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Rapid Production of *trans*-Cyclooctenes in Continuous Flow

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A new method for rapid larger-scale production of *trans*-cyclooctenes (TCOs) in continuous flow was developed: Up to 2.2 g/h of specific TCOs can be produced by using this procedure. This method utilizes the classical photoisomerization of *cis*-cyclooctenes (CCOs) for the synthesis of TCOs but substitutes the conventionally used silver nitrate impregnated

silica gel column for a liquid–liquid extraction module. In addition, this method provides the possibility of external addition of a substrate to scale up and speed up the production of TCOs because the concentration of the CCO is kept constant. This method was applied for the synthesis of several commonly used TCOs.

1. Introduction

trans-Cyclooctenes (TCOs or *E*-COs)^[1] have become tantalizing targets for synthetic chemists during the last two decades because their inherent high reactivity in HOMO-alkene controlled cycloaddition reactions has sparked a large number of applications and, therefore, their demand. The cycloaddition of *E*-COs with 1,2,4,5-tetrazines in a [4+2] inverse-electron-demand Diels–Alder (IEDDA) cycloaddition² displays exceptionally high reaction rates (up to $3.3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$).^[3] This favorable cycloaddition characteristic has converted *E*-COs into a promising tool for bioorthogonal chemistry because fast ligation at very high dilutions can be achieved,^[4] requisite for its application in living systems.

The IEDDA cycloaddition of *E*-COs has been applied in chemoselective reactions for the rapid labeling of biological molecules *in vitro* and in cells.^[5] Two of the most remarkable applications of *E*-COs are in the pretargeted labeling of cancer cells^[6] and in drug delivery with antibody–drug conjugates.^[7] Some derivatives of *E*-COs with a nucleofuge on the allylic position can perform a “click-to-release” reaction, in which a cargo molecule is eliminated from the *E*-CO molecule after cycloaddition with the tetrazine. The “click-to-release” technique has been investigated as a delivery system of bioactive compounds or drugs (e.g., doxorubicin).^[8]

Aside from applications in biomedical sciences, *E*-CO was also employed to make narrowly dispersed polycyclooctene.^[9]

In a nutshell, the striking number of applications of *E*-COs has boosted their demand and any contribution that makes *E*-COs more available is appreciated. Herein we present an optimized method for the efficient multigram-scale synthesis of *E*-COs.

2. Results and Discussion

One of the most common procedures currently used to produce *E*-COs (*E*-1) is by sensitized^[10] photoisomerization of the corresponding *cis*-cyclooctenes (*Z*-1 (CCOs or *Z*-COs) under ultraviolet light irradiation at a wavelength of 254 nm (Scheme 1).^[11]

Scheme 1. Sensitized photoisomerization of (*Z*)-cyclooctenes (*Z*-1) to (*E*)-cyclooctenes (*E*-1) under UV light irradiation (254 nm).^[12]

A rapid equilibrium between the *Z*- and *E*-isomers is established under these conditions in which the *E*-isomer is always the minor product (10–23% of the mixture). The *E/Z* ratio depends on the concentration of the sensitizer, the concentration of the substrate, the irradiation time and the structure of the substrate.^[11d]

The most conventional sensitized photoisomerization method to produce *E*-COs was developed by Fox et al. in 2008.^[11c] This method produces *E*-COs by irradiation of a solution of the corresponding *Z*-isomer and a photosensitizer in an organic solvent (e.g., heptane) that is flushed after irradiation through a silver nitrate impregnated silica gel column. The silver(I) ions selectively immobilize the *E*-isomer on the silica gel, whereas the remaining *Z*-isomer (77–90%, assuming complete scavenging of the *E*-isomer by the silver ions) elutes from the column back into the photoreactor. The solution of the *Z*-isomer is recycled in this way until (almost) full conversion is reached or until the column is saturated with the *E*-isomer. Finally, the *E*-CO is isolated by treating the silica gel with aqueous ammonia to dissociate the *E*-isomer from the silver(I) ions, followed by an extraction with an apolar solvent (e.g., heptane or pentane).

We present herewith a modification of Fox's method in which we have substituted the silica gel column for a liquid–liquid extraction module and with the possibility of

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external addition of substrate. Not only does the addition of substrate during the reaction permit scaling up the production without limitations, but it also maintains a constant substrate concentration allowing a higher output of product per unit of time (the concentration of Z-CO in solution is otherwise lower after every cycle and so is the production of the E-CO). We were able to produce up to 2.2 g/h of specific E-COs with our novel continuous flow method. A schematic representation of our method is shown in Figure 1.

Figure 1. Schematic overview of the production of E-COs via a continuous liquid-liquid extraction with the possibility of external addition of substrate.

Small- and larger-scale photoreactors with similar designs were built in-house to develop our new methodology. An overview and a photo of the larger-scale photoreactor are shown in Figure 2 (a scheme and a photo of the small-scale photoreactor can be found in the Supplementary Information).

The fabricated photoreactor^[13] involves a (cooled) photoreactor^[14] (1; FEP tubing^[15] (4; i.d. 2.7 mm) wound around a UV lamp (3; wavelength of 254 nm, distance between the tubing and the UV lamp = 0.7–1.4 cm) inside a metal jacket with a

Figure 2. Overview and photograph of the production of E-COs by means of a continuous liquid-liquid extraction with the possibility of external addition of substrate.

water-based cooling system) for the isomerization of Z-COs into E-COs, and a liquid-liquid extraction module (5) to physically separate the Z-COs and E-COs. This module consists of a customized 100 mL round-bottom flask with an extended neck and a magnetic stirrer (a hotplate stirrer (7) provides the required vigorous stirring). The extended neck allows both extraction and phase separation. While the Z-COs in the organic layer are resubjected to the photochemical isomerization by a pump (2; from the top of the flask), the E-COs are trapped by the silver nitrate aqueous solution and stay in the aqueous phase in the flask (5; bottom of the flask) and are no longer part of the continuous process. The substrate is added to the system by a syringe pump (6) to maintain the starting concentration.

