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## Graphical Abstract

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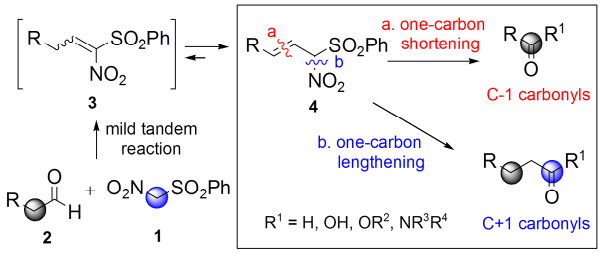

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# Two-way homologation of aliphatic aldehydes: Both one-carbon shortening and lengthening via the same intermediate

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ABSTRACT

Aliphatic aldehydes can be homologated to both one-carbon shorter and one-carbon longer homologous carbonyl compounds through the 2-4 steps of reactions via the same intermediates, β,γ-unsaturated α-nitrosulfones, prepared from the proline-catalyzed sequential reactions of several aliphatic aldehydes with phenylsulfonylnitromethane. While the oxidative cleavage of the key intermediates gave one-carbon less homologous carbonyl compounds, the reduction of the same key intermediates followed by an oxidation produced one-carbon more homologous carbonyl compounds.



## 1. Introduction

Readily accessible and versatile carbonyl compounds are very important synthons in a variety of organic reactions. The homologation of carbonyl compounds to one-carbon less or one-carbon more homologous carbonyl compounds has been investigated as an attractive synthetic methodology.[1] Although large numbers of useful approaches for the homologation have been reported, there is still a need for a homologation that can complement existing ones. Many homologation methods are quite effective but require reactive intermediates or strong bases (e.g., the Arndt-Eistert reaction or the Wittig reaction) and/or provide limited options available to organic chemists. Whereas numerous one-carbon lengthening homologations have been reported,[1,2] there are a small number of one-carbon shortening homologations.[1d,3] Moreover, separate synthetic routes should be selected to obtain either one-carbon shorter or one-carbon longer homologs. To the best of our knowledge, there has been no two-way homologation method to produce both one-carbon shorter and one-carbon longer homologous compounds from the same intermediate, which can also provide the synthetic flexibility of the starting material from either one-carbon shorter or one-carbon longer aldehyde to produce the same target compound.

We have previously reported the effective conversion of readily available α-amino aldehydes into various biologically important β-amino-α-hydroxycarboxylic acids using phenylsulfonylnitromethane (**1**)[4] as a one-carbon synthon.[5] In an application study of **1** with octanal (**2a**) (Figure 1, R = $C_6H_{13}$), β,γ-unsaturated α-nitrosulfone **4a** instead of α,β-unsaturated α-nitrosulfone **3a** was exclusively obtained, albeit in a very low yield. It occurred to us that the preference of **4** over **3** would enable a new approach toward the two-way homologation of carbonyl compounds from the same intermediate **4**.

Our strategy for the two-way homologation of aliphatic aldehydes is shown in Figure 1. The Henry-type aldol reactions[6] of **1** with aliphatic aldehydes **2** followed by a dehydration reaction produce the initial condensation products, α,β-unsaturated α-nitrosulfones **3**, which are isomerized to favored β,γ-unsaturated α-nitrosulfones **4** in one step.[7] Oxidative cleavage of the double bond of **4** is expected to provide one-carbon shorter carbonyl compounds ('a route'), while the reduction of the C–C double bond of **4** followed by an oxidation of the nitrosulfonylmethyl group would yield one-carbon longer carbonyl compounds ('b route').[5,8] We have also tried to design the homologation process to be milder and more practical by avoiding the use of strong base or rather reactive intermediates under anhydrous conditions.

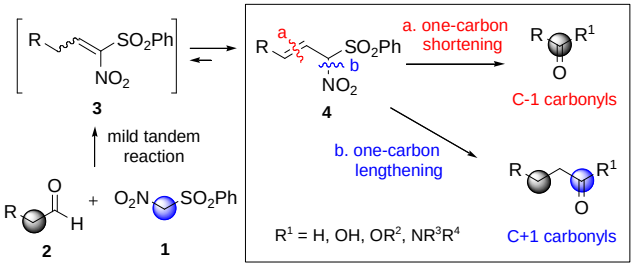
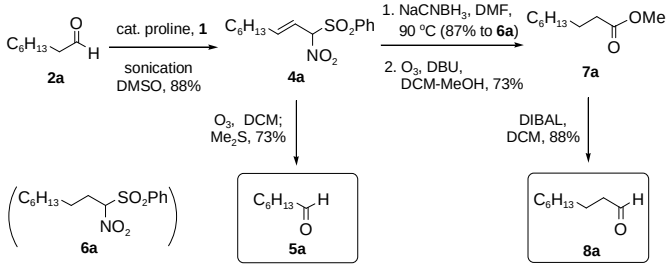



**Fig 1.** A strategy for the two-way homologation.

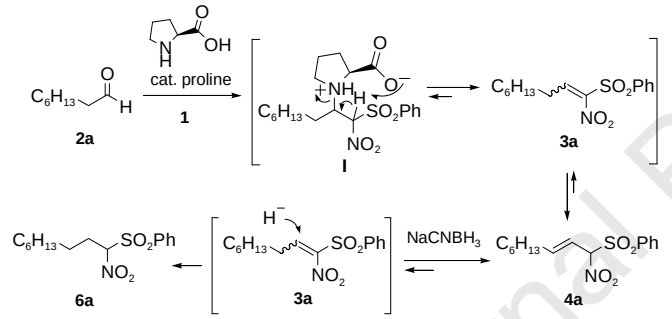
## 2. Results and discussion






**Scheme 1.** A model study for the two-way homologation of octanal (**2a**) to heptanal (**5a**) and nonanal (**8a**).

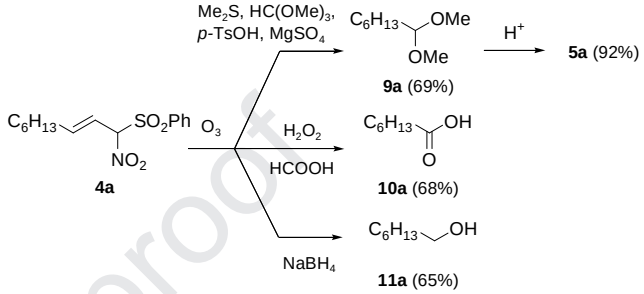
To validate the possibility for the two-way homologation, we carried out a model study with octanal (**2a**) (Scheme 1). In reality, a major hurdle to implement our two-way homologation was a mild and efficient preparation of **4a** because the condensation reactions between **1** and **2a** under the reported nitroaldol reaction conditions[5,6,7b] gave low to poor yields of **4a**. The problem of an effective preparation of the key intermediate **4a** seemed to be a reason why the apparently simple idea of the two-way homologation was not reported yet.




**Scheme 2.** The proline-catalyzed formation of **3a**, its isomerization to **4a**, and the following reduction.

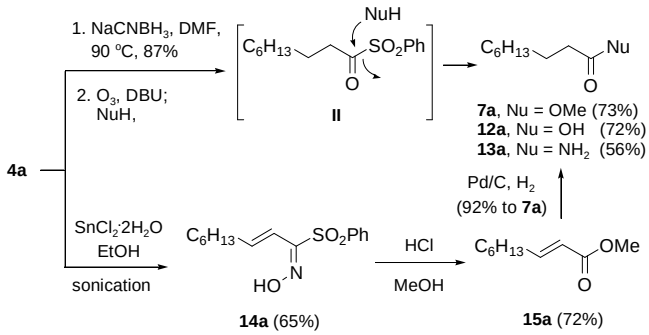
After long and much effort, we found that proline could catalyze the Henry-type reaction with **1** to afford desired β,γ-unsaturated α-nitrosulfone **4a** in one step under mild conditions. It is interesting that proline has been rarely used for the Henry-type aldol reactions of α-unbranched aldehydes due to the competing self-aldol reactions.[6a,9,10] In our case, though, the formation of the intermediate **I** having a rather acidic proton ($pK_a$ of the α-C-H in **I** is ca. 5.7, Scheme 2) during the reaction of α-unbranched aldehyde **2a** with **1** in the presence of proline could facilitate the elimination reaction to yield initially α,β-unsaturated α-nitrosulfone **3a**, which was then isomerized to favored β,γ-unsaturated α-nitrosulfone **4a**. In comparison, the same reactions of **2a** with α-substituted phenylsulfonyl-nitromethane ($PhSO_2CH(R)NO_2$) or nitromethane ($CH_3NO_2$) did not give any desired products.

In addition, employing an ultrasound irradiation could dramatically decrease the reaction time to 4 h from 2-3 days at room temperature. Using the optimized conditions, **4a** was successfully produced in a good yield from octanal (**2a**) (see Experimental). The one-carbon shorter homologous aldehyde, heptanal (**5a**), was obtained in one step as expected by the ozonolysis of **4a** followed by the reductive work-up (Scheme 1). For the one-carbon longer homolog, nonanal (**8a**) on the other hand, the selective reduction of the nitro group[11,12] of **4a** or **6a** to the amino group under the reported conditions[13-18] was troublesome in the presence of the phenylsulfonyl group. Even the selective reduction of the C–C double bond of **4a** did not work under various conditions.[19] That would be another reason to hinder the wider use of β,γ-unsaturated α-nitrosulfones **4** in the homologation or other reactions. The selective reduction of **4a** with sodium cyanoborohydride ($NaCNBH_3$)[20] in DMF was successful to give the saturated intermediate **6a** in a high yield, probably after the in-situ isomerization of β,γ-unsaturated α-nitrosulfone **4a** into α,β-unsaturated α-nitrosulfone **3a** at elevated temperature (Scheme 2). Then, one-carbon lengthening homologation of octanal (**2a**) to methyl nonanoate (**7a**) was achieved after the oxidation of the phenylsulfonylnitromethyl group of **6a** as reported.[5,8] The ester group of **7a** could be converted to the aldehyde group to give the desired nonanal (**8a**).




**Scheme 3.** Functional group transformations of **4a** to other one-carbon shorter carbonyl homologs.

Then, we have explored the functional group transformation of the intermediate **4a** to show the synthetic flexibility of the two-way homologation. Some one-carbon shorter homologs, dimethylacetal **9a**, carboxylic acid **10a** and alcohol **11a**, could be prepared by adding trimethylorthoformate[21], an oxidant and a reductant,[22] respectively, during the work-up (Scheme 3).

