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Synthesis of Carbo- and Heterocyclic Aldehydes Bearing an Adjacent Donor Group – Ozonolysis *versus* OsO_4/KIO_4-Oxidation

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Summary. The synthesis of carbo- and heterocyclic aldehydes bearing an *ipso*-methoxy group is investigated. The synthetic sequence is based on an initial *Grignard* addition of an olefin to a cyclic ketone followed by methylation of the resulting tertiary alcohol. The terminal olefin serves as precursor for the aldehyde functionality. Oxidation by ozonolysis turned out to depend significantly on the distance of the donor methoxy group. The observed side reactions could be circumvented by applying a one-pot OsO_4 mediated diol formation followed by *Malaprade* oxidation using KIO_4. A series of carbo- and heterocyclic precursors were successfully converted to the title products.

Keywords. Oxidation; Ozonolysis; *Malaprade* reaction; Osmium tetroxide; Potassium periodate.

Introduction

Recently we presented a facile and convenient one-pot procedure for the synthesis of β-lactams from imines and various carboxylic acids in a *Staudinger* process (Scheme 1) [1]. We utilized such structures in a bioreductive approach to paclitaxel [2] and analogs [3] as efficient cytostatics. In an ongoing research program we required access to such compounds with sterically demanding and structurally rigid substituents bearing a donor group as versatile building blocks for the preparation of bioactive compounds [4].

In this publication we disclose our synthetic efforts to the required aldehyde precursors with a methoxy donor functionality (Scheme 2). Retrosynthetic analysis suggested a straightforward entry starting from corresponding ketone precursors as

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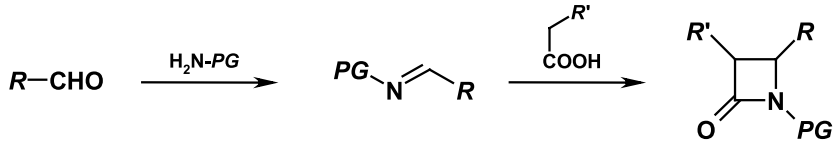
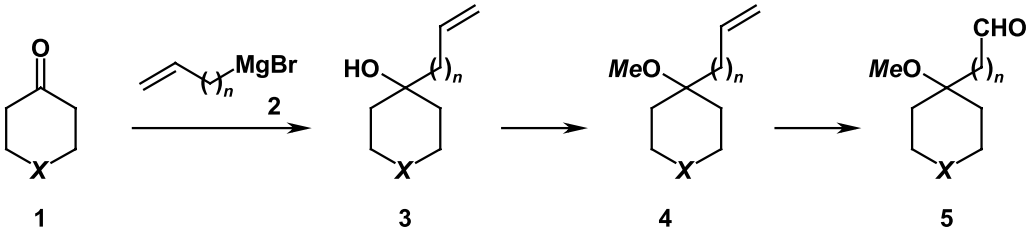


Scheme 1

commodity compounds. The aldehyde functionality was planned to be generated from an olefin *via* oxidation at a later stage. Two major methods are available for such a conversion: (i) transformation of an olefin into a 1,2-diol and subsequent cleavage [5]; (ii) direct ozonolysis of an alkene [6]. Consequently, an olefin moiety served as masked aldehyde group and the corresponding *Grignard* reagent was an obvious first choice to generate the quaternary center. The route to aldehydes **5** is outlined in Scheme 2.

Results and Discussion

Addition of vinyl *Grignard* compound **2a** was based on a procedure by *Marcou* and *Normant* [7] and a series of carbo- and heterocyclic ketones was converted to alcohols **3a**–**3g** (Table 1). The products were usually pure enough to be introduced



Scheme 2

Table 1. Compiled results of the synthetic sequence towards aldehydes **5**

Ketone	*X*	*n*	*Grignard* addition		Methylation		Olefin oxidation	
			Alcohol	Yield/%	Ether	Yield/%	Aldehyde	Yield/%
1a	–	0	**3a**	69	**4a**	71	**5a**[a]	25
1b	CH_2	0	**3b**	66	**4b**	81	**5b**[a]	33
1c	$(CH_2)_2$	0	**3c**	86	**4c**	87	**5c**[a]	56
1d	O	0	**3d**	69	**4d**	76	**5d**[a]	96
1e	N-*Boc*	0	**3e**	98	**4e**	89	**5e**[a]	96
1f	N-COO*Me*	0	**3f**	86	**4f**	97	**5f**[a]	20
1g	N-*Tos*	0	**3g**	98	**4g**	87	**5g**[a]	42
1a	–	1	**3h**	98	**4h**	87	**5h**[b]	64
1b	CH_2	1	**3i**	83	**4i**	83	**5i**[b]	74
1c	$(CH_2)_2$	1	**3j**	96	**4j**	87	**5j**[b]	74