Four of the most common Z-COs [(Z)-2–5] were selected for their isomerization to E-COs [(E)-2–5] to proof the concept of our new method. First, the conversion ratios as function of irradiation time were determined by using an exposure gradient on 100–130 mM solutions of the Z-isomers (PhCO₂Me as sensitizer) in deoxygenated heptane (Table 1; see the

Table 1. Conversion [%] of cyclooctenes (Z)-2–5 to (E)-2–5 at different irradiation times.^[a]

Entry	Substrate	Time [min]			
		20–30	30–40	40–50	50–60
1	(Z)-2	18.7	20.6	21.9	23.1
2	(Z)-3	17.4	18.7	20.0	20.0
3	(Z)-4	16.7	17.6	19.0	20.1
4	(Z)-5	18.0	19.4	20.0	19.4

[a] Ratios of (Z)/(E)-isomers calculated by integration of the ¹H NMR resonance signals.

Experimental Section). These results were employed to estimate the molar output of E-CO and determine the addition rate of substrate after isomerization. The highest conversions were observed after 40–50 (entries 2 and 4) or 50–60 min (entries 1 and 3) of irradiation time. From these results, an irradiation time of 20 min was applied to future experiments because the small differences of conversion after this time would be balanced out by the higher output of E-CO per unit of time. The output of E-CO is determined by the volume throughput and the conversion ratio, which are both parameters related to the flow rate. The conversion ratio decreases with an increased flow rate (lower irradiation time), whereas the volume throughput increases.

Concurrently with the determination of the optimal irradiation time, we observed that the separation of the isomers was

efficient when the *Z*-COs were completely insoluble in the aqueous silver nitrate solution and fully soluble in heptane (cyclooctenes (*Z*-4 and (*Z*-5), and the *E*-CO–silver complexes presented the opposite behavior (cyclooctenes (*E*-4 and (*E*-5; entries 3 and 4). In contrast, cyclooctenes (*Z*-2 and (*Z*-3 (with a hydroxy group) were soluble enough in the aqueous phase to thwart their separation from the *E*-isomers (entries 1 and 2). We assume that there was silver complexation to the hydroxy groups of these compounds because these products were more soluble in the aqueous silver nitrate solution than the pure compounds are in water.^[16] The solubility of (*Z*-2 was then altered by acetylation of the hydroxy group. The synthesis of (*E*-3 entails two steps of synthesis: reduction of (*Z*-3 followed by *Z/E*-isomerization or vice versa; therefore the latter procedure must be used when using our photoisomerization method. Finally, cyclooctenes (*Z*-4–7 (Figure 3) were chosen to test our continuous flow photoreactors of the present study.

Figure 3. Cyclooctenes (*Z*-4–7 investigated for the *Z/E*-isomerization.

We commenced our study performing the first experiments in the small-scale photoreactor (total volume: 15.5 mL; irradiated volume: 10.7 mL) for 24 h. We applied the best conditions found after further optimization: concentration of *Z*-CO in deoxygenated heptane: 130 mM; concentration of PhCO_2Me : 20 mM; irradiation time (254 nm): 20 min.

Nitric acid was added to the aqueous silver nitrate solution (pH 4) to prevent the formation of a brown-black foam that was occasionally formed at the interface between the two phases in the extraction module.^[17] Additional preventive measures against the formation of this foam included the use of deoxygenated solvents, an argon atmosphere and protection of the extraction module from light with aluminum foil. The rate of addition of substrate was determined by estimating the *E*-CO output from the conversion ratios found in earlier experiments. The remaining *Z*-CO and PhCO_2Me were recovered by evaporating heptane after the reaction was terminated. The results of these experiments are summarized in Table 2.

All the experiments had almost perfect separation (> 99% *E*-isomer) of the *E*- and *Z*-isomers and the *E*-COs were obtained in modest to good yields (48–79%; calculated from the added amount of substrate). Chiral (*Z*-4 gave a 13:4 mixture of diastereoisomers (*E*-4a)/(E-4b in 60% yield after 16.5 h (entry 1). Compounds (*Z*-5 and (*Z*-6 gave the corresponding *E*-isomers (*E*-5 and (*E*-6 in 48% and 79% yields, respectively (entries 2 and 3). A white foam formed after 18–20 h at the interface of the phases in the extraction module when performing the reaction with (*Z*-5. The white foam was the (*E*-5–Ag(I) complex (likely [(*E*-5–AgNO₃)]^[18] according to analysis by ¹H

Table 2. *Z/E*-Isomerization experiments (24 h) of (*Z*-4–7 to (*E*-4–7 in the small-scale photoreactor.

Entry	Substrate [g] ^[a]	Addition [g] ^[b]	Product(s) [g]	Yield [%] ^[c]
1	(<i>Z</i> -4) 0.94	2.28	(<i>E</i> -4a) 1.36 (<i>E</i> -4b)	60 ^[d]
2	(<i>Z</i> -5) 1.00	2.50	(<i>E</i> -5) 1.20	48
3	(<i>Z</i> -6) 1.00	1.40	(<i>E</i> -6) 1.10	79
4	(<i>Z</i> -7) 0.99 ^[e]	–	(<i>E</i> -7a) 0.75 (<i>E</i> -7b)	75 ^[f]

[a] Initial amount. [b] Added amount of substrate during the experiment. [c] Based on the amount of addition of substrate. [d] The experiment ran for 16.5 h. [e] Initial concentration was 150 mM. [f] The experiment ran for 23 h.

NMR. It was hypothesized that the precipitation of this white solid was caused by saturation of the aqueous phase with the (*E*-5–Ag(I) complex, which was insoluble in heptane.^[19] Lastly, compound (*Z*-7 gave a 7:4 mixture of diastereoisomers (*E*-7a/(E-7b in 75% yield (entry 4). All compounds were sufficiently pure after the standard extraction with aqueous ammonia/heptane so that further purification was not required.