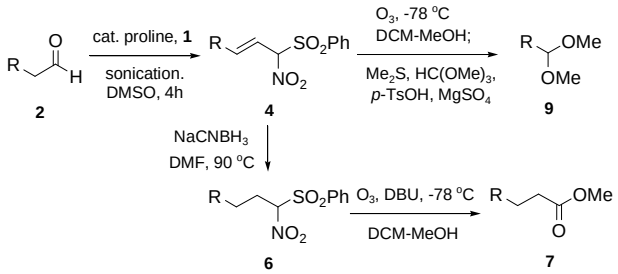



**Scheme 4.** Functional group transformations of **4a** to other one-carbon longer carbonyl homologs.

Other one-carbon longer carbonyl homologs, **12a** and **13a**, could be also obtained by the simple change of the nucleophile from methanol to water and ammonia in the oxidation reaction, respectively (Scheme 4), because the nitronate produced in-situ from **6a** under the basic conditions was readily oxidized with ozone to give the α-ketophenylsulfone intermediate **II**.[5,8] We have also found that the selective reduction of the nitro group of **4a** in the presence of both the C–C double bond and the phenylsulfonyl group was possible with tin(II) chloride[16,18] to give the partially reduced oxime **14a**, which was hydrolyzed in MeOH under acidic conditions to give synthetically useful one-carbon longer α,β-unsaturated ester **15a**. A homologation method to one-carbon longer α,β-unsaturated esters from

aldehydes is rare although two-carbon longer α,β-unsaturated esters have been usually prepared by the reaction with two carbon synthons such as malonates or by the Horner-Wadsworth-Emmons reactions.[23] It would be a complementary way to convert the phenylsulfonylnitromethyl group into the ester group in the presence of a C-C double bond that is incompatible under the ozonolysis conditions. Finally, the catalytic hydrogenation of **15a** yielded **7a** without an event.

**Table 1.** One-carbon less and one-carbon more homologation of various aliphatic aldehydes




| Entry | R | Yields (%) | | | |
|---|---|---|---|---|---|
| | | **4**[a] | **6** | **7** | **9** |
| a | *n*-$C_6H_{13}$ | 88 | 87 | 73 | 69 |
| b | *n*-$C_{10}H_{21}$ | 81 | 86 | 80 | 78 |
| c | 4-PrO-Ph | 87[b] | 45 | 68 | 53 |
| d | $PhCH_2$ | 86[b] | 85 | 78 | 53 |
| e | 3-Cl-$PhCH_2$ | 70[b] | 72 | 74 | 74 |
| f | 4-MeO-$PhCH_2$ | 76[b] | 69 | 73 | 48 |
| g | Ph(Me)CH | 75[b] | 70 | 80 | 67 |
| h | $CbzNHCH_2$ | 61[b] | 78 | 88 | 59 |
| i | $BnOCH_2CH_2$ | 83 | 89 | 66 | 73 |
| j | $PhCH_2CH_2$ | 84 | 84 | 88 | 73 |
| k | $MeO_2C(CH_2)_7$ | 70 | 83 | 71 | 79 |

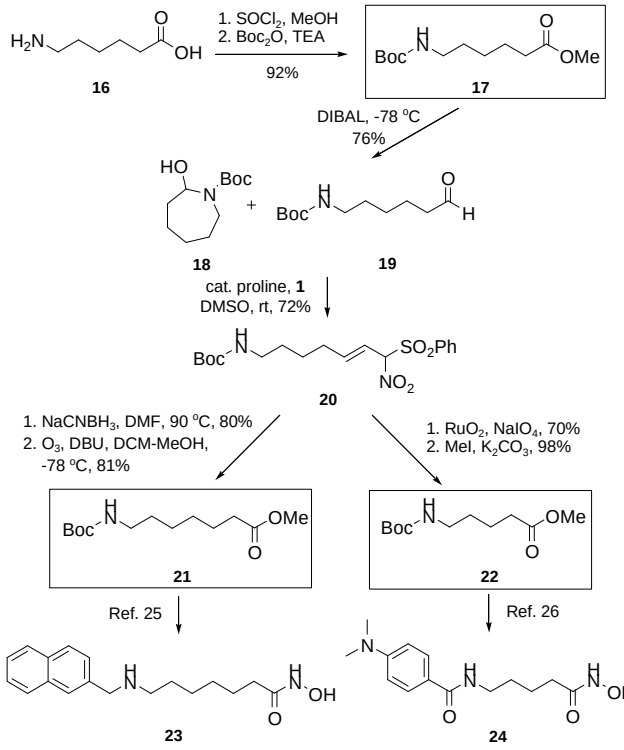
[a] The yields based on $PhSO_2CH_2NO_2$ (**1**).

[b] An antioxidant (Tinogard TT®, 0.0025 eq.) was added in the reaction.

After the successful model study with octanal (**2a**), we have screened various aldehydes to show the scope and limitations of the two-way homologation (Table 1). The aliphatic aldehydes with two α-protons to the aldehyde group gave the expected β,γ-unsaturated α-nitrosulfones **4** (entries a-k), whereas the aldehydes with no α-proton such as pivaldehyde or benzaldehyde did not yield any desired products (not shown). The aliphatic aldehyde with one α-proton such as 2-ethylhexanal or diphenylacetaldehyde gave the corresponding β,γ-unsaturated α-nitrosulfone **4** but the following reduction reaction to give **6** was not successful under various conditions (not shown). Some substrates showed lower yields of **4** due to the side reactions such as the oxidation of the starting materials and/or the formation of polymeric substances during the reaction (entries c-h). However, their yields were improved when deoxygenated DMSO by purging with argon gas for several minutes before the reactions was used as a solvent, and a small amount of an antioxidant such as Tinogard TT® (pentaerythritol tetrakis-(3,5-di-*tert*-butyl-4-hydroxyhydrocinnamate))[24] was added in the reaction mixture. In the preparation of β,γ-unsaturated α-nitrosulfones **4d-4g** from the hydrocinnamaldehyde derivatives **2d-2g**, neither the formation of α,β-unsaturated α-nitrosulfones **3d-3g** nor further isomerization of β,γ-unsaturated α-nitrosulfones into γ,δ-unsaturated α-nitrosulfones was observed.

An aliphatic aldehyde with a nitrogen atom at the β-carbon (entry h) or with an oxygen atom at the γ-carbon (entry i) to the aldehyde group was a successful substrate. Note here that the Cbz protecting group and CbzN-H proton was compatible under the reaction conditions. In the substrate with an ester group (entry k), the phenylsulfonylnitromethane group selectively reacted with the aldehyde carbonyl group over the ester carbonyl group. Overall, the key intermediates, β,γ-unsaturated α-nitrosulfones **4a-4k**, were successfully obtained in 61-88% yields from various aliphatic aldehydes.

The selective reduction of the C–C double bond of **4** was possible as expected to give saturated nitrosulfones **6** in 69-89% yields with $NaCNBH_3$ in DMF at 90 °C (Table 1, **6a-6b** and **6d-6k**) except **6c**. The starting material **4c** having a C–C double bond conjugated with the phenyl group showed a lower yield (45%) than other substrates. Then, one-carbon longer homologs of **2** were obtained as esters **7** in 66-88% yields after the oxidation of the phenylsulfonylnitromethyl group in **6** with ozone in MeOH (Table 1, **7a-7k**). One-carbon shorter homologs of **2** were isolated as more stable and less volatile dimethylacetals **9** from **4** in 48-79% yields by the one-pot reaction[21] (see also Scheme 3) (Table 1, **9a-9k**). In the case of aliphatic aldehyde with one α-proton such as 2-ethylhexanal or diphenylacetaldehyde, the one-carbon shortening reaction was possible to give the corresponding ketone product (not shown).




**Scheme 5.** An application of the two-way homologation for the synthesis of two key intermediates of HDAC inhibitors.

To demonstrate the synthetic utility of the two-way homologation, the synthesis of the two key intermediates, **21** and

**22**, for biologically active histone deacetylase (HDAC) inhibitors **23** and **24** was shown from readily available common starting material, 6-aminohexanoic acid (**16**) (Scheme 5). In the previous reports, the two amino acid derivatives, a $C_7$-amino acid derivative **21**[25] and a $C_5$-amino acid derivative **22**,[26] were obtained separately from rather expensive 7-aminoheptanoic acid and 5-aminopentanoic acid, respectively. We could produce both **21** and **22** from the common intermediate **20** that was derived in a few steps from cheap 6-aminohexanoic acid (**16**), a monomer of Nylon 6®. One-carbon lengthening of **20** to yield **21** was successful as described above by following the same reduction and oxidation protocol. Unfortunately, one-carbon shortening of **20** to produce **22** was not successful with the ozonolysis conditions. The acid-labile *N*-Boc group in the intermediate **20** was probably not compatible with formic acid used in the oxidative work-up after the ozonolysis. However, we could produce **22** successfully by an oxidative cleavage reaction of the C–C double bond with catalytic $RuO_4$.

## 3. Conclusion

The novel two-way homologation of aliphatic aldehydes comprising a mild proline-catalyzed sequential reaction with phenylsulfonylnitromethane (**1**) has been developed. Unlike the known one-way homologation methods, it can afford both one-carbon shorter and one-carbon longer carbonyl homologs such as aldehydes, acetals, carboxylic acids, saturated esters, α,β-unsaturated esters and amides from the corresponding aliphatic aldehydes via the same intermediate, β,γ-unsaturated α-nitrosulfones **4**. Its synthetic value was demonstrated by the synthesis of the two key intermediates, a $C_7$-amino acid derivative **21** and a $C_5$-amino acid derivative **22**, for biologically active histone deacetylase inhibitors **23** and **24**, from cheap and readily available 6-aminohexanoic acid (**16**) ($C_6$-amno acid). In addition, the two-way homologation method could be useful to select the starting material from either one-carbon shorter or one-carbon longer aldehydes to synthesize the same target carbonyl compounds because of the cheaper price or ready availability of the starting carbonyl compounds. For example, methyl nonanoate (**7a**), prepared from octanal (**2a**) by the one-carbon lengthening homologation, could be also prepared from decanal by the one-carbon shortening homologation.