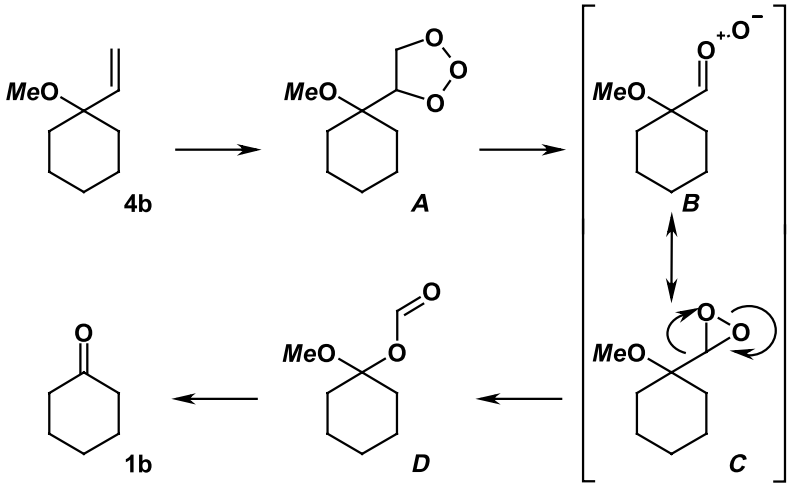
[a] OsO_4/KIO_4 oxidation; [b] ozonolysis

directly into the next step or were purified by Kugelrohr distillation. Preparation of the corresponding methyl ethers **4a**–**4g** was carried out with NaH and one equivalent of dimethyl sulfate in excellent yields [8]. The slightly decreased yield for **4a** can be explained by the volatility of the compound.

First aldehyde formation *via* ozonolysis was performed in analogy to a report by *Clark et al.* [9], where a similar vinyl group adjacent to a quaternary carbon center bearing a protected peroxo group was converted to the corresponding carbonyl functionality. The reaction with **4b** was carried out in dry *Me*OH at $-65 \pm 5^{\circ}$C using Me_2S to quench the secondary ozonide and the starting material was completely consumed. Although a tenfold excess of Me_2S was used, over-oxidation to the corresponding carboxylic acid [10] was observed, however. Only traces of the desired aldehyde **5b** were detected. Changing from methylene chloride to methanol as solvent did not improve the yield of **5b**.

Consequently, we carried out the reaction in the presence of tetracyanoethene as reducing agent to avoid over-oxidation [11]. While this modification decreased the amount of carboxylic acid produced to some extent, a new side reaction was observed: significant amounts of cyclohexanone (**1b**) were detected in the crude reaction mixture after work-up. We attribute the formation of this unexpected compound to a so called ''abnormal'' ozonolysis process [12]. This reaction pathway can be observed when substituents with strong +I- or +M-effects are present adjacent to the C–C double bond, as demonstrated for groups OH, O*R*, and OCO*R*. In the case of **1b** both the +M-effect of the methoxy group and the +I-effect of an adjacent quaternary carbon seem to promote this alternative pathway for ozonolysis, as outlined in Scheme 3.

After the formation of the primary ozonide ***A*** the rearrangement process towards the secondary ozonide proceeds *via* the *zwitterionic* form ***B*** and its mesomeric structure ***C***. In the case of strong donating effects at the quaternary center a migration reaction can take place to form the ester ***D***. This of course represents a very susceptible structure to hydrolysis upon aqueous work-up to finally generate



Scheme 3

the ketone **1b**. Although this undesired pathway could be suppressed to some extent by the utilization of protic solvents and addition of reducing agents (Me_2S), the amount of aldehyde **5b** could not be increased to more than 10% according to NMR based on the crude material after work-up.

These findings prompted us to extend our study to the corresponding homologs **4h**–**4j** with an additional methylene moiety between the quaternary center an the terminal olefin. Synthesis of these compounds was carried out according to the above methodology (Table 1). As expected, the ozonolysis in methanol followed by quenching with Me_2S proceeded smoothly to the corresponding aldehydes **5h**–**5j** in this series. This further supports our hypothesis of the significant influence of the adjacent quaternary center bearing a donor functionality.