With these results in hand and eager to explore the scalability of our new method, we proceeded to test the larger-scale photoreactor (total volume: 140 mL; irradiated volume: 105 mL) with compounds (*Z*-5–7 (Table 3). First, we performed the isomerization of (*Z*-5 and (*Z*-7 with an irradiation time of 20 min and without extra addition of substrate during the experiments to check the performance of the photoreactor (entries 1 and 2). Gratifyingly, we obtained ca. 3.5 g of (*E*-5 and the mixture (*E*-7a)/(E-7b (74% yield in both cases) after 17 h. We carried on then with the experiments with addition of substrate. Thus, cyclooctene (*Z*-5 gave product (*E*-5 (5.75 g) in 93% yield in 5.5 h (entry 3). Compound (*Z*-7 yielded the 7:4 mixture of products (*E*-7a and (*E*-7b (4.90 g) in 57% yield also in 5.5 h (entry 4). The starting concentration of compound (*Z*-7 was higher (205 mM) than in the small-scale experiments, but unfortunately the output of *E*-CO was lower probably due to lower penetration of the UV light in the solution. To investigate the limitations of the photoreactor, an irradiation time of 5 min (flow rate: 21 mL/min) was used for substrates (*Z*-6 and (*Z*-7. This way, we obtained 2.20 g of (*E*-6 in 66% yield in the stunning time of 1 h from (*Z*-6 (entry 5) and cyclooctene (*Z*-7

Table 3. *Z/E*-Isomerization experiments of (*Z*)-5–7 to (*E*)-5–7 in the larger-scale photoreactor.

Entry	Substrate [g] ^[a]	Time [h]	Addition [g] ^[b]	Product(s) [g]	Yield [%] ^[c]
1	(<i>Z</i>)-5	17	–	(<i>E</i>)-5	74
2	(<i>Z</i>)-7	17	–	(<i>E</i>)-7a	74
3	4.60 (<i>Z</i>)-5	5.5	6.20	3.40 (<i>E</i>)-5	93
4	3.00 (<i>Z</i>)-7	5.5	8.60	5.75 (<i>E</i>)-7a/(<i>E</i>)-7b	57
5	5.00 (<i>Z</i>)-6	1.0	3.36	4.90 (<i>E</i>)-6	66
6	3.00 (<i>Z</i>)-7	1.0	2.80	2.20 (<i>E</i>)-7a/(<i>E</i>)-7b	74
	3.00			2.06	

[a] Initial amount. [b] Added amount of substrate during the experiment.

[c] Based on the amount of addition of substrate.

gave the 7:4 mixture of (*E*)-7a/(*E*)-7b (2.06 g) in 74% yield in the same time (entry 6).

Finally, cyclooctenes (*E*)-2a/(*E*)-2b, (*E*)-3 and (*E*)-8 were synthesized from (*E*)-7a/(*E*)-7b, (*E*)-6 and (*E*)-5, respectively (Scheme 2). These hydroxy-substituted cyclooctenes present

Scheme 2. Synthesis of hydroxy *E*-COs (*E*)-2a/(*E*)-2b, (*E*)-3 and (*E*)-8.

the highest number of applications up to date. In fact, most commercially available *E*-COs are derived from (*E*)-2a/(*E*)-2b.^[20]

The mixture (*E*)-7a/(*E*)-7b was hydrolyzed under standard conditions to afford the mixture (*E*)-2a/(*E*)-2b in excellent yield (88%; Scheme 2a). The reduction of compounds (*E*)-6 and (*E*)-5 with lithium aluminum hydride afforded compounds (*E*)-3 and (*E*)-8 in 81 and 83% yields, respectively (Scheme 2b). The mixture (*E*)-2a/(*E*)-2b was also obtained from the mixture (*E*)-7a/(*E*)-7b under the same reduction conditions in 84% yield.

3. Conclusions

In this study we have improved the standard method of synthesis of *E*-cyclooctenes via photoisomerization of *Z*-cyclooctenes by means of replacing the silver nitrate impregnated silica gel column with a liquid–liquid extraction module. In addition, our new process includes the possibility of adding extra substrate during the production, allowing for scaling up and faster production of *E*-COs. Our continuous flow process is generally applicable to synthesize functionalized *E*-COs on larger scale than any other known procedure. With this method up to 2.2 g/h of specific *E*-COs can be produced. Two photoreactors were fabricated for production scales lower and higher than 1.5 g. This methodology will certainly make *E*-COs more available and might entail a reduction of their prices in the future. Our new method is only applicable for *E*-COs whose *Z*-counterparts are not soluble in the silver nitrate solution.

Experimental Section

Reagents were obtained from commercial suppliers and were used without purification: Rhodium (II) acetate dimer (46% Rh, Sigma-Aldrich), (1*Z*,5*Z*)-cycloocta-1,5-diene (COD, 99%, Sigma-Aldrich), ethyl diazoacetate (13 wt.% in dichloromethane, Sigma-Aldrich), peroxyacetic acid (ca. 39% in acetic acid, Sigma-Aldrich), 3-chlorobenzeneperoxy acid (mCPBA, 77%, Sigma-Aldrich), 2,2-dimethoxypropane (98%, Acros), 4-methylbenzenesulfonic acid (TsOH, 98%, Sigma-Aldrich), methyl benzoate (99%, Sigma-Aldrich), silver nitrate (99%, Honeywell Fluka), *N,N*-dimethylpyridin-4-amine (DMAP, 98%, Sigma-Aldrich). Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. Reactions were followed, and *R_f* values were obtained, using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV light, and/or by charring at ca. 150 °C after dipping into a solution of KMnO₄. High-resolution or accurate mass measurement ($\Delta M < 3$ mmu or 5 ppm) was recorded on a JEOL AccuTOF-GCv JMS-T100GCv (GC/Electron Ionization MS, column bleeding at high temperature used as internal mass drift compensation standard). NMR spectra were recorded at 298 K on a Varian Inova 400 (400 MHz), Bruker Avance III 400 MHz or Bruker Avance III 500 MHz spectrometer in the solvent indicated. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (0.00 ppm) as internal standard for ¹H NMR and to CDCl₃ (77.16 ppm) as internal standard for ¹³C NMR. Coupling constants are reported as *J* values in hertz (Hz). ¹H NMR data are reported as follows: chemical shift (ppm), multiplicity (s=singlet, d=doublet, t=triplet, ddd=doublet of doublets, dt=doublet of triplets, q=quartet, dddd=doublet of doublets of doublets, ddt=doublet of doublets of triplets, dtd=doublet of triplet of doublets, m=multiplet, br=broad), coupling constants (Hz) and integration. Column or flash chromatography was carried out using ACROS silica gel (0.035–0.070 mm, and 60 Å pore diameter). The photoirradiation was done with a Rayonet RMR-600 photoreactor (254 nm) with FEP tubing (i.d. 1.57 mm, o.d. 3.18 mm; distance between the tubing and the UV lamp=4.0 cm) and a self-fabricated photoreactor consisting of a OSAGA RVS UV-C 55w pond filter with a Philips PL-L 55 W UV-C lamp (254 nm) and FEP tubing (i.d. 2.7 mm, o.d. 3.18 mm; distance between the tubing and the UV lamp=0.7–1.4 cm).