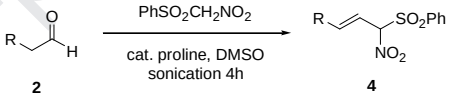
We hope that the two-way homologation approach would expand the choice of reactions available to organic and medicinal chemists who have tackled the homologation reactions of carbonyl compounds from many different angles.

## 4. Experimetal

### *4.1. General information*

Materials were purchased from commercial suppliers and used without further purification unless otherwise mentioned. Aldehydes were used after purification by vacuum distillation or column chromatography when necessary. Phenylsulfonyl-nitromethane (**1**) was prepared according to the literature procedure.[4c] Dimethyl sulfoxide and *N*,*N*-dimethylformamide were stored over 4Å molecular sieves before use. All experimental glassware, syringes, and magnetic stirring bars were oven-dried and stored in a desiccator before use. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 glass plates pre-coated with a 0.25-mm thickness of silica gel, which was visualized by UV (254 nm), cerium molybdate, $KMnO_4$, or a ninhydrin staining solution. Upon work-up, solvents were evaporated by using a rotary evaporator. Column chromatography was performed on kieselgel 60 (70-230 mesh) silica gel. Sonication was performed in an ultrasonic cleaner bath for laboratory (Branson 5210, 140 W, 47 kHz). During the sonication, the temperature of the water bath was controlled at less than 40 ºC. NMR spectra were measured on commercially available spectrometers at 500 MHz for $^1$H spectra and 125 MHz for $^{13}$C spectra in $CDCl_3$ unless otherwise mentioned. $^1$H spectra were calibrated from internal standard TMS (0.0 ppm) or solvent resonance ($CHCl_3$: 7.26 ppm). $^{13}$C spectra were calibrated from solvent resonance ($CHCl_3$: 77.23). NMR data were reported as: chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. Infrared spectra were recorded on a Bruker TENSOR 27 FT-IR spectrometer and reported in frequency of absorption ($cm^{-1}$). High-resolution mass spectra were measured by the electron ionization (EI), the chemical ionization (CI), or fast atom bombardment (FAB) ionization method and analyzed by magnetic sector mass analyzer. Melting points were determined with an open capillary melting point apparatus.

### *4.2. General Procedure for the preparation of β,γ-unsaturated α-nitrosulfones **4***



**2** **4**

To a solution of phenylsulfonylnitromethane (**1**) (402 mg, 2.00 mmol) in DMSO (2.0 mL) were added at room temperature aldehyde **2** (2.00 mmol) and proline (12 mg, 0.10 mmol). If necessary, pentaerythritol tetrakis(3,5-di-tert-butyl-4-hydroxy-hydrocinnamate) (6 mg, 0.005 mmol) was additionally added. The reaction flask was placed in a sonicator for 2 h. Then, aldehyde **2** (0.60 mmol) was added again to the reaction mixture, which was then placed in the sonicator for further 2 h. The mixture was diluted with ether (20 mL) and an aqueous 0.1 *N* HCl solution (20 mL) and extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **4** in 61 - 88% yields. The yields were calculated based on the amount of phenylsulfonylnitromethane (**1**).

*1-Benzenesulfonyl-1-nitronon-2-ene (**4a**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); colorless oil; yield 88%; $^1$H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.22-1.34 (m, 6H), 1.36-1.44 (m, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 5.64 (dd, *J* = 9.5, 15.0 Hz, 1H), 5.87 (d, *J* = 9.5 Hz, 1H), 6.14 (dt, *J* = 7.0, 15.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 14.3, 22.7, 28.2 28.9, 31.7, 32.9, 103.8, 115.0, 129.5, 130.5, 134.5, 135.6, 147.6 ppm; IR (film): 2956, 1561, 1341, 1157 $cm^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{15}H_{22}NO_4S$: 312.1270, Found: 312.1269.

*1-Benzenesulfonyl-1-nitrotridec-2-ene (**4b**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 9:1); colorless oil; yield 81%; $^1$H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.21-1.33 (m, 14H), 1.35-1.43 (m, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 5.64 (dd, *J* = 9.5, 14.5 Hz, 1H), 5.87 (d, *J* = 9.5 Hz, 1H), 6.14 (dt, *J* = 7.0, 14.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 14.3, 22.9, 28.3 29.3, 29.5,

29.5, 29.7, 29.8, 32.1, 32.9, 103.7, 114.9, 129.5, 130.5, 134.4, 135.6, 147.6 ppm; IR (film): 2926, 1562, 1343, 1157 $cm^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{19}H_{30}NO_4S$: 368.1896, Found: 368.1890.

*1-(3-Benzenesulfonyl-3-nitropropenyl)-4-propoxybenzene (**4c**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); yellowish oil; yield 87%; $^1H$ NMR δ 1.04 (t, *J* = 7.0 Hz, 3H), 1.82 (sex, *J* = 7.0 Hz, 2H), 3.94 (t, *J* = 7.0 Hz, 2H), 6.02-6.04 (m, 1H), 6.04 (dd, *J* = 9.5, 15.5 Hz, 1H), 6.83 (dt, *J* = 5.5, 15.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}C$ NMR δ 10.6, 22.6, 69.8, 104.3, 109.7, 115.0, 126.7, 129.2, 129.5, 130.5, 134.5, 135.6, 142.9, 160.9 ppm; IR (film): 1559, 1511, 1337, 1256, 1155 $cm^{-1}$; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{18}H_{19}NO_5S$: 361.0984, Found: 361.0979.

*(4-Benzenesulfonyl-4-nitrobut-2-enyl)benzene (**4d**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 7:1 to hexane:EtOAc = 5:1); yellowish oil; yield 86%; $^1H$ NMR δ 3.49 (d, *J* = 6.5 Hz, 2H), 5.67 (dd, *J* = 10.0, 15.0 Hz, 1H), 5.90 (d, *J* = 10.0 Hz, 1H), 6.28 (dt, *J* = 6.5, 15.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.22-7.28 (m, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 2H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H) ppm; $^{13}C$ NMR δ 39.0, 103.3, 116.3, 127.0, 128.8, 129.0, 129.5, 130.4, 134.2, 135.6, 137.4, 145.4 ppm; IR (film): 1561, 1338, 1155 $cm^{-1}$; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_{16}H_{14}NO_4S$: 316.0644, Found: 316.0648.

*1-(4-Benzenesulfonyl-4-nitrobut-2-enyl)-3-chlorobenzene (**4e**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); yellowish oil; yield 70%; $^1H$ NMR 3.47 (d, *J* = 7.0 Hz, 2H), 5.67 (dd, *J* = 9.5, 15.5 Hz, 1H), 5.90 (d, *J* = 9.5 Hz, 1H), 6.25 (dt, *J* = 7.0, 15.5 Hz, 1H), 7.01 (d, *J* = 6.0 Hz, 1H), 7.10 (s, 1H), 7.22-7.28 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz) 38.6, 103.2, 116.9, 127.1, 127.4, 129.0, 129.6, 130.3, 130.5, 134.2, 134.8, 135.7, 139.4, 144.3 ppm; IR (film): 1562, 1339, 1156 $cm^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{16}H_{15}ClNO_4S$: 352.0410, Found: 352.0413.

*1-(4-Benzenesulfonyl-4-nitrobut-2-enyl)-4-methoxybenzene (**4f**):*

Silica gel column chromatography (eluent eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 5:1); yellowish oil; yield 76%; $^1H$ NMR δ 3.43 (d, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 5.64 (dd, *J* = 9.5, 15.5 Hz, 1H), 5.89 (d, *J* = 9.5 Hz, 1H), 6.27 (dt, *J* = 7.0, 15.5 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}C$ NMR δ 38.2, 55.5, 103.4, 114.4, 115.9, 129.4, 129.5, 129.9, 130.5, 134.3, 135.6, 145.9, 158.7 ppm; IR (film): 1561, 1512, 1338, 1247, 1156 $cm^{-1}$; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{17}H_{17}NO_5S$: 347.0827, Found: 347.0824.

*(4-Benzenesulfonyl-1-methyl-4-nitrobut-2-enyl)benzene (**4g**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 9:1); yellowish oil; yield 75%; $^1H$ NMR δ 1.39 (t, *J* = 6.5 Hz, 3H), 3.52-3.63 (m, 1H), 5.57-5.69 (m, 1H), 5.89 (d, *J* = 10.0 Hz, 1H), 6.27 (td, *J* = 6.5, 16.5 Hz, 1H), 7.13 (t, *J* = 6.0 Hz, 2H), 7.22-7.28 (m, 1H), 7.32 (q, *J* = 6.0 Hz, 2H), 7.52 (t, *J* = 7.0 Hz, 1H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.69-7.78 (m, 2H), 7.85 (d, *J* = 7.0 Hz, 1H) ppm; $^{13}C$ NMR δ 20.4, 20.4, 42.7, 42.8, 103.5, 114.2, 114.4, 127.2, 127.4, 129.0, 129.5, 129.6, 130.5, 130.6, 134.3, 134.4, 135.5, 135.6, 143.0, 143.1, 150.6, 150.8 ppm; IR (film): 1561, 1340, 1156 $cm^{-1}$; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_{17}H_{16}NO_4S$: 330.0800, Found: 330.0797.

*(4-Benzenesulfonyl-4-nitrobut-2-enyl)carbamic acid benzyl ester (**4h**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 4:1 to hexane:EtOAc = 2:1); yellowish oil; yield 61%; $^1H$ NMR δ 3.95 (s, *2*H), 4.91 (br s, 1H), 5.13 (s, 2H), 5.84 (dd, *J* = 9.0, 15.5 Hz, 1H), 5.91 (d, *J* = 9.0 Hz, 1H), 6.16 (d, *J* = 15.5 Hz, 1H), 7.31-7.40 (m. 5H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}C$ NMR δ 42.2, 67.3, 102.8, 115.8, 128.3, 128.5, 128.8, 129.6, 130.6, 134.0, 135.8, 136.3, 142.4, 156.3 ppm; IR (film): 1708, 1562, 1339, 1246, 1156 $cm^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{18}H_{19}N_2O_6S$: 391.0964, Found: 391.0963.