In order to complete our synthetic route to aldehydes **5a**–**5g** we utilized a two-step sequence based on 1,2-diol oxidation followed by *Malaprade* type cleavage. Such transformations have been developed into one-pot protocols based on catalytic amounts of $RuCl_3$ [13] or OsO_4 [14] in the presence on an additional oxidant. We chose KIO_4 as suitable oxidant for both regeneration of the OsO_4 and diol cleavage and the reaction was carried out in a mixture of *THF* and water. Isolated yields of aldehydes **5a**–**5g** were moderate to good. All aldehydes **5a**–**5j** required storage at $-20°C$ in inert atmosphere after purification to avoid oxidation to the corresponding acids upon exposure to air. Especially in the case of volatile products **5a** and **5b** removal of solvent by distillation led to decreased yields. However, considering the range of functionally different precursors, the methodology allows access to a large variety of sterically demanding aldehydes bearing a donor group.

Conclusion

We have developed a general synthetic route to sterically demanding olefin precursors bearing a donor functionality for the subsequent oxidative formation of aldehydes. While ozonolysis failed to give the desired products **5** in those cases, when the alkene was directly attached to a quaternary carbon center, the homologs with an additional methylene linker gave smooth oxidation to the aldehydes. A mechanistic rationale was developed for the observed side products based on the ''abnormal'' ozonolysis concept.

Alternatively, the oxidation of the olefin substrates by OsO_4 in presence of KIO_4 as both regenerating oxidant for osmium and reagent for the 1,2-diol cleavage was demonstrated to circumvent the obstacles of the ozonolysis. Using a one-pot protocol, aldehydes **5a**–**5g** were prepared in moderate to excellent yields from a broad range of carbo- and heterocyclic precursors.

We consider the two complementary strategies as versatile and convenient methods to access the desired aldehydes as valuable intermediates for subsequent bioactive compound synthesis.

Experimental

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Flash column chromatography was performed on silica gel 60 from Merck (40–63 μm). Kugelrohr distillation was carried out using a Büchi

GKR-51 apparatus. Melting points were determined using a *Kofler*-type Leica Galen III micro hot stage microscope and are uncorrected. NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) or Bruker Avance UltraShield 400 (400 MHz) spectrometer and chemical shifts are reported in ppm using *TMS* as internal standard.

General Procedure for Grignard Addition

The Grignard reagent (1.3 equiv of commercial vinyl magnesium bromide, 1 *M* in *THF*; 1.5 equiv of freshly prepared allyl magnesium bromide [15], 10% solution in dry diethyl ether) was added to a solution of **1** (1 equiv, 10% in dry diethyl ether) at $-5 \pm 5°C$. The reaction mixture was kept at this temperature for 2 h and then warmed to room temperature. Stirring was continued until TLC showed complete conversion (2–12 h). The mixture was hydrolyzed with NH_4Cl solution (10%) and extracted with diethyl ether. The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and concentrated.

1-Ethenylcyclopentanol (**3a**)

Cyclopentanone (**1a**, 5.00 g, 59 mmol) was converted with vinyl magnesium bromide according to the above procedure to give 4.54 g of **3a** [7] (69%) as colorless liquid after Kugelrohr distillation; bp 80–90°C/16 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.53$–2.00 (m, 8H), 5.05 (dd, $J = 9$, ~1 Hz, 1H), 5.27 (dd, $J = 16$, ~1 Hz, 1H), 6.03 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 23.7$ (t), 40.2 (t), 82.1 (s), 111.0 (t), 144.4 (d) ppm.

1-Ethenylcyclohexanol (**3b**)

Cyclohexanone (**1b**, 7.00 g, 71 mmol) was converted with vinyl magnesium bromide according to the above procedure to give 5.92 g of **3b** [7] (66%) as colorless liquid after distillation; bp 71°C/16 mbar; ^{1}H NMR (200 MHz): $\delta = 1.35$–1.75 (m, 10H), 4.97 (dd, $J = 13$, ~1 Hz, 1H), 5.16 (dd, $J = 16$, ~1 Hz, 1H), 5.92 (dd, $J = 16$, 12.7 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.9$ (t), 25.5 (t), 37.5 (t), 71.7 (s), 111.4 (t), 146.0 (d) ppm.