(1R,4Z,8S)-9-Oxabicyclo[6.1.0]non-4-ene ((Z)-9)

Peroxyacetic acid (59.42 g, 305 mmol; ca. 39% in acetic acid) was added dropwise to a stirred suspension of (1Z,5Z)-cycloocta-1,5-diene (30.00 g, 34.1 mL, 277 mmol) and Na₂CO₃ (117.44 g, 1.108 mol) in CH₂Cl₂ (400 mL) at 0 °C. The reaction mixture was slowly warmed to 15 °C over 17 h, then filtered and washed with CH₂Cl₂ (2 × 50 mL). The filtrate was washed with a saturated aqueous solution of NaHCO₃ up to neutral pH and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were then washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo to give the corresponding epoxide (Z)-9 as a clear yellow oil. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.60–5.49 (m, 2 H), 3.05–2.97 (m, 2 H), 2.50–2.34 (m, 2 H), 2.19–2.06 (m, 2 H), 2.06–1.94 (m, 4 H). *R*_F (heptane/AcOEt 19:1): 0.31. Epoxide (Z)-9 was used for the synthesis of (Z)-2 without further purification. The ¹H NMR data were in accordance with published data.^[21]

rac-(1R,4Z)-Cyclooct-4-en-1-ol ((Z)-2)

A solution of the crude of epoxide (Z)-9 in Et₂O (500 mL) at 0 °C was added dropwise to a suspension of LiAlH₄ (9.45 g, 249 mmol) in Et₂O (350 mL) at 0 °C under an argon atmosphere. The reaction mixture was then stirred at 21 °C for 17 h. The flask was then cooled to 0 °C and the reaction mixture was quenched by slow addition of H₂O (25 mL). The reaction mixture was allowed to warm to 21 °C and was then filtered. The filtrate was dried (Na₂SO₄), filtered and concentrated in vacuo to give the corresponding alcohol (Z)-2 as a colorless oil (21.45 g). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.69 (ddd, *J* = 10.6, 8.3, 7.1 Hz, 1 H), 5.59 (dt, *J* = 10.4, 7.9 Hz, 1 H), 3.81 (dddd, *J* = 9.4, 8.3, 4.4, 1.1 Hz, 1 H), 2.35–2.23 (m, 1 H), 2.19–2.05 (m, 3 H), 1.98–1.80 (m, 2 H), 1.76–1.45 (m, 5 H). Alcohol (Z)-2 was used for the synthesis of (Z)-7 without further purification. The ¹H NMR data were in accordance with published data.^[22]

Ethyl (1R,4Z,8S,9r)-bicyclo[6.1.0]non-4-ene-9-carboxylate ((Z)-5) and ethyl (1R,4Z,8S,9s)-bicyclo[6.1.0]non-4-ene-9-carboxylate ((Z)-6)

A solution of ethyl 2-diazoacetate (21.76 mL, 180 mmol; 13 wt.% CH₂Cl₂ as stabilizer) in CH₂Cl₂ (140 mL) was added dropwise over 18 h to a solution of (1Z,5Z)-cycloocta-1,5-diene (107.1 g, 121.7 mL, 990 mmol; COD) and [Rh₂(OAc)₄] (501 mg, 1.134 mmol) in CH₂Cl₂ (140 mL) at 21 °C. The solution was stirred for 1 h after the addition was completed. The rhodium catalyst was partially recovered (and reused) by filtration over a pad of diatomaceous earth. After the mixture was concentrated in vacuo, a large part of the excess of COD was recovered and removed by vacuum distillation (40 mbar, 60 °C). The residue was purified by column chromatography on silica gel (heptane/AcOEt 24:1) to afford (Z)-5 (17.25 g, 88.8 mmol, 49%) and (Z)-6 (10.2 g, 52.6 mmol, 29%) in 78% overall yield. The ¹H NMR data were in accordance with published data.^[23]

(Z)-5: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.68–5.59 (m, 2 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 2.35–2.25 (m, 2 H), 2.24–2.14 (m, 2 H), 2.13–2.02 (m, 2 H), 1.61–1.53 (m, 2 H), 1.53–1.42 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.18 (t, *J* = 4.5 Hz, 1 H). *R*_F (heptane/AcOEt 24:1): 0.20.

(Z)-6: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.64–5.55 (m, 2 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 2.55–2.44 (m, 2 H), 2.24–2.14 (m, 2 H), 2.09–1.98 (m, 2 H), 1.86–1.76 (m, 2 H), 1.69 (t, *J* = 8.8 Hz, 1 H), 1.41–1.32 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H). *R*_F (heptane/AcOEt 24:1): 0.30.