*(5-Benzenesulfonyl-5-nitropent-3-enyloxymethyl)benzene (**4i**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 5:1); yellowish oil; yield 83%; $^1H$ NMR δ 2.47 (q, *J* = 6.5 Hz, 2H), 3.55 (t, *J* = 6.5 Hz, 2H), 4.50 (s, 2H), 5.72 (dd, *J* = 9.5, 15.0 Hz, 1H), 5.88 (d, *J* = 9.5 Hz, 1H), 6.19 (dt, *J* = 6.5, 15.0 Hz, 1H), 7.28-7.38 (m, 5H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}C$ NMR δ 33.3, 68.3, 73.3, 103.6, 116.8, 127.9, 128.0, 128.7, 129.5, 130.6, 134.3, 135.6, 138.1, 143.9 ppm; IR (film): 1562, 1340, 1157, 1083 $cm^{-1}$; HRMS (FAB, $[M+H]^+$) *m/z* calcd for $C_{18}H_{20}NO_5S$: 362.1062, Found: 362.1067.

*(5-Benzenesulfonyl-5-nitropent-3-enyl)benzene (**4j**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); white solid; yield 84%; mp 84-85 ℃; $^1H$ NMR δ 2.46-2.54 (m, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 5.63 (dd, J = 10.0, 15.0 Hz, 1H), 5.85 (d, *J* = 10.0 Hz, 1H), 6.17 (dt, J = 6.5, 15.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.21-7.28 (m, 1H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 2H), 7.72-7.79 (m, 3H) ppm; $^{13}C$ NMR δ 34.6, 103.5, 115.8, 126.5, 128.6, 128.8, 129.5, 130.5, 134.3, 135.6, 140.5, 146.2 ppm; IR (film): 1560, 1338, 1155 $cm^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{17}H_{18}NO_4S$: 332.0957, Found: 332.0958.

*11-Benzenesulfonyl-11-nitroundec-9-enoic acid methyl ester (**4k**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 7:1 to hexane:EtOAc = 5:1); colorless oil; yield 70%; $^1H$ NMR δ 1.25-1.35 (m, 6H), 1.36-1.44 (m, 2H), 1.59-1.66 (m, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 2.31 (t, *J* = 7.0 Hz, 2H), 3.67 (s, 3H), 5.65 (dd, *J* = 10.0, 15.0 Hz, 1H), 5.86 (d, *J* = 10.0 Hz, 1H), 6.14 (dt, *J* = 7.0, 15.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}C$ NMR δ 25.1, 28.2, 29.0, 29.1, 29.2, 32.8, 34.2, 51.7, 103.7, 115.0, 129.5, 130.5, 134.5, 135.6, 147.5, 174.4 ppm; IR (film): 2929, 1731, 1561, 1339, 1156 $cm^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{18}H_{26}NO_6S$: 384.1481, Found: 384.1484.

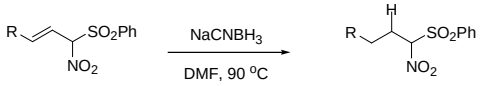
*4.3. Procedure for the preparation of heptanal (**5a**)*


**4a** **5a**

· β,γ-Unsaturated α-nitrosulfone **4a** (280 mg, 0.90 mmol) was dissolved in dichloromethane (10 mL) and cooled to -78 ºC in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ºC. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.5 mL, 6.5 mmol) at -78 ºC. The reaction mixture was allowed to warm up to room temperature, and stirred for 4h. Then, the reaction mixture was concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (hexane:EtOAc = 19:1) to afford **5a**.

Colorless liquid; yield 73%; $^1$H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.24-1.37 (m, 6H), 1.63 (quin, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 9.77 (s, 1H) ppm; $^{13}$C NMR δ 14.2, 22.2, 22.6, 29.0, 31.7, 44.1, 203.1 ppm; IR (film): 2956, 1716, 1463 cm$^{-1}$; HRMS (CI, [M-H]$^+$) *m/z* calcd for $C_7H_{13}O$: 113.0966, Found: 113.0968.

*4.4. General Procedure for the preparation of saturated α-nitrosulfones **6***




**4** **6**

To a solution of **4** (2.00 mmol) in DMF (10 mL) was added at room temperature sodium cyanoborohydride (6.0 mmol). The reaction mixture was stirred overnight at 90 ºC and quenched with aqueous 0.1 *N* HCl solution (20 mL). Then, the reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **6** in 69 - 89% yields except **6c**.

*1-Benzenesulfonyl-1-nitrononane (**6a**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); white solid; yield 87%; mp 48-49 ℃; $^1$H NMR δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.19-1.30 (m, 8H), 1.31-1.42 (m, 4H), 2.16-2.30 (m, 2H), 5.48 (dd, *J* = 4.0, 10.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 14.3, 22.8, 25.6, 28.0 28.8, 29.2, 29.2, 31.9, 102.6, 129.7, 130.2, 134.2, 135.7 ppm; IR (film): 2928, 1562, 1340, 1158 cm$^{-1}$; HRMS (FAB, [M+H]$^+$) *m/z* calcd for $C_{15}H_{24}NO_4S$: 314.1426, Found: 314.1427.

*1-Benzenesulfonyl-1-nitrotridecane (**6b**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 19:1 to hexane:EtOAc = 15:1); white solid; yield 86%; mp 57-58 ℃; $^1$H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.20-1.42 (m, 20H), 2.17-2.31 (m, 2H), 5.48 (dd, *J* = 4.0, 11.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 2H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H) ppm; $^{13}$C NMR 14.3, 22.9, 25.6, 28.0 28.8, 29.2, 29.5, 29.5, 29.7, 29.8, 29.8, 32.1, 102.6, 129.7, 130.2, 134.2, 135.7 ppm; IR (film): 2926, 1562, 1341, 1158 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{19}H_{32}NO_4S$: 370.2052, Found: 370.2054.

*1-(3-Benzenesulfonyl-3-nitropropyl)-4-propoxybenzene (**6c**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 9:1); colorless oil; yield 45%; $^1$H NMR δ 1.04 (t, *J* = 7.5 Hz, 3H), 1.80 (sex, J = 7.5 Hz, 2H), 2.48-2.56 (m, 3H), 2.7-2.81 (m, 1H), 3.90 (t, *J* = 6.5 Hz, 2H), 5.41 (dd, *J* = 6.0, 7.5 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 10.7, 22.8, 29.9, 30.6, 69.7, 101.5, 115.1, 129.6, 129.7, 130.2, 134.1, 135.7, 158.4 ppm; IR (film): 1561, 1511, 1338, 1246, 1157 cm$^{-1}$; HRMS (EI, [M]$^+$) *m/z* calcd for $C_{18}H_{21}NO_5S$: 363.1140, Found: 363.1138.

*(4-Benzenesulfonyl-4-nitrobutyl)benzene (**6d**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); colorless oil; yield 85%; $^1$H NMR (400 MHz) δ 1.64-1.76 (m, 2H), 2.23-2.32 (m, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 5.46 (dd, *J* = 5.6, 9.6 Hz, 1H), 7.09 (d, *J* = 6.8 Hz, 2H), 7.19 (tt, *J* = 1.2 Hz, 6.8 Hz, 1H), 7.23-7.29 (m, 2H), 7.59 (td, *J* = 1.2, 7.6 Hz, 2H), 7.75 (tt, *J* = 1.2, 7.6 Hz, 1H), 7.84 (dd, *J* = 1.2, 7.6 Hz, 2H) ppm; $^{13}$C NMR (100 MHz) δ 27.0, 27.5. 34.8, 102.2, 126.4, 128.4, 128.7, 129.6, 130.0, 134.1, 135.6, 140.3 ppm; IR (film): 1561, 1338, 1157 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{16}H_{18}NO_4S$: 320.0957, Found: 320.0954.

*1-(4-Benzenesulfonyl-4-nitrobutyl)-3-chlorobenzene (**6e**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 9:1); colorless oil; yield 72%; $^1$H NMR δ 1.64-1.77 (m, 2H), 2.23-2.32 (m, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 5.47 (dd, *J* = 5.0, 10.0 Hz, 1H), 7.00 (d, *J* = 6.5 Hz, 1H), 7.10 (s, 1H), 7.18-7.23 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 27.0, 27.5. 34.6, 102.2, 126.7, 126.9, 128.6, 129.8, 130.1, 130.2, 134.1, 134.6, 135.8, 142.3 ppm; IR (film): 1561, 1338, 1157 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{16}H_{17}ClNO_4S$: 354.0567, Found: 354.0568.

*1-(4-Benzenesulfonyl-4-nitrobutyl)-4-methoxybenzene (**6f**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); colorless oil; yield 69%; $^1$H NMR δ 1.63-1.72 (m, 2H), 2.20-2.32 (m, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 5.46 (dd, *J* = 5.0, 9.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 27.4, 27.5, 34.0, 55.5, 102.3, 114.2, 129.4, 129.7, 130.2, 132.3, 134.1, 135.7, 158.3 ppm; IR (film): 1561, 1513, 1338, 1246, 1178 cm$^{-1}$; HRMS (EI, [M]$^+$) *m/z* calcd for $C_{17}H_{19}NO_5S$: 349.0984, Found: 349.0984.

*5-Benzenesulfonyl-5-nitro-2-phenylpentane (**6g**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1); colorless oil; yield 70%; $^1$H NMR δ 1.25 (dd, *J* = 3.0, 7.0 Hz, 3H), 1.58-1.74 (m, 2H), 2.03-2.15 (m, 1H), 2.15-2.26 (m, 1H), 2.70 (dq, *J* = 7.0 Hz, 21.0 Hz, 1H), 5.30 (dd, *J* = 3.0, 11.0 Hz, 0.5H), 5.44 (dd, *J* = 3.0, 11.0 Hz, 0.5H), 7.11 (dd, *J* = 7.5, 14.0 Hz, 2H), 7.22 (quin, *J* = 7.0 Hz, 1H), 7.26-7.34 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.75 (dd, *J* = 7.5,11.5 Hz, 1H), 7.81 (dd, *J* = 7.5,11.5 Hz, 2H) ppm; $^{13}$C NMR (100 MHz) δ 21.9, 22.1, 26.1, 26.5, 33.4, 33.8, 39.1, 39.7, 102.2, 126.7, 126.8, 128.7, 129.5, 129.9, 134.0, 134.1, 135.4, 145.0, 145.3 ppm; IR (film): 1561, 1339, 1157 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{17}H_{20}NO_4S$: 334.1113, Found: 334.1111.