1-Ethenylcycloheptanol (**3c**)

Cycloheptanone (**1c**, 5.00 g, 45 mmol) was converted with vinyl magnesium bromide according to the above procedure to give 5.30 g of **3c** [7] (86%) as colorless liquid after Kugelrohr distillation; bp 125–130°C/20 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.32$–2.10 (m, 12H), 5.00 (dd, $J = 9$, ~1 Hz, 1H), 5.20 (dd, $J = 16$, ~1 Hz, 1H), 6.02 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 22.1$ (t), 29.5 (t), 41.1 (t), 75.6 (s), 110.1 (t), 146.6 (d) ppm.

1-Ethenyltetrahydropyran-4-ol (**3d**)

Tetrahydropyran-4-one (**1d**, 5.00 g, 50 mmol) was converted with vinyl magnesium bromide according to the above procedure to give 4.42 g of **3d** [16] (69%) as colorless liquid after Kugelrohr distillation; bp 145–150°C/11 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.40$–1.58 (m, 2H), 1.70–1.90 (m, 2H), 2.19 (bs, 1H), 3.58–3.90 (m, 4H), 5.10 (dd, $J = 12.7$, ~1 Hz, 1H), 5.26 (dd, $J = 16$, ~1 Hz, 1H), 5.99 (dd, $J = 16$, 12.7 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 37.3$ (t), 63.5 (t), 68.9 (s), 112.2 (t), 145.0 (d) ppm.

4-Ethenyl-4-hydroxypiperidin-1-carboxylic acid 1,1-dimethylethyl ester (**3e**)

4-Oxopiperidin-1-carboxylic acid 1,1-dimethylethyl ester (**1e**, 5.00 g, 25 mmol) was converted with vinyl magnesium bromide according to the above procedure to give 5.56 g of **3e** [16] (98%) as beige oil

after Kugelrohr distillation; bp 205–210°C/11 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.45$ (s, 9H), 1.50–1.90 (m, 4H), 3.11–3.30 (m, 2H), 3.70–3.89 (m, 2H), 5.10 (dd, $J = 9$, ~1 Hz, 1H), 5.27 (dd, $J = 16$, ~1 Hz, 1H), 5.94 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 28.3$ (q), 28.4 (q), 36.6 (t), 41.1 (t), 39.6 (bt), 42.9 (bt), 70.0 (s), 79.4 (s), 80.4 (s), 112.3 (t), 144.9 (d), 154.8 (s) ppm (carbon NMR showed presence of E/Z isomers).

4-Ethenyl-4-hydroxypiperidin-1-carboxylic acid methyl ester (**3f**, $C_9H_{15}NO_3$)

4-Oxopiperidin-1-carboxylic acid methyl ester (**1f**, 3.05 g, 19 mmol) was converted with vinyl magnesium bromide according to the above procedure to give 3.10 g of **3f** (86%) as beige oil; ^{1}H NMR (200 MHz): $\delta = 1.45$–1.84 (m, 4H), 3.10–3.39 (m, 2H), 3.70 (s, 3H), 3.71–3.99 (m, 2H), 5.10 (dd, $J = 9$, ~1 Hz, 1H), 5.28 (dd, $J = 16$, ~1 Hz, 1H), 5.94 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 36.5$ (t), 39.7 (t), 52.5 (q), 69.8 (s), 112.4 (t), 144.8 (d), 155.9 (s) ppm.

1-[(4-Methylphenyl)sulfonyl]-4-ethenylpiperidin-4-ol (**3g**, $C_{14}H_{19}NO_3S$)

1-[(4-Methylphenyl)sulfonyl]piperidin-4-one (**1g**, 5.00 g, 26 mmol) was converted with vinyl magnesium bromide according to the above procedure to give 5.45 g of **3g** (98%) as beige crystals; mp 95–98°C; ^{1}H NMR (200 MHz): $\delta = 1.30$–1.97 (m, 4H), 2.45 (s, 3H), 2.60–2.80 (m, 2H), 3.45–3.80 (m, 2H), 5.08 (dd, $J = 9$, ~1 Hz, 1H), 5.22 (dd, $J = 16$, ~1 Hz, 1H), 5.90 (dd, $J = 16$, 9 Hz, 1H), 7.32 (d, $J = 6$ Hz, 2H), 7.64 (d, $J = 6$ Hz, 2H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.5$ (q), 36.2 (t), 42.0 (t), 69.0 (s), 112.7 (t), 127.6 (d), 129.6 (d), 133.4 (s), 143.4 (s), 144.5 (d) ppm.

