), 85 (6), 59 (11), 43 (100). HRMS (ESI): calcd. for $C_{12}H_{16}NaO_6^+$ 279.0839; found 279.0839 [M + Na]$^+$.

Dimethyl (1*S*,2*S*,3*R*,4*R*)-3,4-Diacetylcyclobutane-1,2-dicarboxylate [(–)-6]: Compound (–)-**6** was synthesized by acidic cleavage of

either (+)-**11c** (yield: 8.00 mg, 0.03 mmol, 71 %, 98 % *ee*, Figure 4) or (–)-**11b** (yield: 12.0 mg, 0.05 mmol, 78 %, 98 % *ee*, Figure 4) following the same procedure as used for (+)-**6**. All recorded spectroscopic data, with the exception of the optical rotary power, were identical to those for (+)-**6**. $[\alpha]_D^{21} = -30.0$ (c = 1, $CHCl_3$).

Dimethyl (1*R*,2*R*,3*S*,4*S*)-2,4-Diacetylcyclobutane-1,3-dicarboxylate (12a) and Dimethyl (1*r*,2*R*,3*s*,4*S*)-2,4-Diacetylcyclobutane-1,3-dicarboxylate (12b): Photodimerization product (+)-**11d** (36.0 mg, 0.10 mmol, 1.0 equiv.) was dissolved in MeOH (3 mL) and conc. H_2SO_4 (0.3 mL) was added carefully. The reaction mixture was heated at 70 °C for 16 h. After complete reaction, the mixture was diluted with EtOAc and washed with water. The organic phase was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 1:2) and **12a** (9.00 mg, 0.035 mmol, 35 %) and **12b** (4.00 mg, 0.016 mmol, 16 %) were isolated as colourless solids.

Analytical data for **12a**: R_f = 0.3. GC (HP-5MS): I = 1729. M.p. 77–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84–3.77 (m, 2 H, 2 CH), 3.73–3.67 (m, 2 H, 2 CH), 3.69 (s, 6 H, 2 CH_3), 2.20 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.7 (2 C_q), 171.8 (2 C_q), 52.5 (2 CH_3), 47.2 (2 CH), 40.4 (2 CH), 29.4 (2 CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3005 (w), 2954 (w), 2921 (w), 2851 (w), 1722 (s), 1706 (s), 1440 (m), 1358 (m), 1298 (w), 1233 (s), 1193 (s), 1073 (m), 1038 (w), 982 (w), 953 (w), 935 (w), 797 (m), 724 (w), 661 (w), 510 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 256 (3), 241 (9), 225 (22), 214 (9), 209 (3), 196 (10), 182 (26), 171 (19), 155 (6), 150 (43), 140 (35), 139 (35), 123 (20), 111 (25), 95 (14), 79 (2), 69 (2), 59 (4), 43 (100). HRMS (ESI): calcd. for $C_{12}H_{16}NaO_6^+$ 279.0839; found 279.0839 $[M + Na]^+$.

Analytical data for **12b**: R_f = 0.2. GC (HP-5MS): I = 1689. M.p. 99–101 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.06 (dd, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 10.0 Hz, 1 H, CH), 3.78 (s, 3 H, CH_3), 3.67 (s, 3 H, CH_3), 3.67 (dd, $^3J_{H,H}$ = 9.0, $^3J_{H,H}$ = 9.0 Hz, 1 H, CH), 3.40 (dd, $^3J_{H,H}$ = 9.5, $^3J_{H,H}$ = 9.5 Hz, 2 H, 2 CH), 2.13 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.6 (2 C_q), 172.9 (C_q), 172.0 (C_q), 52.7 (CH_3), 52.4 (CH_3), 46.4 (2 CH), 42.9 (CH), 41.4 (CH), 27.5 (2 CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3003 (w), 2942 (w), 2919 (w), 2851 (w), 1717 (s), 1706 (s), 1441 (m), 1378 (w), 1358 (w), 1282 (s), 1184 (m), 1158 (s), 1132 (s), 1054 (m), 1040 (w), 996 (w), 934 (m), 806 (w), 589 (w), 486 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 256 (<1), 241 (9), 224 (56), 214 (3), 209 (4), 193 (12), 181 (15), 171 (12), 165 (4), 155 (4), 150 (40), 139 (30), 123 (12), 111 (25), 95 (13), 85 (9), 59 (5), 59 (12), 43 (100). HRMS (ESI): calcd. for $C_{12}H_{16}NaO_6^+$ 279.0839; found 279.0839 $[M + Na]^+$.

($^2H_6$)Dimethyl (1*R*,2*R*,3*S*,4*S*)-($^2H_8$)-3,4-Diacetylcyclobutane-1,2-dicarboxylate [($^2H_{14}$)-6]: Photodimer (+)-**11b** (19.0 mg, 0.05 mmol) was dissolved in ($^2H_4$)methanol (3 mL) and ($^2H_2$)sulfuric acid (98 % in D_2O, 0.3 mL) was added carefully. The reaction was heated for 16 h at 70 °C, diluted with D_2O (10 mL) and extracted with DCM. The organic phase was dried with $MgSO_4$ and the solvent was removed under reduced pressure to yield ($^2H_{14}$)-**6** (11.0 mg, 0.04 mmol, 78 %). GC (HP-5MS): I = 1650. MS (EI, 70 eV): *m/z* (%) = 270 (3), 252 (7), 235 (33), 224 (17), 216 (5), 206 (4), 200 (4), 188 (5), 180 (5), 172 (3), 161 (10), 155 (9), 146 (11), 116 (41), 100 (8), 62 (8), 46 (100). For the NMR spectroscopic data, see Table S1 in the Supporting Information.

Analysis of the Enantiomeric Excess of 6: The enantiomeric excesses of (+)- and (–)-**6** obtained from acidic cleavage of either (+)-**11b**, (–)-**11b** or (+)-**11c** were analysed by HPLC using the following conditions: system: Fa. Knauer GmbH (Berlin, Germany), HPG-pump P6.1L, oven CT 2.1, photodiode array detector DAD 6.1L (190–1020 nm); column: DAICEL Chiralpak IB; 5 µm, 4.6 mm × 250 mm; solvent: *n*-hexane/2-propanol (85:15); flow rate: 1.0 mL/min; pressure: 42 bar; temperature: 25 °C.

CCDC 1552548 [for (+)-**11b**], and 1552549 [for (+)-**6**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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