*(4-Benzenesulfonyl-4-nitrobutyl)carbamic acid benzyl ester (**6h**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 5:1 to hexane:EtOAc = 2:1); colorless oil; yield 78%; $^1$H NMR δ 1.52-1.72 (m, 2H), 2.24-2.42 (m, 2H), 3.17-3.32 (m, 2H), 4.81 (br s, 1H), 5.09 (s, 2H), 5.64 (dd, *J* = 2.0, 10.5 Hz, 1H), 7.30-7.40 (m, 5H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR (100 MHz) δ 24.8, 25.8, 39.4, 66.8, 101.4, 128.0, 128.1, 128.5, 129.5, 129.8, 133.9, 135.4, 136.3, 156.5 ppm; IR (film): 1703, 1560, 1337, 1249, 1156 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{18}H_{21}N_2O_6S$: 393.1120, Found: 393.1119.

*(5-Benzenesulfonyl-5-Nitropentyloxymethyl)benzene (**6i**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 9:1); colorless oil; yield 89%; $^1$H NMR δ 1.44-1.55 (m, 2H), 1.60-1.70 (m, 2H), 2.22-2.36 (m, 2H), 3.45 (t, *J* = 6.0 Hz, 2H), 4.46 (s, 2H), 5.52 (dd, *J* = 4.0, 10.5 Hz, 1H), 7.28-7.32 (m, 3H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 22.8, 27.9, 28.9, 69.5, 73.3, 102.5, 127.9, 128.6, 129.7, 130.2, 134.2, 135.7, 138.4 ppm; IR (film): 1560, 1337, 1158, 1083 cm$^{-1}$; HRMS (EI, [M]$^+$) *m/z* calcd for $C_{18}H_{21}NO_5S$: 363.1140, Found: 363.1140.

*(5-Benzenesulfonyl-5-nitropentyl)benzene (**6j**):*

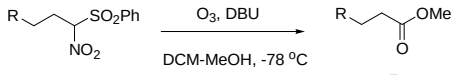
Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 9:1); white solid; yield 84%; mp 66-67 ℃; $^1$H NMR δ 1.34-1.48 (m, 2H), 1.62-1.72 (m,

2H), 2.23-2.31 (m, 2H), 2.53-2.66 (m, 2H), 5.46 (dd, *J* = 5.0, 9.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.26-7.30 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 25.1, 27.9, 30.5, 35.4, 102.4, 126.2, 128.5, 128.7, 129.7, 130.2, 134.1, 135.7, 141.5 ppm; IR (film): 1560, 1338, 1157 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{17}H_{20}NO_4S$: 334.1113, Found: 334.1114.

*11-Benzenesulfonyl-11-nitroundecanoic acid methyl ester (**6k**):*

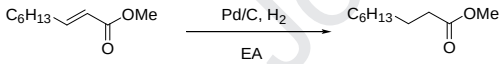
Silica gel column chromatography (gradient eluent from hexane:EtOAc = 7:1 to hexane:EtOAc = 5:1); white solid; yield 83%; mp 62-63 ℃; $^1$H NMR δ 1.20-1.45 (m, 12H), 1.60 (quin, *J* = 7.0 Hz, 2H), 2.19-2.27 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 5.48 (dd, *J* = 3.5, 11.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 25.1, 25.6, 28.1, 28.8, 29.2, 29.3, 34.3, 51.7, 102.6, 129.8, 130.3, 134.2, 135.7, 174.5 ppm; IR (film): 2930, 1735, 1561, 1340, 1158 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{18}H_{28}NO_6S$: 386.1637, Found: 386.1635.

*4.5 General Procedure for the preparation of one-carbon longer homologous methyl esters **7***




**6** **7**

To a solution of **6** (1.00 mmol) in dichloromethane (5 mL) and MeOH (5 mL) was added at 0 ºC in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3 mmol). The reaction mixture was stirred for 10 min and replaced in a Dewar bath containing dry ice/acetone. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ºC. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.1 mL, 1.3 mmol) and acetic acid (1.0 mL) at -78 ºC, allowed to warm up to room temperature, and stirred for 1 h. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **7** in 66 - 88% yields.




**15a** **7a**

To a solution of α,β-unsaturated ester **15a** (200 mg, 1.17 mmol) in ethyl acetate (20 mL) was added 5% Pd/C (20 mg). The mixture was stirred at room temperature under $H_2$ (3 atm) atmosphere for 2 h. After the hydrogenation was completed, the reaction mixture was filtered through a bed of Celite. The filtrate was concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **7a** in a 92% yield.

*Nonanoic acid methyl ester (**7a**):*

Silica gel column chromatography (hexane:EtOAc = 20:1); colorless liquid; yield 73%; $^1$H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20-1.36 (m, 10H), 1.62 (quin, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H) ppm; $^{13}$C NMR δ 14.3, 22.8, 25.2, 29.3, 29.4, 29.4, 32.0, 34.3, 51.6, 174.5 ppm; IR (film): 2928, 1743, 1168 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{10}H_{21}O_2$: 173.1542, Found: 173.1541.

*Tridecanoic acid methyl ester (**7b**):*

Silica gel column chromatography (hexane:EtOAc = 20:1); colorless liquid; yield 80%; $^1$H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.22-1.34 (m, 18H), 1.62 (quin, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H) ppm; $^{13}$C NMR δ 14.3, 22.9, 25.2, 29.4 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.1, 34.3, 51.6, 174.6 ppm; IR (film): 2925, 1743, 1171 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{14}H_{29}O_2$: 229.2168, Found: 229.2171.

*3-(4-Propoxyphenyl)propionic acid methyl ester (**7c**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 12:1); colorless liquid; yield 68%; $^1$H NMR δ 1.03 (t, *J* = 7.0 Hz, 3H), 1.79 (sex, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 3.89 (t, *J* = 7.0 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H) ppm; $^{13}$C NMR δ 10.7, 22.8, 30.3, 36.2, 51.8, 69.7, 114.7, 129.4, 132.6, 157.8, 173.6 ppm; IR (film): 1738, 1513, 1244 cm$^{-1}$; HRMS (EI, [M]$^+$) *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256, Found: 222.1259.

*4-Phenylbutyric acid methyl ester (**7d**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 20:1 to hexane:EtOAc = 15:1); colorless liquid; yield 78%; $^1$H NMR (400 MHz) δ 2.01 (quin, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 3.70 (s, 3H), 7.20-7.28 (m, 3H), 7.33 (t, *J* = 7.2 Hz, 2H) ppm; $^{13}$C NMR (100 MHz) δ 26.5, 33.4, 35.2, 51.5, 126.0, 128.4, 128.5, 141.4, 173.9 ppm; IR (film): 1738, 1204 cm$^{-1}$; HRMS (FAB, [M+H]$^+$) *m/z* calcd for $C_{11}H_{15}O_2$: 179.1072, Found: 179.1068.

*4-(3-Chloro-phenyl)butyric acid methyl ester (**7e**):*

Silica gel column chromatography (hexane:EtOAc = 15:1); colorless liquid; yield 74%; $^1$H NMR δ 1.95 (quin, *J* = 7.5 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.15-7.19 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H) ppm; $^{13}$C NMR δ 26.4, 33.4, 35.0, 51.8, 126.4, 126.9, 128.8, 129.8, 134.3, 143.6, 173.9 ppm; IR (film): 1738, 1435, 1205 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{11}H_{14}ClO_2$: 213.0682, Found: 213.0676.

*4-(4-Methoxyphenyl)butyric acid methyl ester (**7f**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 8:1); colorless liquid; yield 73%; $^1$H NMR δ 1.92 (quin, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 3.66 (s, 3H), 3.79 (s, 3H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H) ppm; $^{13}$C NMR δ 26.9, 33.5, 34.4, 51.7, 55.4, 114.0, 129.6, 133.6, 158.0, 174.2 ppm; IR (film): 1737, 1513, 1247 cm$^{-1}$; HRMS (EI, [M]$^+$) *m/z* calcd for $C_{12}H_{16}O_3$: 208.1099, Found: 208.1098.

*4-Phenylpentanoic acid methyl ester (**7g**):*

Silica gel column chromatography (hexane:EtOAc = 20:1); colorless liquid; yield 80%; $^1$H NMR δ 1.27(d, *J* = 7.0 Hz, 3H), 1.84-1.98 (m, 2H), 2.13-2.26 (m, 2H), 2.71 (sex, *J* = 7.0 Hz, 1H), 3.63 (s, 3H), 7.15-7.22 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 22.4, 32.5, 33.4, 39.6, 51.7, 126.4, 127.2, 128.6, 146.4, 174.3 ppm; IR (film): 1738, 1166 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{12}H_{17}O_2$: 193.1229, Found: 193.1228.

*4-Benzyloxycarbonylaminobutyric acid methyl ester (**7h**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 8:1 to hexane:EtOAc = 3:1); colorless oil; yield 88%; $^1$H NMR δ 1.85 (quin, *J* = 7.0 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 3.25 (q, *J* = 7.0 Hz, 2H), 3.66 (s, 3H), 4.87 (br s, 1H), 5.09 (s, 2H), 7.28-7.38 (m, 5H) ppm; $^{13}$C NMR δ 25.3, 31.4, 40.6, 51.9, 66.9, 128.3, 128.7, 136.7, 156.6, 173.9 ppm; IR (film): 1723, 1712, 1531, 1254 cm$^{-1}$; HRMS (EI, [M]$^+$) *m/z* calcd for $C_{13}H_{17}NO_4$: 251.1158, Found: 251.1155.

*5-Benzyloxypentanoic acid methyl ester (**7i**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 12:1); colorless oil; yield 66% $^1$H NMR δ 1.65 (quin, *J* = 7.5 Hz, 2H), 1.73 (quin, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.48 (t, *J* = 6.5 Hz, 2H),

3.66 (s, 3H), 4.50 (s, 2H), 7.26-7.30 (m, 1H), 7.31-7.37 (m, 4H) ppm; $^{13}$C NMR δ 22.0, 29.4, 34.0, 51.7, 70.0, 73.1, 127.7, 127.8, 128.6, 138.7, 174.2 ppm; IR (film): 1738, 1168, 1099 cm$^{-1}$; HRMS (EI, [M]$^{+}$) *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256, Found: 222.1256.