1-(2-Propenyl)cyclopentanol (**3h**)

Cyclopentanone (**1a**, 10 cm^3, 113 mmol, 9.52 g) was converted with freshly prepared allyl magnesium bromide according to the above procedure to give 13.52 g of **3h** [17] (98%) as colorless liquid; ^{1}H NMR (200 MHz): $\delta = 1.55$–1.82 (m, 9H), 2.34 (d, $J = 7$ Hz, 2H), 5.02–5.12 (m, 1H), 5.17 (bs, 1H), 5.80–6.01 (m, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 23.8$ (t), 39.3 (t), 45.8 (t), 81.3 (s), 118.3 (t), 134.6 (d) ppm.

1-(2-Propenyl)cyclohexanol (**3i**)

Cyclohexanone (**1b**, 9.02 g, 92 mmol) was converted with freshly prepared allyl magnesium bromide according to the above procedure to give 10.69 g of **3i** [17] (83%) as colorless liquid; ^{1}H NMR (200 MHz): $\delta = 1.12$–1.75 (m, 11H), 2.21 (d, $J = 7$ Hz, 2H), 5.05–5.17 (m, 2H), 5.82–6.03 (m, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 22.1$ (t), 25.7 (t), 37.3 (t), 46.7 (t), 70.9 (s), 118.5 (t), 133.7 (d) ppm.

1-(2-Propenyl)cycloheptanol (**3j**)

Cycloheptanone (**1c**, 9.50 g, 85 mmol) was converted with freshly prepared allyl magnesium bromide according to the above procedure to give 12.60 g of **3j** [17] (97%) as colorless oil; ^{1}H NMR (200 MHz): $\delta = 1.22$–1.70 (m, 13H), 2.20 (d, $J = 10$ Hz, 2H), 5.00–5.22 (m, 2H), 5.75–6.05 (m, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 22.3$ (t), 29.7 (t), 41.0 (t), 47.8 (t), 74.8 (s) 118.5 (t), 134.1 (d) ppm.

General Procedure for O-Methylation

Alcohol **1** (1 equiv) was added to a suspension (5%) of NaH (3 equiv) in dry *THF*. After refluxing for 2 h the mixture was cooled to room temperature and dimethyl sulfate (1.2 equiv) was added slowly.

The resulting mixture was refluxed overnight, cooled to room temperature, and hydrolyzed with ice cooled NH_4Cl solution. After extraction with diethyl ether, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated.

1-Ethenyl-1-methoxycyclopentane (**4a**)

Alcohol **3a** (4.50 g, 40 mmol) was converted according to the above procedure to give 3.58 g of **4a** [18] (71%) as colorless liquid after Kugelrohr distillation; bp 50–60°C/24 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.50$–1.91 (m, 8H), 3.13 (s, 3H), 5.10–5.22 (m, 2H), 5.88 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 23.0$ (t), 35.4 (t), 50.7 (q), 87.0 (s), 114.1 (t), 140.9 (d) ppm.

1-Ethenyl-1-methoxycyclohexane (**4b**)

Compound **3b** (4.89 g, 38 mmol) was converted according to the above procedure to give 4.36 g of **4b** [19] (81%) as colorless liquid after Kugelrohr distillation; bp 75–80°C/22–40 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.10$–1.82 (m, 10H), 3.11 (s, 3H), 5.01–5.23 (m, 2H), 5.71 (dd, $J = 16$, 12.7 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.7$ (t), 25.7 (t), 33.8 (t), 49.2 (q), 75.6 (s), 114.7 (t), 142.8 (d) ppm.

1-Ethenyl-1-methoxycycloheptane (**4c**, $C_{10}H_{18}O$)

Product **3c** (5.38 g, 38 mmol) was converted according to the above procedure to give 5.13 g of **4c** (87%) as colorless liquid after Kugelrohr distillation; bp 115–120°C/30 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.30$–1.90 (m, 12H), 3.12 (s, 3H), 5.05–5.20 (m, 2H), 5.72 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.6$ (t), 29.5 (t), 36.8 (t), 49.8 (q), 80.0 (s), 113.8 (t), 143.6 (d) ppm.

4-Ethenyl-4-methoxytetrahydropyrane (**4d**, $C_8H_{14}O_2$)

Alcohol **3d** (4.00 g, 31 mmol) was converted according to the above procedure to give 3.32 g of **4d** (76%) as colorless liquid; ^{1}H NMR (200 MHz): $\delta = 1.70$ (t, $J = 6$ Hz, 4H), 3.11 (s, 3H), 3.58–3.81 (m, 4H), 5.16 (dd, $J = 9$, ~1 Hz, 1H), 5.22 (dd, $J = 16$, ~1 Hz, 1H), 5.69 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 33.9$ (t), 49.4 (q), 63.5 (t), 73.3 (s), 115.7 (t), 141.4 (d) ppm.