{(1R,4Z,8S,9s)-Bicyclo[6.1.0]non-4-en-9-yl}methanol ((Z)-3)

A solution of (Z)-6 (6.00 g, 30.9 mmol) in Et₂O (100 mL) was added dropwise to a suspension of LiAlH₄ (1.10 g, 29.0 mmol) in Et₂O (30 mL) at 0 °C under an argon atmosphere. This suspension was then stirred at 21 °C for 15 min, then cooled to 0 °C, and water was added carefully until the grey solid turned white. Sodium sulfate (2.00 g, 14.1 mmol) was added; the solid was filtered off and washed thoroughly with Et₂O. The filtrate was concentrated in vacuo to afford (Z)-3 (4.03 g, 26 mmol, 86%). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.69–5.58 (m, 2 H), 3.72 (d, *J* = 7.6 Hz, 2 H), 2.42–2.30 (m, 2 H), 2.16–2.05 (m, 2 H), 2.05–1.93 (m, 2 H), 1.64–1.51 (m, 2 H), 1.41 (br s, 1 H), 1.19–1.08 (m, 1 H), 1.07–0.95 (m, 2 H). The ¹H NMR data were in accordance with published data.^[24]

rac-(1R,2R,5Z)-Cyclooct-5-ene-1,2-diol ((Z)-10)

Concentrated H₂SO₄ (90 mg, 50 μL, 0.92 mmol) was added to a solution of (Z)-9 (5.00 g, 40.3 mmol) in H₂O (80 mL) under vigorous stirring at 21 °C. The reaction mixture was allowed to react at 21 °C for 7 h. The product was then extracted with Et₂O (3 × 50 mL) and then washed with a saturated aqueous solution of NaHCO₃. The organic phase was then washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo to yield diol (Z)-10 as a clear colorless oil (3.99 g, 28.1 mmol, 70%). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.64–5.53 (m, 2 H), 3.71–3.61 (m, 2 H), 2.92 (br s, 2 H), 2.43–2.28 (m, 2 H), 2.19–2.04 (m, 4 H), 1.62–1.52 (m, 2 H). Diol (Z)-10 was used for the synthesis of (Z)-4 without further purification. The ¹H NMR data were in accordance with published data.^[25]

rac-(1R,4Z,8R)-10,10-Dimethyl-9,11-dioxabicyclo[6.3.0]undec-4-ene ((Z)-4)

2,2-Dimethoxypropane (7.32 g, 8.6 mL, 70.3 mmol) and a catalytic amount of TsOH·H₂O (16 mg, 0.084 mmol) were added to a solution of (Z)-10 (3.99 g, 28.1 mmol) in acetone (120 mL). The resulting reaction mixture was stirred at 21 °C for 4 h. Solid NaHCO₃ (1.61 g, 19.1 mmol) was added and the mixture was stirred for 30 min. The mixture was then filtered through a pad of silica gel and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (heptane/AcOEt 19:1) to afford acetal (Z)-4 as a colorless oil (4.12 g, 22.6 mmol, 80%). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.63–5.53 (m, 2 H), 3.91–3.81 (m, 2 H), 2.24–2.13 (m, 2 H), 2.13–1.99 (m, 4 H), 1.47–1.36 (m, 2 H), 1.30 (s, 6 H). The ¹H NMR data were in accordance with published data.^[26]

rac-(1R,4Z)-Cyclooct-4-en-1-yl acetate ((Z)-7)

Triethylamine (84.09 g, 115.8 mL, 831 mmol) and DMAP (1.00 g, 8.19 mmol) were added to a solution of alcohol (Z)-2 in dry CH₂Cl₂ (400 mL) at 0 °C. The mixture was stirred for 15 min, then Ac₂O (127.25 g, 117.8 mL, 1.248 mol) was slowly added and the mixture was warmed to 21 °C. The solution turned from clear yellow to red-brownish after stirring for 17 h. The reaction mixture was cooled to 0 °C and was quenched by slow addition of H₂O (175 mL). The phases were separated and the organic phase was washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo to afford a crude product (34.02 g). The residue was purified by column chromatography on silica gel (heptane/AcOEt 9:1) to afford acetate (Z)-7 as a clear yellow oil (19.30 g, 115 mmol, 41% after three steps). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.66 (ddd, *J* = 10.6, 8.3, 6.6 Hz, 1 H), 5.59 (dt, *J* = 10.5, 7.6 Hz, 1 H), 4.79 (dddd, *J* = 9.8, 8.5, 4.4, 1.0 Hz, 1 H), 2.30 (dddd, *J* = 14.5, 10.7, 8.3, 4.0 Hz, 1 H), 2.18–2.02 (m, 3 H), 1.98 (s, 3 H), 1.91–1.76 (m, 2 H), 1.73–1.64 (m, 1 H),

1.62–1.50 (m, 3 H). The ^1H NMR data were in accordance with published data.^[27]

General Procedure for the Optimization of the Irradiation Time

A solution of the substrate (130 mM) and methyl benzoate (26 mM) in deoxygenated heptane was pumped into the photoreactor with an irradiation time of 55 min. The output was collected in fractions; the first fraction had a full exposure of 55 min. Next, only the irradiation was terminated and the vial with the substrate was replaced with a vial only with heptane. A fraction was collected every 5 min. Each fraction represents an irradiation time interval of 5 min. Conversion ratios for each fraction were determined by ^1H NMR.

General Procedure for the Photochemical Isomerization in the Small-Scale Photoreactor

The tubing of the photoreactor (total volume: 15.5 mL, irradiated volume: 10.7 mL) was filled with deoxygenated heptane (15.5 mL) after rinsing it with deoxygenated heptane. A solution of the substrate (5.15 mmol) and methyl benzoate (140 mg, 129 μL , 1.029 mmol, 0.2 equiv) in deoxygenated heptane (25 mL) was added to a solution of silver nitrate (3.50 g, 20.6 mmol, 4.0 equiv) in a 0.1 mM nitric acid solution in water (80 mL) in the 50 mL extraction module. The inlet tube of the pump was placed at the top of the organic phase; the outlet tube of the reactor was placed just above the stirring magnet in the aqueous phase.

The organic phase was pumped through the entire system for about five cycles without irradiation while argon was bubbled through the extraction module. The irradiation was done at a wavelength of 254 nm and the irradiation time was set to 20 min (flow rate: 0.540 mL/min). A syringe pump added pure substrate to the system after the irradiation and before entering the extraction module to maintain the concentration of the substrate in the organic phase. The addition rate was determined by the estimated generation of *E*-CO: $Y_{E\text{-CO}}$ (mg/min) with equation (1). The photoreactor ran between 18 and 24 h for several experiments.

$$Y_{E\text{-CO}} = Q_{\text{ECO}} \cdot C_{Z\text{-CO}} \cdot v_{\text{flow}} \cdot M \quad (1)$$

$Q_{E\text{-CO}}$ = ratio of *E*-CO conversion; $C_{Z\text{-CO}}$ = initial concentration of substrate (mmol/mL); v_{flow} = flow rate (mL/min); M = molar mass (mg/mmol). After isomerization, the aqueous silver nitrate solution (1 equiv) was separated with a separatory funnel and washed with two portions of heptane (2 $\times$ 25 vol.%). Heptane and aqueous ammonia (4 equiv) were added to the aqueous phase (50 vol.%) to extract the product. The organic phase was washed with water (2 $\times$ 25 vol.%), dried (Na_2SO_4) and concentrated in vacuo to afford the product in pure condition most of the times.

rac-(1*R*,4*E*,4*M*,8*R*)-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undec-4-ene ((*E*)-4*a*) and *rac*-(1*R*,4*E*,4*P*,8*R*)-10,10-dimethyl-9,11-dioxabicyclo[6.3.0]undec-4-ene ((*E*)-4*b*)

The isomerization of compound (*Z*)-4 (0.94 g, 5.15 mmol), as described in the general procedure with an irradiation time of 20 min, afforded a 13:4 mixture of diastereoisomers (*E*)-4*a*/*E*-4*b* (1360 mg, 7.47 mmol, 60%) in 16.5 h with addition of substrate (2.28 g, 12.51 mmol). The major product was partly separated by

column chromatography (heptane/AcOEt 32:1). Both ^1H and ^{13}C NMR data were in accordance with published data.^{11c}

(*E*)-4*a*: ^1H NMR [500 MHz, δ (ppm), CDCl_3]: 5.43–5.34 (m, 2 H), 3.72–3.65 (m, 2 H), 2.31–2.24 (m, 2 H), 2.24–2.14 (m, 4 H), 1.77–1.64 (m, 2 H), 1.29 (s, 6 H). ^{13}C NMR [126 MHz, δ (ppm), CDCl_3]: 133.0, 106.4, 84.4, 38.2, 31.6, 26.6.

rac-Ethyl (1*R*,4*E*,4*P*,8*S*,9*r*)-bicyclo[6.1.0]non-4-ene-9-carboxylate ((*E*)-5)

The isomerization of compound (*Z*)-5 (1.00 g, 5.15 mmol), as described in the general procedure with an irradiation time of 20 min, afforded compound (*E*)-5 (1.20 g, 6.18 mmol, 48%) in 24 h with addition of substrate (2.50 g, 12.88 mmol). ^1H NMR [500 MHz, δ (ppm), CDCl_3]: 5.85 (ddd, J = 16.8, 9.4, 6.2 Hz, 1 H), 5.12 (dddd, J = 16.9, 10.6, 3.9, 1.2 Hz, 1 H), 4.07 (q, J = 7.2 Hz, 2 H), 2.41–2.33 (m, 1 H), 2.31–2.16 (m, 3 H), 2.00–1.87 (m, 2 H), 1.29–1.20 (m, 1 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.13 (ddt, J = 11.7, 9.5, 4.9 Hz, 1 H), 0.90 (t, J = 5.2 Hz, 1 H), 0.95–0.81 (m, 1 H), 0.59 (dddd, J = 14.1, 12.8, 11.7, 2.5 Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), CDCl_3]: 174.7, 138.1, 131.6, 60.4, 38.0, 33.4, 32.0, 27.33, 27.28, 26.9, 25.9, 14.3. The ^1H NMR data were in accordance with published data.^[28]

(*E*)-5–Ag(I) complex

White precipitate formed at the interface when performing the photoisomerization of compound (*Z*)-5. ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 6.06 (ddd, J = 16.8, 9.1, 6.2 Hz, 1 H), 5.29 (ddd, J = 16.9, 10.6, 3.4 Hz, 1 H), 4.11 (q, J = 7.0 Hz, 2 H), 2.59–2.47 (m, 2 H), 2.38 (dt, J = 12.9, 4.0 Hz, 1 H), 2.33–2.17 (m, 2 H), 2.04–1.92 (m, 1 H), 1.36 (dddd, J = 12.6, 8.7, 5.4, 3.2 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.25–1.15 (m, 1 H), 1.04 (t, J = 5.2 Hz, 1 H), 1.03–0.91 (m, 1 H), 0.83–0.71 (m, 1 H).

rac-Ethyl (1*R*,4*E*,4*P*,8*S*,9*s*)-bicyclo[6.1.0]non-4-ene-9-carboxylate ((*E*)-6)

The isomerization of compound (*Z*)-6 (1.00 g, 5.15 mmol), described in the general procedure with an irradiation time of 20 min, afforded compound (*E*)-6 (1.10 g, 5.67 mmol, 79%) in 24 h with addition of substrate (1.40 g, 7.22 mmol). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 5.75 (ddd, J = 16.8, 9.3, 6.1 Hz, 1 H), 5.24 (dddd, J = 16.8, 10.4, 3.9, 1.2 Hz, 1 H), 4.04 (q, J = 7.1, 0.7 Hz, 2 H), 2.38–2.23 (m, 2 H), 2.00–1.82 (m, 4 H), 1.76 (t, J = 9.0 Hz, 1 H), 1.73–1.61 (m, 1 H), 1.51–1.37 (m, 1 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.11 (dtd, J = 12.4, 8.9, 3.2 Hz, 1 H), 1.00 (dtd, J = 11.9, 8.9, 4.8 Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), CDCl_3]: 172.0, 137.7, 132.3, 59.8, 33.6, 33.0, 27.1, 25.9, 24.4, 23.5, 20.9, 14.4. HRMS [EI^+ (m/z)] calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$ = 194.1307, found for [M^+] = 194.1308 ($|\Delta|$ = 0.43 ppm).

rac-(1*R*,4*E*,4*P*)-Cyclooct-4-en-1-yl acetate ((*E*)-7*a*) and *rac*-(1*R*,4*E*,4*M*)-cyclooct-4-en-1-yl acetate ((*E*)-7*b*)

The isomerization of compound (*Z*)-7 (994 mg, 5.91 mmol), as described in the general procedure with an irradiation time of 20 min, afforded a 7:4 mixture of diastereoisomers (*E*)-7*a*/*E*-7*b* (750 mg, 4.46 mmol, 75%) in 23 h without addition of substrate. ^1H NMR [500 MHz, δ (ppm), CDCl_3]: 5.64–5.44 (m, 3.2 H; 2 H (*E*)-7*a* + 2 H (*E*)-7*b*), 4.98 (dd, J = 10.5, 5.2 Hz, 1 H (*E*)-7*b*), 4.45–4.38 (m, 1 H; (*E*)-7*a*), 2.41–2.21 (m, 5.4 H; 3 H (*E*)-7*a* + 4 H (*E*)-7*b*), 2.14–2.08 (m, 0.6 H; 1 H (*E*)-7*b*), 2.09 (s, 1.8 H; 3 H (*E*)-7*b*), 1.97 (s, 3 H; (*E*)-7*a*), 1.99–1.88 (m, 4 H; (*E*)-7*a*), 1.88–1.71 (m, 3.8 H; 2 H (*E*)-7*a* + 3 H (*E*)-7*b*), 1.56 (dddd, J = 15.6, 11.9, 5.9, 1.3, 1 H; (*E*)-7*a*), 1.49–1.39 (m, 0.6 H; 1 H (*E*)-7*b*), 1.21 (ddt, J = 14.6, 12.2, 1.2 Hz, 0.6 H; 1 H (*E*)-7*b*). ^{13}C NMR [126 MHz, δ (ppm), CDCl_3]: 170.3, 170.2, 135.3, 134.9,

133.1, 131.7, 80.1, 70.0, 41.0, 40.8, 38.7, 34.33, 34.31, 32.6, 32.3, 31.0, 30.0, 28.2, 21.5, 21.1. HRMS [EI+ (*m/z*)] calcd for C₁₀H₁₆O₂ = 168.1150, found for [M⁺] = 168.1168 (|Δ| = 10.6 ppm).

General Procedure for the Photochemical Isomerization in the Larger-Scale Photoreactor

The tubing of the photoreactor (total volume: 140 mL, irradiated volume: 105 mL) was filled with a solution of the substrate (15.5 mmol) and methyl benzoate (422 mg, 388 μL, 3.1 mmol, 0.2 equiv) in deoxygenated heptane (100 mL) after rinsing it with deoxygenated heptane. A solution of silver nitrate (11.89 g, 70 mmol, 4.5 equiv) in a 0.1 mM nitric acid solution in water (140 mL) was added to deoxygenated heptane (30 mL) in the 100 mL extraction module. The inlet tube of the pump was placed at the top of the organic phase; the outlet tube of the reactor was placed just above the stirring magnet in the aqueous phase.

The organic phase was pumped through the entire system for about five cycles without irradiation while argon was bubbled through the extraction module. The irradiation was done at a wavelength of 254 nm and the irradiation time was set to either 5 (flow rate: 20 mL/min) or 20 min (flow rate: 5 mL/min). A syringe pump added pure substrate to the system after the irradiation and before entering the extraction module to maintain the concentration of the substrate in the organic phase. The addition rate was determined by the estimated *E*-CO generation: Y_{E-CO} (mg/min) with equation (1). The photoreactor ran between 1 and 5.5 h for several experiments.

rac-Ethyl (1*R*,4*E*,4*P*,8*S*,9*r*)-bicyclo[6.1.0]non-4-ene-9-carboxylate ((*E*)-5)

Procedure 1: The isomerization of compound (Z)-5 (4.60 g, 23.7 mmol), as described in the general procedure with an irradiation time of 20 min, afforded compound (E)-5 (3.40 g, 29.6 mmol, 74%) in 17 h without addition of substrate.

Procedure 2: The isomerization of compound (Z)-5 (3.00 g, 15.4 mmol), as described in the general procedure with an irradiation time of 20 min, afforded compound (E)-5 (5.75 g, 29.6 mmol, 93%) in 5.5 h with addition of substrate (6.20 g, 31.9 mmol).

rac-Ethyl (1*R*,4*E*,4*P*,8*S*,9*s*)-bicyclo[6.1.0]non-4-ene-9-carboxylate ((*E*)-6): The isomerization of compound (Z)-6 (3.00 g, 15.4 mmol), described in the general procedure with an irradiation time of 5 min, afforded compound (E)-6 (3.36 g, 17.3 mmol, 66%) in 1 h with addition of substrate (3.40 g, 17.2 mmol).

rac-(1*R*,4*E*,4*P*)-Cyclooct-4-en-1-yl acetate ((*E*)-7 a) and *rac*-(1*R*,4*E*,4*M*)-cyclooct-4-en-1-yl acetate ((*E*)-7 b)

Procedure 1: The isomerization of compound (Z)-7 (4.70 g, 27.9 mmol), as described in the general procedure with an irradiation time of 20 min, afforded a 7:4 mixture of diastereoisomers (E)-7 a/(E)-7 b (3.47 g, 20.6 mmol, 74%) in 17 h without addition of substrate.

Procedure 2: The isomerization of compound (Z)-7 (5.00 g, 29.7 mmol), as described in the general procedure with an irradiation time of 20 min, afforded a 7:4 mixture of diastereoisomers (E)-7 a/(E)-7 b (4.90 g, 29.1 mmol, 57%) in 5.5 h with addition of substrate (8.60 g, 51.1 mmol).

Procedure 3: The isomerization of compound (Z)-7 (3.00 g, 17.8 mmol), as described in the general procedure with an

irradiation time of 20 min, afforded a 7:4 mixture of diastereoisomers (E)-7 a/(E)-7 b (2.06 g, 12.2 mmol, 73%) in 1 h with addition of substrate (2.80 g, 16.6 mmol).

rac-(1*R*,4*E*,4*P*)-Cyclooct-4-en-1-ol ((*E*)-2 a) and *rac*-(1*R*,4*E*,4*M*)-cyclooct-4-en-1-ol ((*E*)-2 b)

Procedure 1: A solution of 1 M NaOH (26.9 mL) was added to a solution of the 7:4 mixture of diastereoisomers (E)-7 a/(E)-7 b (452 mg, 2.69 mmol) in 1,4-dioxane (9 mL). The resulting mixture was stirred at 21 °C for 17 h. 1,4-Dioxane was then evaporated and the water phase was extracted with CH₂Cl₂ (3×9 mL). The combined organic extracts were then washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo to yield a 7:4 mixture of diastereoisomers (E)-2 a/(E)-2 b (298 mg, 2.36 mmol, 88%). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.61–5.47 (m, 2.2 H; 1 H (E)-2 a + 2 H (E)-2 b), 5.35 (ddd, *J* = 15.8, 10.9, 3.6 Hz, 1 H; (E)-2 a), 4.00 (dd, *J* = 10.3, 5.3 Hz, 0.6 H; 1 H (E)-2 b), 3.44–3.76 (m, 1 H; (E)-2 a), 2.40–2.14 (m, 4.8 H; 3 H (E)-2 a + 3 H (E)-2 b), 2.13–2.00 (m, 1.2 H; 2 H (E)-2 b), 2.00–1.71 (m, 6.4 H; 4 H (E)-2 a + 4 H (E)-2 b), 1.68–1.46 (m, 3.6 H; 3 H (E)-2 a + 1 H (E)-2 b), 1.28–1.18 (m, 0.6 H; 1 H (E)-2 b). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 135.1, 134.4, 133.0, 132.8, 77.7, 67.4, 44.6, 43.1, 41.1, 34.4, 34.2, 34.1, 32.7, 31.3, 29.4, 27.7. Both ¹H and ¹³C NMR data were in accordance with published data.^{11c}

Procedure 2: A solution of the mixture of diastereoisomers (E)-7 a/(E)-7 b (500 mg, 2.97 mmol) in Et₂O (16 mL) was added dropwise to a suspension of LiAlH₄ (102 mg, 2.67 mmol) in Et₂O (16 mL) at 0 °C under an argon atmosphere. This suspension was then stirred at 21 °C for 15 min, then cooled to 0 °C, and water was added carefully until the grey solid had turned white. Sodium sulfate was added; the solid was filtered off and washed thoroughly with Et₂O. The filtrate was concentrated in vacuo to afford a diastereomeric mixture of (E)-2 a/(E)-2 b (313 mg, 2.48 mmol, 84%).

{{(1*R*,4*E*,4*P*,8*S*,9*s*)-Bicyclo[6.1.0]non-4-en-9-yl}methanol ((*E*)-3)

A solution of (E)-6 (1.10 g, 5.66 mmol) in Et₂O (30 mL) was added dropwise to a suspension of LiAlH₄ (193 mg, 5.10 mmol) in Et₂O (30 mL) at 0 °C under an argon atmosphere. This suspension was then stirred at 21 °C for 30 min, then cooled to 0 °C, and water was added carefully until the grey solid had turned white. Sodium sulfate was added; the solid was filtered off and washed thoroughly with Et₂O. The filtrate was concentrated in vacuo to afford (E)-3 (701 mg, 4.60 mmol, 81%). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.87 (ddd, *J* = 16.1, 9.3, 6.2 Hz, 1 H), 5.15 (dddd, *J* = 16.9, 10.5, 3.9, 1.1 Hz, 1 H), 3.57 (dd, *J* = 11.3, 7.8 Hz, 1 H), 3.54 (dd, *J* = 11.3, 7.9 Hz, 1 H), 2.33 (dtd, *J* = 11.5, 3.9, 2.5 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.19 (dtd, *J* = 14.0, 3.9, 2.4 Hz, 1 H), 2.11 (dddd, *J* = 12.6, 4.9, 3.0, 0.8 Hz, 1 H), 2.00–1.84 (m, 2 H), 1.33–1.18 (m, 1 H), 1.04 (tdd, *J* = 12.7, 11.1, 7.1 Hz, 1 H), 0.83–0.68 (m, 2 H), 0.59 (dtd, *J* = 12.9, 8.7, 4.4 Hz, 1 H). The ¹H NMR data were in accordance with published data.²⁹

{{(1*R*,4*E*,4*P*,8*S*,9*r*)-Bicyclo[6.1.0]non-4-en-9-yl}methanol ((*E*)-8)

A solution of (E)-5 (971 mg, 5.00 mmol) in Et₂O (30 mL) was added dropwise to a suspension of LiAlH₄ (193 mg, 5.10 mmol) in Et₂O (30 mL) at 0 °C under an argon atmosphere. This suspension was then stirred at 21 °C for 15 min, then cooled to 0 °C, and water was added carefully until the grey solid had turned white. Sodium sulfate was added; the solid was filtered off and washed thoroughly with Et₂O. The filtrate was concentrated in vacuo to afford (E)-8 (631 mg, 4.14 mmol, 83%). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 5.87 (ddd, *J* = 16.1, 9.3, 6.2 Hz, 1 H), 5.15 (dddd, *J* = 16.9, 10.5, 3.9, 1.1 Hz, 1 H), 3.57–3.46 (m, 2 H), 2.43–2.33 (m, 1 H), 2.33–2.16 (m, 3 H), 2.00–

1.85 (m, 2 H), 0.87 (tdd, $J=12.6, 11.4, 7.1$ Hz, 1 H), 0.59 (dddd, $J=13.8, 12.4, 11.3, 2.2$ Hz, 1 H), 0.54–0.31 (m, 3 H). The ^1H NMR data were in accordance with published data.^[3b]

Conflict of Interest

The authors declare no conflict of interest.

Keywords: bioorthogonal chemistry • continuous extraction • continuous flow • photoisomerization • *trans*-cyclooctenes

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