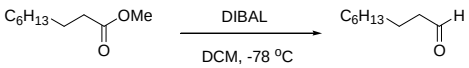
*5-Phenylpentanoic acid methyl ester (**7j**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 12:1); colorless liquid; yield 88%; $^{1}$H NMR δ 1.62-171 (m, 4H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 3.66 (s, 3H), 7.15-7.20 (m, 3H), 7.27-7.30 (m, 2H) ppm; $^{13}$C NMR δ 24.8, 31.1, 34.1, 35.8, 51.7, 126.0, 128.5, 128.6, 142.3, 174.3 ppm; IR (film): 1739, 1200, 1173 cm$^{-1}$; HRMS (EI, [M]$^{+}$) *m/z* calcd for $C_{12}H_{16}O_2$: 192.1150, Found: 192.1151

*Undecanedioic acid dimethyl ester (**7k**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 8:1); colorless liquid; yield 71%; $^{1}$H NMR δ 1.25-1.34 (m, 10H), 1.61 (t, *J* = 7.5 Hz, 4H), 2.30 (t, *J* = 7.5 Hz, 4H), 3.67 (s, 6H) ppm; $^{13}$C NMR δ 25.1, 29.3, 29.3, 29.4, 34.3, 51.6, 174.5 ppm; IR (film): 2930, 1740, 1172 cm$^{-1}$; HRMS (CI, [M+H]$^{+}$) *m/z* calcd for $C_{13}H_{25}O_4$: 245.1753, Found: 245.1755.

*4.6. Procedure for the preparation of Nonanal (**8a**):*

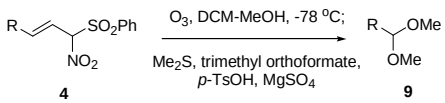



**7a** **8a**

A solution of **7a** (258 mg, 1.50 mmol) in anhydrous dichloromethane (20 mL) was cooled to -78 ºC using a dry ice/acetone bath. To the reaction mixture was slowly added 1 M solution of DIBAL in dichloromethane (2.0 mL, 2.0 mmol) under nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred at -78 °C for 30 min and then quenched by addition of MeOH (1.0 mL) and aqueous saturated solution of Rochelle salt (20 mL). Then, the reaction mixture was allowed to warm up to room temperature and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to afford **8a**.

Colorless liquid; yield 88%; $^{1}$H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.21-1.37 (m, 10H), 1.63 (quin, *J* = 7.5 Hz, 2H), 2.42 (td, *J* = 2.0, 7.5 Hz, 2H), 9.77 (t, *J* = 2.0 Hz, 1H) ppm; $^{13}$C NMR δ 14.3, 22.3, 22.8, 29.3, 29.4, 29.5, 32.0, 44.1, 203.2 ppm; IR (film): 2927, 1728, 1461 cm$^{-1}$; HRMS (CI, [M-H]$^{+}$) *m/z* calcd for $C_9H_{17}O$: 141.1279, Found: 141.1277.

*4.7. General Procedure for the preparation of one-carbon shorter homologous acetals **9***




**4** **9**

A solution of **4** (1.00 mmol) in dichloromethane (5 mL) and MeOH (5 mL) was cooled to -78 ºC using a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.5 mL, 6.5 mmol) at -78 ºC, and *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol), $MgSO_4$ (1.0 g), and trimethyl orthoformate (3.0 mL) were added to the reaction mixture. The reaction mixture was allowed to warm up to room temperature, and stirred for overnight. Then, the reaction mixture was filtered and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **9** in 48 - 79% yields.

*1,1-Dimethoxyheptane (**9a**):*

Silica gel column chromatography (hexane:EtOAc = 20:1); colorless liquid; yield 69%; $^{1}$H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.24-1.38 (m, 8H), 1.56-1.62 (m, 2H), 3.31 (s, 6H), 4.36 (t, *J* = 6.0 Hz, 1H) ppm; $^{13}$C NMR δ 14.3, 22.8, 24.8, 29.4, 32.0, 32.7, 52.8, 104.8 ppm; IR (film): 2929, 1458 cm$^{-1}$; HRMS (CI, [M-H]$^{+}$) *m/z* calcd for $C_9H_{19}O_2$: 159.1385, Found: 159.1385.

*1,1-Dimethoxyundecane (**9b**):*

Silica gel column chromatography (hexane:EtOAc = 19:1); colorless liquid; yield 78%; $^{1}$H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.20-1.37 (m, 16H), 1.54-1.63 (m, 2H), 3.31 (s, 6H), 4.36 (t, *J* = 6.0 Hz, 1H) ppm; $^{13}$C NMR δ 14.3, 22.9, 24.8, 29.6, 29.7, 29.8, 29.8, 32.1, 32.7, 52.8, 104.8 ppm; IR (film): 2926, 1464, 1127, 1057 cm$^{-1}$; HRMS (CI, [M-H]$^{+}$) *m/z* calcd for $C_{13}H_{27}O_2$: 215.2011, Found: 215.2015.

*1-Dimethoxymethyl-4-propoxybenzene (**9c**):*

Silica gel column chromatography (hexane:EtOAc = 19:1); colorless liquid; yield 53%; $^{1}$H NMR δ 1.03 (t, *J* = 7.0 Hz, 3H), 1.81 (sex, *J* = 7.0 Hz, 2H ), 3.31 (s, 6H), 3.92 (t, *J* = 7.0 Hz, 2H), 5.35 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H) ppm; $^{13}$C NMR δ 10.7, 22.8, 52.8, 69.7, 103.3, 114.3, 128.1, 130.3, 159.4 ppm; IR (film): 1510, 1260, 1161 cm$^{-1}$; HRMS (EI, [M]$^{+}$) *m/z* calcd for $C_{12}H_{18}O_3$: 210.1256, Found: 210.1259.

*(2,2-Dimethoxyethyl)benzene (**9d**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 19:1 to hexane:EtOAc = 15:1); colorless liquid; yield 53%; $^{1}$H NMR (400 MHz) δ 2.91 (d, *J* = 5.6 Hz, 2H ), 3.33 (s, 6H), 4.54 (t, *J* = 5.6 Hz, 1H), 7.17-7.34 (m, 5H) ppm; $^{13}$C NMR (100 MHz) δ 39.7, 53.3, 105.4, 126.4, 128.3, 129.4, 137.1 ppm; IR (film): 1122, 1063 cm$^{-1}$. The analytical data are in agreement with those in literature.[27]

*1-Chloro-3-(2,2-dimethoxyethyl)benzene (**9e**):*

Silica gel column chromatography (hexane:EtOAc = 20:1); colorless liquid; yield 74%; $^{1}$H NMR δ 2.88 (d, *J* = 5.5 Hz, 2H), 3.35 (s, 6H), 4.52 (t, *J* = 5.5 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 1H), 7.18-7.25 (m, 3H) ppm; $^{13}$C NMR δ 39.5, 53.7, 105.1, 126.8, 127.9, 129.7, 129.8, 134.2, 139.2 ppm; IR (film): 1121, 1075 cm$^{-1}$; HRMS (CI, [M-H]$^{+}$) *m/z* calcd for $C_{10}H_{12}ClO_2$: 199.0526, Found: 199.0523.

*1-(2,2-Dimethoxyethyl)-4-methoxybenzene (**9f**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 20:1 to hexane:EtOAc = 15:1); colorless liquid; yield 48%; $^{1}$H NMR δ 2.85 (d, *J* = 5.5 Hz, 2H), 3.34 (s, 6H), 3.79 (s, 3H), 4.50 (t, *J* = 5.5 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H) ppm; $^{13}$C NMR δ 38.9, 53.6, 55.4, 105.7, 113.9, 129.3, 130.5, 158.4 ppm; IR (film): 1514, 1248, 1121, 1067, 1039 cm$^{-1}$; HRMS (CI, [M+H]$^{+}$) *m/z* calcd for $C_{11}H_{17}O_3$: 197.1178, Found: 197.1183.

*(2,2-Dimethoxy-1-methylethyl)benzene (**9g**):*

Silica gel column chromatography (hexane:EtOAc = 20:1); colorless liquid; yield 67%; $^{1}$H NMR δ 1.28 (d, *J* = 7.0 Hz, 3H), 3.01 (quin, *J* = 7.0 Hz, 1H), 3.24 (s, 3H), 3.38 (s, 3H), 4.37 (d, *J* = 7.0 Hz, 1H), 7.19-7.27 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 17.1, 43.1, 54.2, 54.7, 108.8, 126.6, 128.1, 128.5, 143.3 ppm; IR (film): 1453, 1071 cm$^{-1}$; HRMS (CI, [M-H]$^{+}$) *m/z* calcd for $C_{11}H_{15}O_2$: 179.1072, Found: 179.1075.

*(2,2-Dimethoxyethyl)carbamic acid benzyl ester (**9h**):*

Silica gel column chromatography (grdient eluent from hexane:EtOAc = 7:1 to hexane:EtOAc = 5:1); colorless liquid; yield 59%; $^1$H NMR δ 3.34 (t, *J* = 5.0 Hz, 2H), 3.39 (s, 6H), 4.38 (t, *J* = 5.0 Hz, 1H), 4.94 (br s, 1H), 5.11 (s, 2H), 7.29-7.39 (m, 5H) ppm; $^{13}$C NMR δ 42.7, 54.6, 67.0, 103.0, 128.3, 128.7, 128.8, 136.6, 156.6 ppm; IR (film): 1717, 1532, 1251, 1129, 1065 cm$^{-1}$; HRMS (EI, [M]$^+$) *m/z* calcd for $C_{12}H_{17}NO_4$: 239.1158, Found: 239.1157.

*3-Benzyloxy-1,1-dimethoxypropane (**9i**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 20:1 to hexane:EtOAc = 15:1); colorless liquid; yield 73%; $^1$H NMR δ 1.92 (q, *J* = 6.0 Hz, 2H), 3.33 (s, 6H), 3.55 (t, *J* = 6.0 Hz, 2H), 4.51 (s, 2H), 4.56 (t, *J* = 6.0 Hz, 1H), 7.26-7.31 (m, 1H), 7.31-7.36 (4H) ppm; $^{13}$C NMR δ 33.4, 53.3, 66.5, 73.3, 102.5, 127.8, 127.8, 128.6, 138.6 ppm; IR (film): 1453, 1275, 1104 cm$^{-1}$; HRMS (CI, [M-H]$^+$) *m/z* calcd for $C_{12}H_{17}O_3$: 209.1178, Found: 209.1179.