4-Ethenyl-4-methoxypiperidin-1-carboxylic acid 1,1-dimethylethyl ester (**4e**, $C_{13}H_{21}NO_3$)

Compound **3e** (5.56 g, 25 mmol) was converted according to the above procedure to give 5.25 g of **4e** (89%) as colorless oil after flash column chromatography (SiO_2, *LP*:*EtOAc* = 5:1); ^{1}H NMR (200 MHz): $\delta = 1.45$ (s, 9H), 1.50–1.90 (m, 4H), 3.05–3.30 (m, 2H), 3.14 (s, 3H), 3.47–3.98 (m, 2H), 5.17 (dd, $J = 9$, ~1 Hz, 1H), 5.25 (dd, $J = 16$, ~1 Hz, 1H), 5.72 (dd, $J = 16$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 28.4$ (q), 33.0 (bt), 39.5 (bt), 49.6 (q), 74.0 (s), 79.3 (s), 115.8 (t), 141.5 (d), 154.9 (s) ppm.

4-Ethenyl-4-methoxypiperidin-1-carboxylic acid methyl ester (**4f**, $C_{10}H_{17}NO_3$)

Product **3f** (3.10 g, 17 mmol) was converted according to the above procedure to give 3.22 g of **4f** (97%) as colorless oil; ^{1}H NMR (200 MHz): $\delta = 1.48$–1.89 (m, 4H), 3.14 (s, 3H), 3.08–3.30 (m, 2H), 3.70 (s, 3H), 3.71–3.93 (m, 2H), 5.17 (dd, $J = 19$, ~1 Hz, 1H), 5.24 (dd, $J = 9$, ~1 Hz, 1H), 5.27 (dd, $J = 19$, 9 Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 32.9$ (t), 39.5 (t), 49.5 (q), 52.4 (q), 73.8 (s), 115.8 (t), 141.3 (d), 155.9 (s) ppm.

4-Ethenyl-4-methoxy-1-[(4-methylphenyl)sulfonyl]piperidine (**4g**, $C_{15}H_{21}NO_3S$)

Alcohol **3g** (9.84 g, 35 mmol) was converted according to the above procedure to give 8.94 g of **4g** (87%) as beige oil; ^{1}H NMR (200 MHz): $\delta = 1.60–1.96$ (m, 4H), 2.45 (s, 3H), 2.57–2.74 (m, 2H), 3.01 (s, 3H), 3.45–3.60 (m, 2H), 5.14 (dd, $J = 9$, ~1 Hz, 1H), 5.22 (dd, $J = 16$, ~1 Hz, 1H), 5.68 (dd, $J = 16$, 9 Hz, 1H), 7.32 (d, $J = 6$ Hz, 2H), 7.68 (d, $J = 6$ Hz, 2H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.4$ (q), 32.5 (t), 41.7 (t), 49.4 (q), 72.9 (s), 116.0 (t), 127.5 (d), 129.6 (d), 133.4 (s), 140.9 (d), 143.4 (s) ppm.

1-Methoxy-1-(2-propenyl)cyclopentane (**4h**, $C_9H_{16}O$)

Compound **3h** (13.52 g, 107 mmol) was converted according to the above procedure to give 13.04 g of **4h** (87%) as beige liquid after distillation; bp 83–84°C/81 mbar; ^{1}H NMR (200 MHz): $\delta = 1.38–1.89$ (m, 8H), 2.35 (d, $J = 7$ Hz, 2H), 3.18 (s, 3H), 5.00–5.15 (m, 2H), 5.78–5.85 (m, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 23.8$ (t), 35.4 (t), 40.1(t), 49.5 (q), 86.3 (s), 116.8 (t), 134.8 (d) ppm.

1-Methoxy-1-(2-propenyl)cyclohexane (**4i**)

Product **3i** (10.69 g, 76 mmol) was converted according to the above procedure to give 9.70 g of **4i** [20] (83%) as beige liquid after distillation; bp 113–115°C/100 mbar; ^{1}H NMR (200 MHz): $\delta = 1.06–1.75$ (m, 10H), 2.12 (d, $J = 9$ Hz, 2H), 3.12 (s, 3H), 4.85–5.10 (m, 2H), 5.60–5.85 (m, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 19.7$ (t), 23.8 (t), 31.8 (t), 39.9 (t), 47.0 (q), 74.4 (s), 116.1 (t), 133.0 (d) ppm.

1-Methoxy-1-(2-propenyl)cycloheptane (**4j**, $C_{12}H_{20}O$)

Alcohol **3j** (12.57 g, 81 mmol) was converted according to the above procedure to give 12.00 g of **4j** (87%) as beige liquid after distillation; bp 112–115°C/40 mbar; ^{1}H NMR (200 MHz): $\delta = 1.06–1.90$ (m, 12H), 2.20 (d, $J = 10$ Hz, 2H), 3.20 (s, 3H), 4.90–5.20 (m, 2H), 5.70–6.00 (m, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 22.0$ (t), 29.7 (t), 37.2 (t), 42.3 (t), 48.5 (q), 79.0 (s), 117.0 (t), 134.4 (d) ppm.

General Procedure for OsO_4/KIO_4 Oxidation

A solution (5%) of ether **4** (1 equiv) in *THF*/H_2O (3/1) was treated with OsO_4 (0.05 equiv). Subsequently, KIO_4 (2 equiv) was added in portions over a period of 4 h and the reaction was stirred overnight at room temperature. Water was added to the mixture followed by repeated extraction with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated.

1-Methoxycyclopentanecarboxaldehyde (**5a**)

Ether **4a** (3.55 g, 28 mmol) was converted according to the above procedure to give 0.87 g of **5a** [18] (25%) as colorless liquid after Kugelrohr distillation; bp 60–65°C/100 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.60–1.90$ (m, 8H), 3.31 (s, 3H), 9.70 (s, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 24.3$ (t), 32.2 (t), 67.9 (q), 92.2 (s), 204.2 (d) ppm.

1-Methoxycyclohexanecarboxaldehyde (**5b**, $C_8H_{14}O_2$)

Compound **4b** (3.00 g, 21 mmol) was converted according to the above procedure to give 1.00 g of **5b** (33%) as colorless liquid after Kugelrohr distillation; bp 70–75°C/35 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.18–1.80$ (m, 10H), 3.28 (s, 3H), 9.51 (s, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 20.9$ (t), 25.1 (t), 28.5 (t), 51.7 (q), 81.0 (s), 204.9 (d) ppm.

1-Methoxycycloheptanecarboxaldehyde (**5c**, $C_9H_{16}O_2$)

Product **4c** (5.10 g, 33 mmol) was converted according to the above procedure to give 2.86 g of **5c** (56%) as colorless liquid after Kugelrohr distillation; bp 130–135°C/15 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.40$–1.85 (m, 12H), 3.25 (s, 3H), 9.50 (s, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.5$ (t), 29.6 (t), 31.3 (t), 52.0 (q), 84.9 (s), 204.5 (d) ppm.

4-Methoxytetrahydropyran-4-carboxaldehyde (**5d**)

Olefin **4d** (4.30 g, 30 mmol) was converted according to the above procedure to give 4.25 g of **5d** [21] (95%) as colorless liquid; ^{1}H NMR (200 MHz): $\delta = 1.63$–1.95 (m, 4H), 3.31 (s, 3H), 3.66–3.81 (m, 4H), 9.53 (s, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 28.8$ (t), 51.9 (q), 62.9 (t), 78.7 (s), 203.2 (d) ppm.

4-Formyl-4-methoxypiperidin-1-carboxylic acid 1,1-dimethylethyl ester (**5e**)

Alkene **4e** (5.25 g, 27 mmol) was converted according to the above procedure to give 5.07 g of **5e** [22] (96%) as colorless liquid after Kugelrohr distillation; bp 145–150°C/0.2 mbar (KRD); ^{1}H NMR (200 MHz): $\delta = 1.28$–1.50 (m, 9H), 1.50–1.79 (m, 4H), 3.00–3.28 (m, 2H), 3.25 (s, 3H), 9.50 (s, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 28.1$ (t), 28.3 (q), 38.7 (t), 52.1 (q), 79.6 (s), 154.5 (s), 203.6 (d) ppm.

4-Formyl-4-methoxypiperidin-1-carboxylic acid methyl ester (**5f**, $C_9H_{15}NO_4$)

Ether **4f** (3.22 g, 16 mmol) was converted according to the above procedure to give 0.65 g of **5f** (20%) as colorless liquid after flash column chromatography (SiO_2, *LP*:*Et*OA*c* = 4:1); ^{1}H NMR (200 MHz): $\delta = 1.64$–1.88 (m, 4H), 3.16–3.32 (m, 2H), 3.31 (s, 3H), 3.70 (s, 3H), 3.71–3.92 (m, 2H), 9.58 (s, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 28.0$ (t), 38.8 (t), 52.0 (q), 52.4 (q), 79.4 (s), 155.6 (s), 203.3 (d) ppm.

4-Methoxy-1-[(4-methylphenyl)sulfonyl]piperidin-4-carboxaldehyde (**5g**, $C_{14}H_{19}NO_4S$)

Compound **4g** (6.80 g, 23 mmol) was converted according to the above procedure to give 2.88 g of **5g** (42%) as colorless crystals after flash column chromatography (SiO_2, *LP*:*Et*OA*c* = 4:1); mp 98–102°C; ^{1}H NMR (200 MHz): $\delta = 1.75$–1.97 (m, 4H), 2.45 (s, 3H), 2.62–2.82 (m, 2H), 3.20 (s, 3H), 3.37–3.58 (m, 2H), 7.32 (d, $J = 6$ Hz, 2H), 7.65 (d, $J = 6$ Hz, 2H), 9.51 (s, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.5$ (q), 27.9 (t), 41.3 (t), 52.0 (q), 78.6 (s), 127.6 (d), 129.8 (d), 133.4 (s), 143.6 (s), 203.0 (d) ppm.

General Procedure for Ozonolysis

The alkene **4** was dissolved in dry *Me*OH (5% solution) and cooled to −80°C. Ozone generated by a Sander laboratory ozonizer (1 bar pre-pressure, 0.4 A, 4 cm^3) was passed through the reaction mixture until the solution got dark blue. This process was repeated until the blue color remained for more than 10 min. Dry N_2 was passed through the reaction mixture to remove excess of ozone. The reaction was quenched by addition of dimethylsulfide (10 equiv) and slowly warmed to room temperature upon stirring overnight. Subsequent removal of solvents gave the crude aldehydes, which were purified by flash column chromatography.

1-Methoxycyclopentane-1-acetaldehyde (**5h**, $C_8H_{14}O_2$)

Ether **4h** (1.00 g, 7.1 mmol) was converted according to the above procedure to give 0.65 g of **5h** (64%) as colorless liquid after flash column chromatography (SiO_2, *LP*:*Et*OA*c* = 5:1); ^{1}H NMR (200 MHz):

$\delta = 1.48–1.85$ (m, 6H), 1.92–2.09 (m, 2H), 2.63 (d, $J = 3$ Hz, 2H), 3.21 (s, 3H), 9.81 (t, $J = 2$ Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 23.4$ (t), 36.0 (t), 40.9 (t), 49.3 (t), 49.8 (q), 67.9 (t), 84.8 (s), 202.1 (d) ppm.

1-Methoxycyclohexane-1-acetaldehyde (**5i**, $C_9H_{16}O_2$)

Ether **4i** (4.27 g, 28 mmol) was converted according to the above procedure to give 3.19 g of **5i** (74%) as beige liquid after flash column chromatography (SiO_2, *LP*:*Et*O*Ac* = 8:1); ^{1}H NMR (200 MHz): $\delta = 1.10–1.93$ (m, 10H), 2.48 (d, $J = 3$ Hz, 2H), 3.23 (s, 3H), 9.80 (t, $J = 2$ Hz, 1H) ppm; ^{13}C NMR (50 MHz): $\delta = 21.6$ (t), 25.4 (t), 34.7 (t), 48.5 (d), 49.7 (t), 75.1 (q), 202.4 (d) ppm.

1-Methoxycycloheptane-1-acetaldehyde (**5j**, $C_{10}H_{18}O_2$)

Ether **4j** (1.00 g, 5.9 mmol) was converted according to the above procedure to give 0.76 g of **5j** (74%) as colorless liquid after flash column chromatography (SiO_2, *LP*:*Et*O*Ac* = 5:1); bp 114–115°C/40 mbar; ^{1}H NMR (200 MHz): $\delta = 1.30–1.67$ (m, 11H), 1.89–1.95 (m, 2H), 2.51 (d, $J = 5$ Hz, Hz, 2H), 3.25 (s, 3H), 9.81 (t, $J = 5$ Hz, 1H) ppm.

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