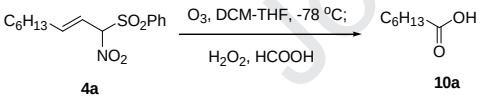
*(3,3-Dimethoxypropyl)benzene (**9j**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 20:1 to hexane:EtOAc = 17:1); colorless liquid; yield 73%; $^1$H NMR δ 1.88-1.96 (m, 2H), 2.68 (t, *J* = 8.0 Hz, 2H), 3.33 (s, 6H), 4.37 (t, *J* = 6.0 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 3H), 7.24-7.31 (m, 2H) ppm; $^{13}$C NMR δ 31.1, 34.3, 52.9, 104.0, 126.1, 128.6, 128.7, 141.8 ppm; IR (film): 1454, 1125, 1055 cm$^{-1}$; HRMS (CI, [M-H]$^+$) *m/z* calcd for $C_{11}H_{15}O_2$: 179.1072, Found: 179.1074.

*9,9-Dimethoxynonanoic acid methyl ester (**9k**):*

Silica gel column chromatography (gradient eluent from hexane:EtOAc = 19:1 to hexane:EtOAc = 15:1); colorless liquid; 79%; $^1$H NMR δ 1.26-1.37 (m, 8H), 1.58-1.65 (m, 4H), 2.30 (t, *J* = 8.0 Hz, 2H), 3.31 (s, 6H), 3.67 (s, 3H), 4.35 (t, *J* = 5.5 Hz, 1H) ppm; $^{13}$C NMR δ 24.7, 25.1, 29.2, 29.4, 29.5, 32.7, 34.3, 51.6, 52.8, 104.7, 174.5 ppm; IR (film): 2936, 1740, 1438, 1127, 1056 cm$^{-1}$; HRMS (CI, [M-H]$^+$) *m/z* calcd for $C_{12}H_{23}O_4$: 231.1596, Found: 231.1590.

*4.8. Procedure for the preparation of Heptanoic acid (**10a**):*

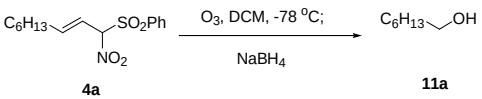



**4a** **10a**

A solution of **4a** (280 mg, 0.90 mmol) in dichloromethane (10 mL) and THF (10 mL) was cooled to -78 ºC using a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min. After the ozonolysis was completed, aqueous hydrogen peroxide solution (2.0 mL) and formic acid (5.0 mL) were added to the reaction mixture, which was then refluxed for 4h. Then, the reaction mixture was concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1) to afford **10a**.

Colorless liquid; yield 68%; $^1$H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.24-1.39 (m, 6H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H); $^{13}$C NMR δ 14.2, 22.7, 24.9, 29.0, 31.6, 34.3, 180.3 ppm; IR (film): 2930, 1710, 1415, 1284 cm$^{-1}$. The analytical data are in agreement with those in literature.[28]

*4.9. Procedure for the preparation of Heptanol (**11a**):*

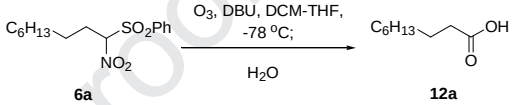



**4a** **11a**

A solution of **4a** (311 mg, 1.00 mmol) in dichloromethane (20 mL) was cooled to -78 ºC using a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min. After the ozonolysis was completed, sodium borohydride (76 mg, 2.0 mmol) and methanol (5 mL) was added to the reaction mixture. The reaction mixture was stirred for overnight. Then, the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 7:1 to hexane:EtOAc = 4:1) to afford **11a**.

Colorless liquid; yield 65%; $^1$H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.23-1.39 (m, 8H), 1.57 (quin, *J* = 7.0 Hz, 2H), 3.64 (t, *J* = 7.0 Hz, 2H) ppm; $^{13}$C NMR δ 14.3, 22.8, 25.9, 29.3, 32.0, 33.0, 63.2 ppm; IR (film): 3331, 2929, 1460, 1057 cm$^{-1}$. The analytical data are in agreement with those in literature.[29]

*4.10. Procedure for the preparation of Nonanoic acid (**12a**):*

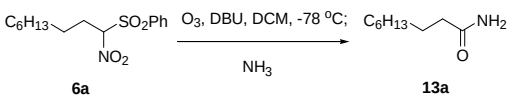



**6a** **12a**

To a solution of **6a** (313 mg, 1.00 mmol) in dichloromethane (5 mL) and THF (5 mL) was added at 0 ºC in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3.0 mmol). The reaction mixture was stirred for 10 min and replaced in a Dewar bath containing dry ice/acetone. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ºC. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.1 mL, 1.3 mmol), acetic acid (1.0 mL), and water (10 mL) at -78 ºC, which was allowed to warm up to room temperature, and stirred for 1 hr. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 15:1 to hexane:EtOAc = 9:1) to afford **12a**.

Colorless liquid; yield 72%; $^1$H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.20-1.38 (m, 10H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 14.3, 22.9, 24.9, 29.3, 29.3, 29.4, 32.0, 34.3, 180.3 ppm; IR (film): 3034, 2926, 1710, 1415, 1287 cm$^{-1}$. The analytical data are in agreement with those in literature.[30]

*4.11. Procedure for the preparation of Nonanoic acid amide (**13a**):*



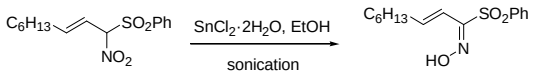

**6a** **13a**

To a solution of **6a** (313 mg, 1.00 mmol) in dichloromethane (10 mL) was added at 0 ºC in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3.0 mmol). The reaction mixture was stirred for 10 min and replaced in a Dewar bath containing dry ice/acetone. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ºC. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.10 mL, 1.3 mmol) at -78 ºC and 0.5 M ammonia solution in 1,4-dioxane (5.0 mL) was added to the reaction mixture, which was allowed to warm up to room temperature, and stirred for 1 hr. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over

$MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 2:1 to hexane:EtOAc = 1:1) to afford **13a**.

White solid; yield 56%; mp 98.5-99.5 ℃; $^1$H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.21-1.37 (m, 10H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 5.32 (br d, 2H) ppm; $^{13}$C NMR δ 14.3, 22.8, 25.7, 29.3, 29.4, 29.5, 32.0, 36.2, 176.2 ppm; IR (film): 3358, 2920, 1659, 1633 cm$^{-1}$. The analytical data are in agreement with those in literature.[31]

*4.12. Procedure for the preparation of 1-Benzenesulfonylnon-2-en-1-one oxime (**14a**):*

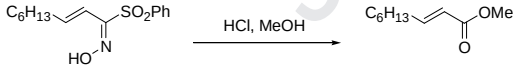



**4a** **14a**

To a solution of **4a** (622 mg, 2.00 mmol) in ethanol (10 mL) was added $SnCl_2.2H_2O$ (1.13 g, 5.00 mmol). The reaction mixture was exposed to ultrasonic irradiation for 2 h until the reaction was complete as indicated by TLC analysis. The solvent was removed under reduced pressure and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 5:1) to afford **14a**.

White solid; yield 65%; mp 72-73 ℃; $^1$H NMR (400 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.20-1.34 (m, 6H), 1.42 (quin, *J* = 7.2 Hz, 2H), 2.21 (q, *J* = 7.2 Hz, 2H), 6.35 (d, *J* = 16.4 Hz, 1H), 7.11 (dt, *J* = 7.2, 16.4 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 9.73 (br s, 1H) ppm; $^{13}$C NMR (100 MHz) δ 13.9, 22.4, 28.0 28.6, 31.4, 34.1, 112.5, 128.5, 129.1, 133.9, 138.4, 147.7, 155.2 ppm; IR (film): 3326, 2956, 1633, 1311, 1149 cm$^{-1}$; HRMS (FAB, $[M+H]^+$) *m/z* calcd for $C_{15}H_{22}NO_3S$: 296.1320, Found: 296.1322.

*4.13. Procedure for the preparation of Non-2-enoic acid methyl ester (**15a**):*

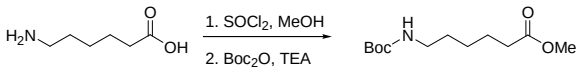



**14a** **15a**

Oxime **14a** (177 mg, 0.60 mmol) was dissolved in 1*N* HCl in MeOH (10 mL). Then, the reaction mixture was heated to reflux for 12 h and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to afford **15a**.

Colorless liquid; yield 72%; $^1$H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.23-1.35 (m, 6H), 1.45 (quin, *J* = 7.5 Hz, 2H), 2.20 (q, *J* = 7.5 Hz, 2H), 3.73 (s, 3H), 5.82 (d, *J* = 15.5 Hz, 1H), 6.97 (dt, *J* = 7.5, 15.5 Hz, 1H) ppm; $^{13}$C NMR δ 14.3, 22.8, 28.2, 29.0, 31.8, 32.4, 51.6, 121.0, 150.0, 167.4 ppm; IR (film): 2930, 1727, 1270 cm$^{-1}$; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{10}H_{18}O_2$: 170.1307, Found: 170.1311.

*4.14. Procedure for the preparation of 6-tert-butoxycarbonyl-aminohexanoic acid methyl ester (**17**):*

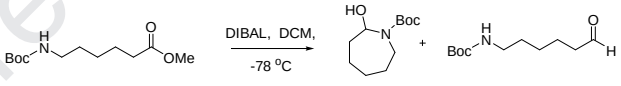



**16** 2 step 92% **17**

6-Aminohexanoic acid (**16**) (13.12 g, 100.0 mmol) was dissolved in methanol (200 mL). The solution was cooled down to 0 ºC, and thionyl chloride (8.7 mL, 120 mmol) was added dropwise into the stirred solution. Then, the reaction mixture was warmed to room temperature and stirred overnight. Then it was concentrated on a rotary evaporator under reduced pressure and dissolved in dichloromethane (200 mL) and triethylamine (34.8 mL, 250 mmol). Di-*tert*-butyldicarbonate (22.91 g, 105.0 mmol) in dichloromethane (50 mL) was added dropwise into the reaction mixture, which was stirred for 12 hr. Then, the reaction mixture was extracted with dichloromethane (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 5:1) to afford **17**.

Colorless liquid; yield 92%; $^1$H NMR δ 1.34 (quin, *J* = 7.5 Hz, 2H), 1.44 (s, 9H), 1.46-1.53 (quin, *J* = 7.5 Hz, 2H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 3.07-3.15 (m, 2H), 3.67 (s, 3H), 4.52 (br s, 1H) ppm; $^{13}$C NMR δ 24.8, 26.5, 28.6, 29.9, 34.1, 40.6, 51.7, 79.2, 156.2, 174.2 ppm; IR (film): 2936, 1738, 1712, 1522, 1171 cm$^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{12}H_{24}NO_4$: 246.1705, Found: 246.1697.

*4.15. Procedure for the preparation of a mixture of a cyclic and an acyclic form of 6-tert-butoxycarbonylaminohexanal (**18** + **19**):*

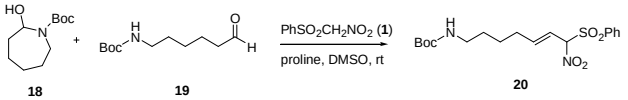



**17** **18** **19**

To a solution of **17** (3.46 g, 14.1 mmol) in 30 mL of anhydrous dichloromethane at -78 °C was slowly added DIBAL-H (1 M solution in dichloromethane, 19.7 mL, 19.7 mmol) under nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred at -78 ºC for 0.5 h and then quenched by addition of MeOH (1.0 mL) and aqueous saturated solution of Rochelle salt (20 mL). Then, the reaction mixture was allowed to warm up to room temperature and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 5:1) to afford the mixture of **18** and **19**.

Colorless oil; yield 76%; $^1$H NMR (major **19**) δ 1.30-1.40 (m, 2H), 1.44 (s, 9H), 1.46-1.53 (m, 2H), 1.65 (qin, *J* = 7.5 Hz, 2H), 2.44 (td, *J* = 1.0, 7.5 Hz, 2H), 3.12 (d, *J* = 6.0 Hz, 2H) 4.52 (br s, 1H), 9.77 (s, 1H) ppm; $^{13}$C NMR (a mixture of **18** and **19**) δ 21.9, 24.6, 26.4, 28.5, 29.9, 30.0, 34.0, 40.5, 44.0, 79.3, 156.2, 177.3, 202.7 ppm; IR (film): 1700, 1522, 1169 cm$^{-1}$; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{11}H_{22}NO_3$: 216.1600, Found: 216.1598.

*4.16. Procedure for the preparation of (7-Benzenesulfonyl-7-nitro-hept-5-enyl)carbamic acid tert-butyl ester (**20**):*



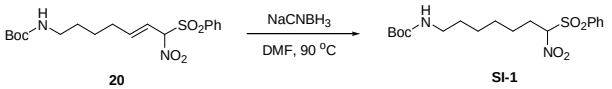

**18** **19** **20**

To a solution of phenylsulfonylnitromethane (**1**) (402 mg, 2.00 mmol) in DMSO (2.0 mL) were added at room temperature a mixture of a cyclic and an acyclic form of an amino aldehyde **18** + **19** (2.00 mmol), proline (12 mg, 0.10 mmol), and pentaerythritol tetrakis(3,5-di-*tert*-butyl-4-hydroxyhydro-

cinnamate) (6 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, a mixture of a cyclic and an acyclic form of an amino aldehyde **18** + **19** (0.60 mmol) was added again to the reaction mixture, which was stirred at room temperature for 24 h. The mixture was diluted with ether (20 mL) and aqueous $NH_4Cl$ solution (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 5:1 to hexane:EtOAc = 3:1) to afford **20**. The yield was calculated based on the amount of phenylsulfonylnitromethane (**1**).

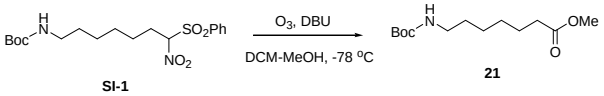
Colorless oil; yield 72%; $^1$H NMR (400 MHz) δ 1.38-1.57 (m, 13H), 2.20 (q, *J* = 6.8 Hz, 2H), 3.10-3.17 (m, 2H), 4.54 (br s, 1H), 5.69 (dd, *J* = 9.6, 15.2 Hz, 1H), 5.89 (d, *J* = 9.6 Hz, 2H), 6.15 (dt, *J* = 6.8, 15.2 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 2H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 2H) ppm; $^{13}$C NMR δ 25.4, 28.6, 29.6, 32.4, 40.3, 79.3, 103.5, 115.3, 129.6, 130.4, 134.3, 135.6, 146.9, 156.2 ppm; IR (film): 1697, 1562, 1340, 1159 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{18}H_{27}N_2O_6S$: 399.1590, Found: 399.1589.

*4.17. Procedure for the preparation of 7-tert-Butoxycarbonyl-aminoheptanoic acid methyl ester (**21**):*




To a solution of **20** (797 mg, 2.00 mmol) in DMF (10 mL) was added at room temperature sodium cyanoborohydride (377 mg, 6.0 mmol). The reaction mixture was stirred overnight at 90 ºC and quenched with aqueous $NH_4Cl$ solution. Then, the reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 7:1 to hexane:EtOAc = 5:1) to afford **SI-1**.

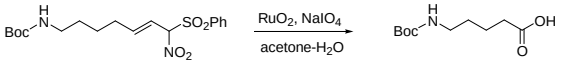
White solid; yield 80%; mp 80-81 ºC; $^1$H NMR δ 1.24-1.33 (m, 2H), 1.33-1.40 (m, 4H), 1.40-1.48 (m, 11H), 2.17-2.30 (m, 2H), 3.08 (q, *J* = 7.0 Hz, 2H), 4.48 (br s, 1H), 5.48 (dd, *J* = 4.0, 10.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H) ppm; $^{13}$C NMR δ 25.5, 26.4, 27.9, 28.5, 28.6, 30.0, 40.5, 79.3, 102.5, 129.7, 130.2, 134.2, 135.7, 156.2 ppm; IR (film): 1698, 1562, 1339, 1160 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{18}H_{29}N_2O_6S$: 401.1746, Found: 401.1742.




To a solution of **SI-1** (400 mg, 1.00 mmol) in dichloromethane (5 mL) and MeOH (5 mL) was added at 0 ºC in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3.0 mmol). The reaction mixture was stirred for 10 min and replaced in a Dewar bath containing dry ice/acetone. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ºC. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.10 mL, 1.3 mmol) and acetic acid (1.0 mL) at -78 ºC, allowed to warm up to room temperature, and stirred for 1 hr. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1) to afford **21**.

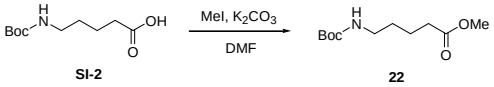
Colorless oil; yield 81%; $^1$H NMR δ 1.28-1.38 (m, 4H), 1.44 (s, 9H), 1.44-1.51 (m, 2H),1.63 (quin, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.10 (q, J = 7.5 Hz, 2H), 3.67 (s, 3H), 4.50 (br s, 1H) ppm; $^{13}$C NMR δ 25.0, 26.6, 28.5, 28.9, 30.0, 34.1, 40.6, 51.6, 79.1, 156.1, 174.3 ppm; IR (film): 1738, 1712, 1521, 1250, 1171 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{13}H_{26}NO_4$: 260.1862, Found: 260.1860.

*4.18. Procedure for the preparation of 5-tert-Butoxycarbonyl-aminopentanoic acid methyl ester (**22**):*




A solution of **20** (199 mg, 0.50 mmol) in acetone (15 mL) was stirred 0 ºC in an ice bath, and a yellow solution containing $NaIO_4$ (802 mg, 3.75 mmol) and 51% $RuO_2$ (8 mg) in $H_2O$ (5 mL) was added. After the ice bath was removed, the reaction mixture was stirred for 20 min while adjusting its pH to *ca*. 4 by adding aqueous saturated $NaHCO_3$ solution. Then, 2-propanol (1.0 mL) was added and further stirring was continued for 10 min. The reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 1:1 to hexane:EtOAc = 1:2) to afford **SI-2**.

White solid; yield 70%; mp 49-50 ℃; $^1$H NMR δ 1.44 (s, 9H), 1.54 (quin, *J* = 7.5 Hz, 2H), 1.67 (quin, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.05-3.19 (m, 2H), 4.58 (br s, 1H) ppm; $^{13}$C NMR δ 22.1, 28.6, 29.6, 33.8, 40.3, 79.5, 156.3, 178.9 ppm; IR (film): 3342, 1708, 1525, 1251, 1169 cm$^{-1}$.




To a solution of **SI-2** (100 mg, 0.46 mmol) and $K_2CO_3$ (190 mg, 1.38 mmol) in DMF (10 mL) was added iodomethane (57 μL, 0.92 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (gradient eluent from hexane:EtOAc = 9:1 to hexane:EtOAc = 7:1) to afford **22**.

Yellowish oil; yield 98%; $^1$H NMR δ 1.44 (s, 9H), 1.51 (quin, *J* = 7.5 Hz, 2H), 1.66 (quin, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.13 (q, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 4.55 (br s, 1H) ppm; $^{13}$C NMR δ 22.2, 28.6, 29.6, 33.7, 40.2, 51.6, 79.2, 156.1, 174.0 ppm; IR (film): 1737, 1711, 1522, 1250, 1170 cm$^{-1}$; HRMS (CI, [M+H]$^+$) *m/z* calcd for $C_{11}H_{22}NO_4$: 232.1549, Found: 232.1549.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.******.

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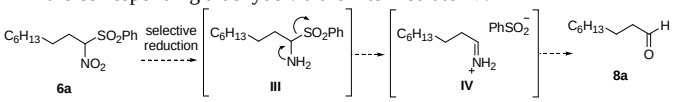


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**Highlights**

- produce both one-carbon shorter and one-carbon longer homologous compounds
- proline-catalyzed sequential reactions of aliphatic aldehydes with phenylsulfonylnitromethane
- the preference of β,γ-unsaturated α-nitrosulfone over α,β-unsaturated α-nitrosulfone

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: