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FULL PAPER

TEMPO-mediated oxidative deformylation of aldehydes – applications in the synthesis of polyketide fragments

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Dedication

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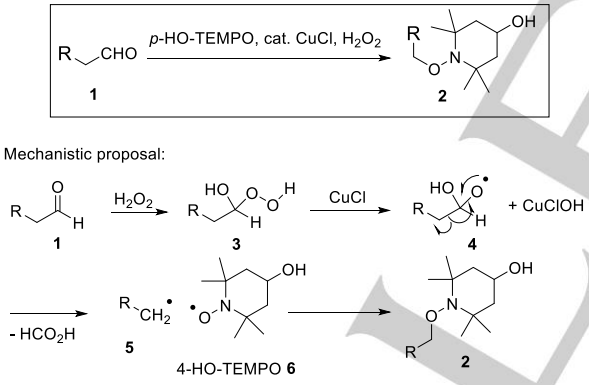
Abstract: The TEMPO-mediated oxidative deformylation of aldehydes is reported that yields the TEMPO adducts which can be further oxidized to the corresponding ketones. The focus of this work was on the optimization of a synthetic protocol for use in natural product synthesis, specifically for the preparation of chiral backbones with 1,2-oxo functionalization found in polyketide antibiotics. In addition, the oxidative deformylation was combined with the oxidation of the alcohol to the precursor aldehyde in a one-pot protocol.

Introduction

Oxidative deformylation reactions are rather rare.[1] Most commonly it is associated with transition metal chemistry such as the oxidative decarbonylation of *m*-terphenyl isocyanide complexes of molybdenum and tungsten[2] or alkyl-Heck-type reactions in which precursor aldehydes are decarbonylated.[3] In addition, it was demonstrated that β-substituted pyruvic acid derivatives undergo oxidative decarbonylation using sodium perborate tetrahydrate to yield the corresponding acetic acid derivatives.[4] Iwasawa and coworkers reported on the catalytic generation of alkyl radicals from aldehydes using a cobalt-salen complex with H_2O_2.[5] Recently, Maiti et al. disclosed a non oxidative palladium-catalyzed deformylation protocol for aromatic aldehydes.[6,7]

Scheme 1. Tempo-mediated oxidative deformylation of aldehydes and proposed mechanism.



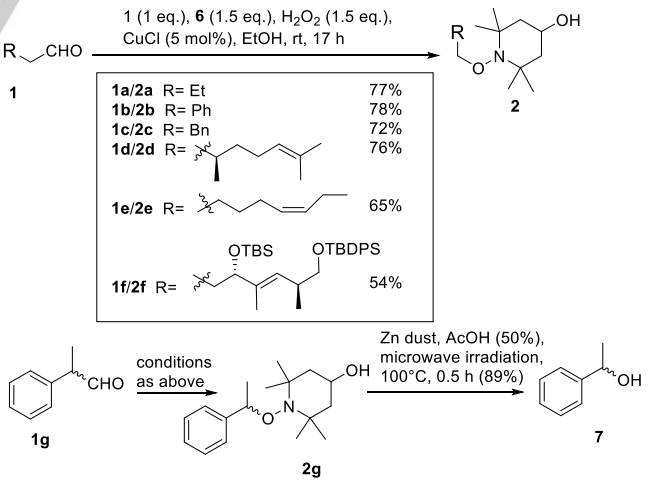
Schöning and coworkers reported on the conversion of aldehydes to the corresponding N-alkoxyamines using stable nitroxide radicals (Scheme 1).[8] Important features of this oxidative deformylation protocol are the presence of a catalytic amount of copper(I) chloride and stoichiometric amounts of hydrogen peroxide. Mechanistically, this reaction may be initiated by nucleophilic addition of hydrogen peroxide to the carbonyl group.[9] The intermediate hydroxy-hydroperoxide **3** decomposes under the influence of the copper (I) catalyst, resulting in the formation of the alkoxy radical **4** and copper(II). As copper(I) is employed catalytically, a reduction step has to be considered. It is unclear, whether hydrogen peroxide decomposes under the influence of copper(II) to oxygen while copper(I) is regenerated. Likewise, 4-HO-TEMPO **6** could provide the electron for reducing copper(II).[10] Upon fragmentation of **4**, formic acid is liberated as well as the C-centered radical **5** which is subsequently trapped by **6** to yield the alkoxyamine **2**. In that context, these mechanistic considerations resemble those suggested by Isawa. In their work on metal-catalyzed deformylation it was thought that homolytic cleavage of peroxohemiacetal intermediates occur to provide alkyl radicals.[8]

Indeed, this transformation bears several synthetic opportunities and this report intends to advance the methodology in several aspects. These cover the issue of chemoselectivity, stereocontrol when the α-position of the aldehyde bears a stereogenic center and the application of this method in creating polyketide backbones with differentiated 1,2-oxy functionalization.

Results and Discussion

In continuation of the work of Schöning et al.[5b] we here disclose improved conditions for carrying out oxidative deformylations with complex aldehydes for application in polyketide synthesis. Ethanol or THF were found to be the solvents of choice. Interestingly, also a solvent mixture composed of water and ethanol provides alkoxyamines of type **2**. The ratio of aldehyde **1** and 4-hydroxy-TEMPO **6** could be varied; commonly a 1:2 mixture gave best yields, while the copper source was employed in catalytic amount (5 mol%). The amount of hydrogen peroxide can be raised to 3 equ. without an observable decrease of yield. Catalytic amounts of additives such as Et_3N, or p-TsOH are tolerated, while the addition of strong Lewis acids such $AlCl_3$ is wreckless. It is also not possible to substitute hydrogen peroxide by NaOCl or *tert*-butyl hydroperoxide, respectively.

Scheme 2. Oxidative deformylation of (un)saturated aldehydes **1a**-**1g** and reductive cleavage of alkoxyamine **2g**.

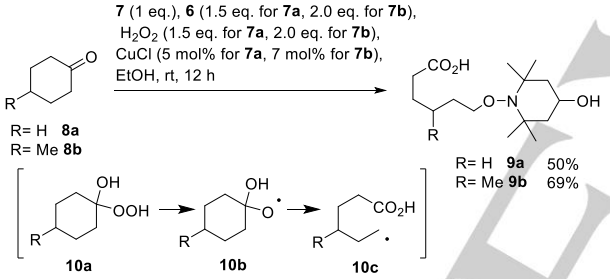


The transformation of structurally diverse new aldehydes not reported before[8] is summarized in Scheme 2. Besides simple linear aliphatic aldehydes **1a**-**1c** also citronellal **1d** was deformylated to smoothly yield alkoxyamine **2d**. Unsaturated aldehyde **2e** reacted likewise. These two examples are remarkable because the intermediate C-radical of type **5** (see

Scheme 1) do not cyclize to the cyclopentylmethyl radicals that would result in the formation of cyclopentane derivatives. Indeed, Iwasawa and coworkers observed such cyclizations when creating the corresponding C-radicals by a cobalt-salen-initiated deformylation. Obviously, the presence of the radical scavenger HO-TEMPO **6** leads to rapid trapping of the intermediate C-radical before the cyclization can occur. The chemoselectivity of this reaction was further demonstrated when using aldehyde **2f** that represents a typical polyketide backbone. For achieving best results for this complex aldehyde, the reaction conditions were slightly modified (**6**, 2.0 eq., H_2O_2 (2.0 eq.), EtOH (0.3 M), CuCl (5 mol%), rt, 16h). Noteworthy, cinnamaldehyde, bearing a sp^2 center in the α-position did not yield any defined product under te typical reaction conditions.

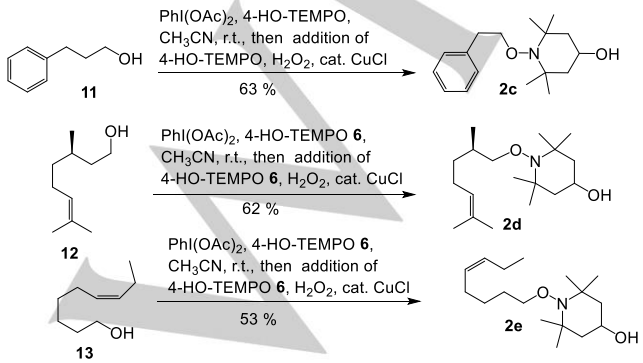
The alkoxamine **2g** obtained from 2-phenypropanal **1g** was used to probe conditions for reductive cleavage of the N,O-bond and formation of the corresponding alcohol **7**. The reagent system acetic acid and Zn dust allowed to promote reductive cleavage, while other options such as catalytic hydrogenation with Pd/C or SmI_2 did not work. However, it needs to be noted, that the transformation with Zn/AcOH worked best, when microwave irradiation served as a source of heat.

Scheme 3. Oxidative deformylation of cyclohexanones **9a**,**b** and proposed intermediates **10a**-**9c**.



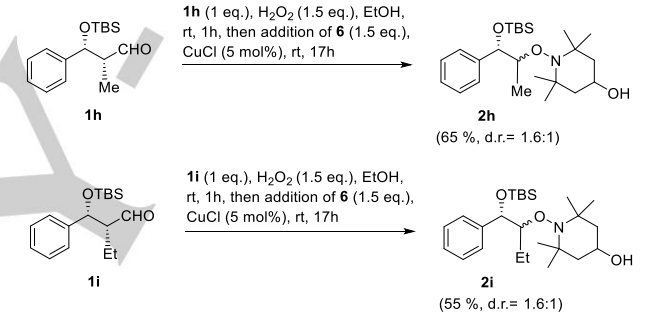
We also included a brief study on the transformation of ketones **8a**,**b** (Scheme 3). Surprisingly, selective ring opening occurred which yielded carboxylic acids **9a** and **9b**, respectively. Mechanistically, a similar route (**10a**→**10b**→**10c**) as described in Scheme 1 can be suggested. However, the scope of this oxidative fragmentation is rather limited, because neither cyclopentanone, cyloheptanone, nor α,β-unsaturated cyclic ketones yielded defined product in preparatively relevant yields.

Scheme 4. One-pot oxidation of alcohols **11**-**13** and oxidative carbonylation of intermediate aldehydes.



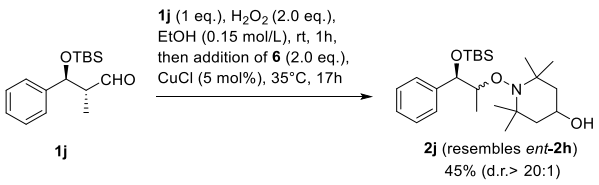
The oxidative deformylation can also be coupled with the initial oxidative formation of the starting aldehyde from the corresponding alcohol. In order to secure the chemoselective character of the deformylation protocol towards olefinic double bonds a reagent system was chosen that also relies on 4-hydroxy-TEMPO **6**. Diacetoxyiodo benzene (DAIB), or bisacetoxyiodo benzene (BAIB) served as possible co-oxidants (Scheme 4). First, 3-phenylpropan-1-ol **11** was subjected to the oxidation conditions. Once the transformation to aldehyde **1b** had gone to completion as judged by tlc a second portion of *p*-HO-TEMPO **6** and H_2O_2 as well as a catalytic amount of CuCl were added to initiate the oxidative deformylation and formation of alkoxyamine **2b**. Likewise, unsaturated alkoxyamines **2c** and **2d** were prepared from citronellol **12** and 6-nonene-1-ol **13**, respectively. Again, no cyclization products that would originate from an intermediate C-radical bearing an olefinic double bond were detected.

Scheme 5. Oxidative deformylation of chiral aldehydes **1h** and **1i** (d.r. determined by ^{1}H-NMR spectroscopy; relative stereochemistry for single diastereomers was not determined).



If α-branched aldehydes are subjected to the oxidative deformylation conditions a new stereogenic center will be generated. In view of developing a method suited for natural product synthesis, specifically for the synthesis of polyketide backbones we investigated, whether the configuration of this newly formed stereogenic center can be controlled by a second stereogenic center present in the starting aldehyde. *Syn*-configured α-methyl-β–oxygenated aldehyde **1h** were obtained by the Evans aldol reaction followed by *O*-silylation and reductive removal of the oxazolidinone auxiliary.[11] The resulting primary alcohol was oxidized to the aldehyde by Dess-Martin oxidation and subjected to the oxidative deformylation conditions to yield alkoxyamine **2i** in good yield for two steps but as a mixture of diastereoisomers (Scheme 5).

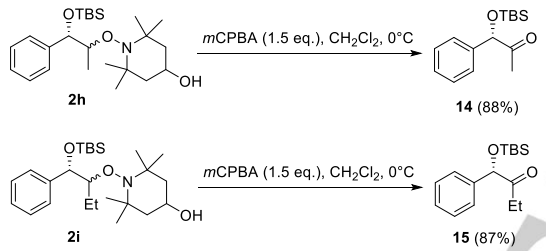
Scheme 6. Oxidative deformylation of chiral aldehyde **1j** (configuration of the newly formed stereogenic center for each diastereomer was not determined; yield of **2j** (resembles *ent*-**2h**) is given for two steps: a) Dess-Martin oxidation of corresponding alcohol and b) oxidative deformylation of resulting crude aldehyde **1j**).



Such good yield was obtained after slightly modifying the procedure. Aldehyde **1h** was first mixed with hydrogen peroxide in ethanol and stirred for one hour after which time the copper salt and 4-hydroxy-TEMPO **6** were added. It has to be noted that changing the silyl protection in **1h** with other silyl groups including bulkier ones (Et_3Si, iPr_3Si, tBuPh$_2$Si, Ph_3Si) or alternatively to the MOM group with chelating properties did not lead to principally other results (yields: 26-54%, d.r.= 1.6:1 to 1:1). Likewise, the homo derivative **1i** gave the same result under the optimized conditions (Scheme 5).

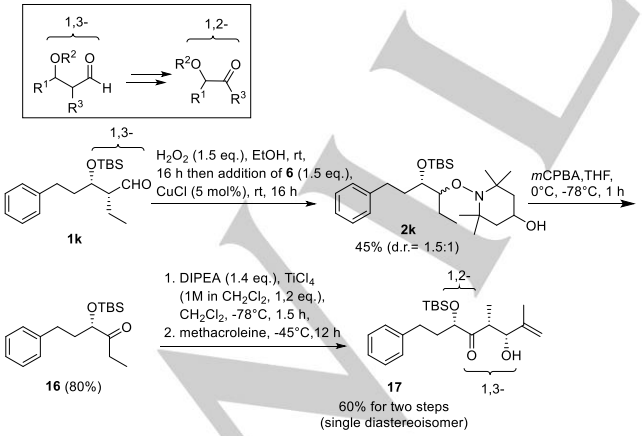
The initial *syn*-stereochemistry in aldehydes **1h** and **1i** may be responsible for the lack of stereocontrol. Therefore, we also subjected the α,β-*anti*-configured aldehyde **1j** to the modified reaction conditions (Scheme 6). This aldehyde was prepared according to Masamune´s aldol protocol.[12] The oxidative deformylation proceeded with moderate and with better diastereoselectivity. Surprisingly, the diastereocontrol was found to be concentration dependent (0.15 mol/L vs. 0.3 mol/L: >20:1 vs. 4:1).

Scheme 7. Oxidative cleavage of alkoxyamines **2h** and **2i**.



Next, we pursued to achieve a controlled oxidative cleavage of alkoxyamines **2**, because for diastereomeric mixtures alkoxyamines **2h** and **2i** the issue of lack of stereocontrol during their formation can be resolved. Thus, treatment with *m*CPBA smoothly yielded ketones **14** and **15**, respectively (Scheme 7).

Scheme 8. Preparation of polyketide fragment **17** bearing a 1,2-oxyfunctionalization.



The oxidative cleavage protocol and liberation of a new carbonyl group has synthetic potential for preparing polyketide backbones. For instance, starting from an aldol product bearing the common 1,3-relationship of oxygen functionalities, products with differentiated 1,2-oxy-functionalization may be obtained through a sequence consisting of oxidative deformylation, *m*CPBA-mediated cleavage followed by Paterson-type aldol chemistry. This is exemplified in the preparation of hydroxyketone **17** (Scheme 8). Starting from aldehyde **1k,** also obtained through the usual Evans *syn*-aldol chemistry, the oxidative deformylation yielded alkoxyamine **2k**. After oxidative removal of the TEMPO moiety, the resulting ketone **16** served as enolate component for Urpi´s variant[13] of the Paterson-aldol reaction with methacroleine as aldehyde component. The resulting polyketide element **17** was formed as one diastereoisomer bearing elements with a 1,2- and a 1,3-oxygen relationship.

Conclusion

In conclusion, we reported on the TEMPO-mediated oxidative deformylation of aldehydes yielding alkoxyamines. In a one-pot procedure, this oxidation can be combined with the initial oxidation of alcohols to aldehydes. When defined diastereomers of β-oxygenated α-branched aldehydes are employed, diastereopurity is lost. However, the resulting alkoxyamines can directly be oxidized to the corresponding ketones with *m*CPBA. As a result, α-alkoxy-ketones are obtained, that were employed in the synthesis of polyketide-type fragments. Oxidative deformylations are very rare reactions in the synthetic chemists` portfolio so that the current work paves the way for further synthetic applications in this field.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded with Bruker DPX-400, AVANCE-400 and DRX-500 with the residual solvent signal as internal standard. The choice of solvents are provided with the data of spectra. Multiplicities are described using the following abbreviations: s= singlet, d= doublet, t= triplet, q= quartet, o= octet, m= multiplet. ^{13}C NMR spectra are reported as values in ppm relative to residual solvent signal as internal standard. The multiplicities refer to the resonances in the off-resonance decoupled spectra and were elucidated using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are reported using the following abbreviations: q (quaternary carbon), t (tertiary carbon = methyne), s (secondary carbon = methylene), p = (primary carbon = methyl). High resolution mass spectra were obtained with a Micromass LCT via loop-mode injection from a Waters (Alliance 2695) HPLC system. Alternatively a Micromass Q-TOF in combination with a Waters Aquity Ultraperformance LC system was employed. Ionization was achieved by ESI or APCI. Microwave-assisted heating was carried out in a Discover S-Class from CEM (max. power 300 W). Analytical thin-layer chromatography was performed using precoated silica gel 60 F_{254} plates (Merck, Darmstadt), and the spots were visualized with UV light at 254 nm or by staining with H_2SO_4/4-methoxybenzaldehyde in ethanol. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). All reagents were used as received from the suppliers. THF was dried over sodium wire with benzophenone as indicator. Specific optical rotations [α] were measured at 20 °C with a polarometer type 341 from Perkin-Elmer with a 10 cm cuvette at λ = 589.3 mm (sodium-D-line). Reagent **6** and alcohols **7** and **11** and **12** are commercially available. The preparation of aldehydes **1h**, **1i**, **1j** and **1k** is reported in references.[14] Alkoxyamine **2g** is described in ref. . The oxidative deformylation of aldehydes **1a**-**1c** as well as **1g** and the analytic and

spectroscopic data of alkoxamines **2a**-**2c** as well as **2g** were reported in reference [8].

General proce8dures for the oxidative deformylation

Method A (4-hydroxy-TEMPO, CuCl and H_2O_2 are added together): If the aldehyde was not commercially available or chemically labile the corresponding alcohol was oxidized by Dess-Martin oxidation and the crude aldehyde **1** (0.18 mmol, 1 eq.) was directly employed in the oxidative deformylation reaction. It was dissolved in ethanol (0.6 mL) and treated with 4-hydroxy-TEMPO (**6**) (46.5 mg, 0.27 mmol, 1.5 eq.) CuCl (0.9 mg, 5 mol%) and H_2O_2 (30%, 30.6 mg, 0.27 mmol, 1.5 eq.). The solution was stirred for 17 h at rt. The reaction was terminated by addition of an aqueous solution of ascorbic acid (10%, 10 mL) and ethyl acetate (10 mL). The phases were separated and the aqueous phase was washed with ethyl acetate (3x 10 mL). The combined organic extracts were washed with an aqueous $NaHCO_3$-solution (saturated), and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure.

Method B: (premixing of aldehyde with H_2O_2 for 1 h): If the aldehyde was not commercially available or chemically labile the corresponding alcohol was oxidized by Dess-Martin oxidation and the crude aldehyde **1** (0.18 mmol, 1 eq.) was directly employed for the oxidative deformylation reaction. It was dissolved in ethanol (0.6 mL), treated with H_2O_2 (30%, 30.6 mg, 0.27 mmol, 1.5 eq.) and stirred at rt for one 1h. Then, 4-hydroxy-TEMPO (**6**) (46.5 mg, 0.27 mmol, 1.5 eq.) and CuCl (0.9 mg, 5 mol%) were added. The solution was stirred for 12 h at rt. The reaction was terminated by addition of an aqueous solution of ascorbic acid (10%, 10 mL) and ethyl acetate (10 mL). The phases were separated and the aqueous phase was washed with ethyl acetate (3x 10 mL). The combined organic extracts were washed with an aqueous $NaHCO_3$-solution (saturated), and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure.

Method C (2 eq. instead of 1.5 eq. of 4-hydroxy-TEMPO (**6**) employed): If the aldehyde was not commercially available or chemically labile the corresponding alcohol was oxidized by Dess-Martin oxidation and the crude aldehyde **1** (0.04 mmol, 1 eq.) was directly employed for the oxidative deformylation. It was dissolved in ethanol (0.3 mL) and treated with 4-hydroxy-TEMPO (**6**) (15.5 mg, 0.09 mmol, 2 eq.) CuCl (0.2 mg, 5 mol%) and H_2O_2 (30%, 10.2 mg, 0.09 mmol, 2 eq.). The solution was stirred for 17 h at rt. The reaction was terminated by addition of an aqueous solution of ascorbic acid (10%, 10 mL) and ethyl acetate (10 mL). The phases were separated and the aqueous phase was washed with ethyl acetate (3x 10 mL). The combined organic extracts were washed with an aqueous $NaHCO_3$-solution (saturated), and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure.

Method D (one pot procedure starting from the corresponding alcohol): To a solution of the alcohol (0.17 mmol, 1 eq.) in CH_3CN (1.0 mL) was added $PhI(OAc)_2$ (0.20 mmol, 1.2 eq.) and 4-hydroxy-TEMPO (**6**) (3.5 mg, 0.02 mmol, 0.12 eq.) and the reaction mixture was stirred at r.t. for 3 h. The progress was monitored by TLC. Then, a second portion of 4-hydroxy-TEMPO (**6**) (42.4 mg, 0.25 mmol, 1.5 eq.), CuCl (0.9 -1.4 mg, 5 – 8 mol%) and H_2O_2 (30%, 29-52 mg, 0.25 – 0.46 mmol, 1.5-2.8 eq.) were added and the solution turned to green after one hour. After stirring for 8 h at rt the reaction was terminated by addition of an aqueous solution of ascorbic acid (10%, 10 mL) and ethyl acetate (10 mL). The phases were separated and the aqueous phase was washed with ethyl acetate (3x 10 mL). The combined organic extracts were washed with an aqueous $NaHCO_3$-solution (saturated), and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure.

(*R*)-1-((2,6-Dimethylhept-5-en-1-yl)oxy)-2,2,6,6-tetramethyl-piperidin-4-ol (2d): 2d was obtained from aldehyde **1d** (23.6 mg, 0.15 mmol; 1 eq.) after applying the general method A of oxidative deformylation; purification by column chromatography (petroleum ether / ethyl acetate= 3:1); yield **2d** (34 mg, 0.11 mmol, 76 %) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ = 5.10 (t, *J* = 7.2 Hz, 1H, =CH-), 3.95 (m, 1H, CH-O), 3.64 (m, 1H, CH_2-O), 3.54 (m, 1H, CH_2-O), 2.04-2.00 (m, 2H, CH_2), 1.80-1.78 (m, 2H, CH_2), 1.68 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.48-1.42 (m, 4H, CH_2), 1.19 (s, 6H, CH_3), 1.15 (s, 6H, CH_3), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$= 77.16 ppm): δ = 131.3, 124.9, 81.9, 63.4, 60.2, 48.4, 34.1, 33.3, 33.0, 25.8, 25.7, 21.6, 17.7, 17.5 ppm; HRMS(ESI): *m/z*: calculated for $C_{18}H_{36}NO_2$ $[M+H]^+$:298.2746, found: 298.2755.

(*Z*)-2,2,6,6-Tetramethyl-1-(oct-5-en-1-yloxy)piperidin-4-ol (2e): 2e was obtained from aldehyde **1e** (21.7 mg, 0.16 mmol, 1 eq.) was subjected to the general method A of oxidative deformylation; purification by column chromatography (petroleum ether / ethyl acetate= 3:1); yield **2e** (29 mg, 0.1 mmol, 65 %) as a colorless oil.

^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ= 5.31-5.39 (m, 2H, -CH=CH-), 4.02-3.92 (m, 1H, CH-O), 3.73 (t, J = 6.4 Hz, 2H, CH_2-O), 2.08-1.99 (m, 4H, CH_2), 1.84-1.76 (m, 2H, CH_2), 1.62-1.40 (m, 6H, CH_2), 1.19 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 0.96 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$, $CDCl_3$= 77.16 ppm): δ= 131.9 (d), 129.1 (d), 77.5 (t), 63.5 (d), 60.1 (s), 48.4 (t), 33.3 (q), 28.4 (t), 27.2 (t), 26.7 (t), 21.1 (q), 20.6 (t), 14.5 (q) ppm; HRMS(ESI): *m/z*: calculated for $C_{17}H_{34}NO_2$ $[M+H]^+$:284.2590, found: 284.2601.

(*2R,5S*)-2-(*tert.*-Butyldimethylsiloxy)-6-(*tert.*-butyldiphenyl-siloxy)-1-(4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy)-3,5-dimethyl-3-hexen (2f): 2f was obtained from the corresponding alcohol (20.0 mg, 0.037 mmol, 1 eq) and the resulting aldehyde **1f** was subjected to the general method C of oxidative deformylation; purification by column chromatography (petroleum ether / ethyl acetate= 3:1); yield **2f** (14 mg, 0.02 mmol, 54 %) as a colorless oil.

$[\alpha]_D^{20}$= -11.6 (c = 1.0, MeOH); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ= 7.67-7.65 (m, 4H, aromatic H), 7.42-7.35 (m, 6H, aromatic H), 5.27 (d, *J* = 9.4 Hz, 1H, H-4), 4.06 (dd, *J* = 4.3, 7.0 Hz, 1H, H-2), 3.96-3.91 (m, 1H, H-10), 3.70-3.61 (m, 2H, H-1), 3.50 (dd, *J* = 5.6, 9.7 Hz, 1H, H-6), 3.41 (dd, *J* = 7.3, 9.7 Hz, 1H, H-6'), 2.62-2.55 (m, 1H, H-5), 1.80-1.76 (m, 2H, H-9, H-9'), 1.53 (d, *J* = 1.3 Hz, 1H, C*H*$_3$C), 1.45-1.39 (m, 2H, H-9, H-9'), 1.20 (s, 3H, H-11), 1.15 (s, 3H, H-11'), 1.14 (s, 3H, H-11''), 1.12 (s, 3H, H-11'''), 1.05 (s, 9H, SiC(C*H*$_3$)$_3$), 0.98 (d, *J* = 6.7 Hz, 3H, H-8), 0.87 (s, 9H, SiC(C*H*$_3$)$_3$), 0.05 (s, 3H, SiC*H*$_3$), -0.02 (s, 3H, SiC*H*$_3$); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ= 135.8 (q, aromatic C), 135.8 (t, aromatic C), 135.5 (q, C-3), 134.2 (t, aromatic C), 134.2 (t, aromatic C), 129.6 (t, aromatic C), 129.0 (t, C-4), 127.7 (t, aromatic C), 81.1 (s, C-1), 76.3 (t, C-2), 68.6 (s, C-6), 63.5 (t, C-10), 60.3 (q, C-12), 60.1 (q, C-12'), 48.5 (C-9 or C-9'), 48.4 (C-9 or C-9'), 35.2 (t, C-5), 33.2 (p, C-11), 33.1 (p, C-11), 27.0 (SiC(*C*H$_3$)$_3$), 26.0 (SiC(CH$_3$)$_3$), 21.4 (p, C-11), 21.3 (p, C-11), 19.4 (SiC(CH$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 17.4 (p, C-8), 13.0 (p, C-7), -4.6 (p, SiCH$_3$), -4.8 (p, SiCH$_3$); HRMS(ESI): *m/z*: calculated for $C_{39}H_{66}N_1O_4Si_1$ $[M+H^+]$: 668.4530, found: 668.4521.

(1*S*)-1-(*tert.*-Butyldimethylsiloxy)-2-(4-hydroxy-2,2,6,6-tetramethyl-piperidinyloxy)-1-phenylpropan (2h): 2h was obtained from the corresponding alcohol (50.5 mg, 0.18 mmol, 1 eq.) after Dess-Martin oxidation; crude aldehyde **1h** was subjected to the general method B of oxidative deformylation; purification by column chromatography (petroleum ether / ethyl acetate= 5:1 to 3:1); yield **2h** (50 mg, 0.12 mmol, 65%, d.r.= 1.6:1) as a colorless oil.

Major diastereoisomer **2h**: ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 7.36-7.18 (m, 5H, aromatic H), 4.70 (d, *J*= 4.2 Hz, 1H, 1-H), 3.99 (m, 1H, 2-H), 3.92 (m, 1H, C*H*OH), 1.80 (m, 1H, *H*CH), 1.72 (m, 1H, HC*H*), 1.48-1.38 (m, 2H, *HCH*),1.16 (d, *J*= 6.4 Hz, 3H,CH-C*H*$_3$), 1.15, 1.13, 1.09, 1.01 (4s, 12 H, 4x CH$_3$), 0.9 (s, 9H, *t*Bu), 0.07 (s, 3H. Si(CH$_3$)), -0.16 (s, 3H, Si(CH$_3$)); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 141.9 (q, C-aromat.), 128.4 (t, C-aromat.), 128.1 (t, C-aromat.), 127.1 (t, C-aromat.), 77.8 (t, C-2), 65.6 (t, C-1), 63.5 (t, COH), 60.1 (q, C-N), 48.9 (s, CH_2), 48.4 (s, CH_2), 33.2 (p, C(*C*H$_3$)$_2$), 25.8 (p, tBu), 21.0 (C(*C*H$_3$)$_2$), 18.2 (*C*(CH$_3$)$_2$), 14.3 (p, C-3), -4.5 (*p,* SiCH$_3$), -5.3 (*p,* SiCH$_3$).

Minor diastereoisomer **2h**: ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 7.36-7.18 (m, 5H, aromatic H), 4.72 (d, *J*= 6.2 Hz, 1H, 1-H), 3.99 (m, 1H, 2-H), 3.92 (m, 1H, C*H*OH), 1.80 (m, 1H, *H*CH), 1.72 (m, 1H, HC*H*), 1.48-1.38 (m, 2H, *HCH*),1.16 (d, *J*= 6.4 Hz, 3H,CH-C*H*$_3$), 1.15, 1.13, 1.09, 1.01 (4s, 12 H, 4x CH$_3$), 0.9 (s, 9H, *t*Bu), 0.07 (s, 3H. Si(CH$_3$)), -0.16 (s, 3H, Si(CH$_3$)); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 143.4 (q, C-aromat.), 127.8 (t, C-aromat.), 127.0 (t, C-aromat.), 126.9 (t, C-aromat.), 83.7 (t, C-2), 77.3 (t, C-1), 63.6 (t, COH), 59.5 (q, C-N), 49.0 (s, CH_2), 48.7 (s, CH_2), 34.8, 34.4 (p, C(*C*H$_3$)$_2$), 26.1 (p, tBu),

21.4 (C(CH_3)$_2$), 18.4 (C(CH_3)$_2$), 14.7 (p, C-3), -4.4 *(p,* SiCH_3*),* -4.7 (*p,* SiCH_3); HRMS (ESI): m/z calculated for $C_{24}H_{44}NO_3Si$ [M+H]$^+$: 422.3090, found: 422.3091.

(1*S*)-1-(*tert.*-Butyldimethylsiloxy)-2-(4-hydroxy-2,2,6,6-tetramethyl-piperidinyloxy)-1-phenylbutan (2i): 2i was obtained from the corresponding alcohol (53.0 mg, 0.18 mmol, 1 eq.) after Dess-Martin oxidation; intermediate aldehyde **1h** was subjected to the general method B of oxidative deformylation; purification by column chromatography (petroleum ether / ethyl acetate= 5:1 to 3:1); yield a mixture of diastereoisomers **2i** (43 mg, 0.1 mmol, 55%, d.r.= 1.6:1) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 7.43-7.18 (m, 5H, aromatic H), 4.80 (d, *J*= 2.3 Hz, 1H, 1-H), 4.73 (d, *J*= 3.5 Hz, 1H, 1-H*), 3.91 (m, 1H, 2-H), 3.92 (m, 1H, C*H*OH), 1.80 (m, 1H, *H*CH), 1.72 (m, 1H, HC*H*), 1.48-1.38 (m, 2H, *HCH*),1.16 (d, *J*= 6.4 Hz, 3H,CH-CH_3), 1.15, 1.13, 1.09, 1.01 (4s, 12H, 4x CH_3), 0.9 (s, 9H, *t*Bu), 0.07 (s, 3H. Si(CH_3)), -0.16 (s, 3H, Si(CH_3)) (minor diastereoisomer marked in *; otherwise overlap of signals); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm) δ= 142.5, 142.2 (q, C-aromat.), 128.2, 128.1, 127.8, 127.4, 127.2, 127.0, 126.8, 126.5, (t, C-aromat.), 88.0, 87.6 (t, C-2), 75.9, 74.7 (t, C-1), 63.6, 63.5 (t, C-5), 61.4, 61.0, 59.8, 59.7 (q, C-7), 49.2, 49.1, 49.0, 48.7 (t, C-6), 34.9, 34.8, 34.2, 33.9 (p, C-8), CH_2), 34.8, 34.4 (p, C(CH_3)$_2$), 26.0, 25.9 (p, *t*Bu), 22.4, 21.9 (s, C-3), 21.6, 21.4, 21.2, 21.0 (p, C-8), 18.3, 18.2 (q, *C*(CH_3)$_2$), 11.8, 11.2 (p, C-4), -4.4, -4.4, -4.8, -5.0 (p, Si(CH_3)$_2$); HRMS (ESI): m/z calculated for $C_{25}H_{45}NO_3SiNa$ [M+Na]$^+$: 458.3006, found: 458.3009.

1-(((4S)-4-((*tert*-Butyldimethylsilyl)oxy)-6-phenylhexan-3-yl)oxy)-2,2,6,6-tetramethylpiperidine (**2k**): **2k** was obtained from the corresponding alcohol (58.0 mg, 0.18 mmol, 1 eq.) after Dess-Martin oxidation; intermediate aldehyde **1l** was subjected to the general method A of oxidative deformylation; purification by column chromatography (petroleum ether / ethyl acetate= 5:1 to 3:1); diastereomeric mixture of **2k** (37 mg, 0.08 mmol, 45%, d.r.= 1.5:1) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 7.30-7.26 (m, 2H, aromatic H), 7.21-7.15 (m, 3H, aromatic H), 3.97 (m, 1H, H-7), 3.84 (m, 1H, H-3), 2.82 (m, 1H, H-1), 2.58 (m, 1H, H-1´), 2.15 (m, 1H, H-5), 1.98 (m, 1H, H-2), 1.80 (m, 3H, H-2´, H-8), 1.45 (m, 2H, H-8´), 1.38-1.31 (m, 1H, H-5´), 1.25 (s, 3H, H-10), 1.23 (s, 3H, H-10´), 1.12 (s, 6H, H-10´´), 0.96-0.92 (m, 12H, H-6, C(CH_3)$_3$), 0.08 (2s, 6H, Si(CH_3)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 143.1 (q, C-aromat.), 128.5 (t, C-aromat.), 128.4 (t, C-aromat.), 125.8 (t, C-aromat.), 87.3 (t, C-4), 74.4 (t, C-3), 63.5 (t, C-7), 61.3 (q, C-9), 59.9 (q, C-9´), 49.3 (s, C-8), 49.1 (s, C-8´), 35.0 (s, C-2), 34.8 (p, C-10), 34.4 (p, C-10), 32.7 (s, C-1), 26.2 (p, TBS), 23.0 (s, C-5), 21.9 (p, C-10), 21.7 (p, C-10), 18.3 (q, *C*(CH_3)$_2$), 11.9 (p, C-6), -3.9 *(p,* SiCH_3*),* -4.2 (*p,* SiCH_3); HRMS (ESI): m/z calculated for $C_{27}H_{49}NO_3SiNa$ [M+Na]$^+$: 486.3379, found: 486.3373.

Phenylethan-2-ol (7) from alkoxyamine 2g: To alkoxyamine **2g**[8b] (120 mg, 0.89 mmol) in acetic acid (15 mL, 50%) was added Zn dust (150 mg) in a microwave vial. The suspension was heated by microwave irradiation at 100°C for 0.5 h. The reaction mixture was cooled to rt, and treated with diethyl ether. The phases were separated, the aqueous phase was extracted with a second portion of diethyl ether and the combined organic phases were washed with brine. The organic phase was dried ($MgSO_4$), filtered and diethyl ether was removed under mild conditions to yield known phenylethan-2-ol (**7**) (97 mg, 0.8 mmol, 89%).

6-((4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexanoic acid (9a): Cyclohexanone **8a** (75 mg, 0.765 mmol) was dissolved in ethanol (2.0 mL) and 4-hydroxy-TEMPO (**6**) (194 mg, 1.126 mmol) and CuCl (3.9 mg, 0.039 mmol) were added at room temperature. The color of the solution turned to red. Then, H_2O_2 (30%, 124.7 mg, 1.1 mmol) was added and the mixture was stirred over night at r.t. By then, the color of the solution had turned to green. The reaction was terminated by addition of ethyl acetate (10 mL) and ascorbic acid (10%, 10 mL). The phases were separated and the aqueous phase was washed three times with ethyl acetate (3x 10 mL). The combined organic extracts were washed with an aqueous Na_2CO_3-solution (5 %) and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (petroleum ether/ ethyl acetate= 1:1) to yield the title compound **9a** (110 mg, 0.383 mmol; 50%).

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 3.96 (m, 1H, CH-O), 3.73 (t, J = 6.2 Hz, 2H, CH_2-O); 2.30 (t, J = 7.2 Hz, 2H, CH_2); 2.12-2.10 (m, 2H, CH_2), 1.82-1.78 (m, 4H, CH_2), 1.68- 1.64 (m, 2H, CH_2), 1.57-1.53 (m, 2H, CH_2), 1.18 (s, 6H, CH_3), 1.14, (s, 6H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 180.9. 76.5, 64.4, 59.7, 48.0, 35.9, 32.9, 28.3, 26.1, 25.8, 20.8 ppm; HRMS (ESI): m/z calculated for $C_{15}H_{30}NO_4$ [M+H]$^+$: 288.2175, found: 288.2168.

6-((4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)oxy)-4-methylhexanoic acid (9b): 4-Methylcyclohexanone **8b** (22 mg, 0.197 mmol) was dissolved in ethanol (0.6 mL) and 4-hydroxy-TEMPO (**6**) (67.0 mg, 0.39 mmol, 2 eq.) and CuCl (1.3 mg, 0.013 mmol) were added at room temperature. The colour of the solution turned to red. Then, H_2O_2 (30%, 44.2 mg, 0.39 mmol) was added and the mixture was stirred over night at r.t. By then, the colour of the solution had turned to green. The reaction was terminated by addition of ethyl acetate (10 mL) and ascorbic acid (10%, 10 mL). The phases were separated and the aqueous phase was washed three times with ethyl acetate (3x 10 mL). The combined organic extracts were washed with an aqueous Na_2CO_3-solution (5 %) and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (petroleum ether/ ethyl acetate= 1:1) to yield the title compound **9b** (41 mg, 0.136 mmol; 69%).

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 3.96 (m, 1H, CH-O), 3.77 (t, J= 6.8 Hz, 2H, CH_2), 2.36-2.32 (m, 2H, CH_2), 2.11-2.09 (m, 1H, CH), 1.81-1.78 (m, 2H, CH_2), 1.59-1.57 (m, 2H, CH_2), 1.56-1.57 (m, 4H, CH_2), 1.19 (s, 6H, CH_3), 1.13 (s, 6H, CH_3), 0.92 (d, *J = 6.4 Hz*, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 179.6, 75.1, 64.9, 63.4, 59.9, 48.2, 35.3, 33.1, 32.5, 30.0, 21.0, 19.5 ppm; HRMS (ESI): m/z calculated for $C_{16}H_{32}NO_4$ [M+H]$^+$: 302.2331, found: 302.2343.

Coupling of carbinol oxidation with oxidative deformylation (see also general method D)

Preparation of **2c** from alcohol **11**: A solution of 3-phenylpropan-1-ol **11** (23 mg, 0.169 mmol), $PhI(OAc)_2$ (65.6 mg, 0.203 mmol) and 4-hydroxy-TEMPO (**6**) (3.9 mg, 0.023 mmol) in acetonitrile (0.8 mL) was stirred for 3 h at room temperature thereby monitoring the progress of alcohol oxidation by TLC. Then, a second portion of 4-hydroxy-TEMPO (**6**) (42.4 mg, 0.246 mmol) and CuCl (1.4 mg, 0.014 mmol) were added. The colour of the solution turned to red. Then, H_2O_2 (30%, 0.46 mmol, 52.0 mg) was added and the mixture was stirred over night at r.t. By then, the colour of the solution had turned to green.

The reaction was terminated by addition of ethyl acetate (10 mL) and ascorbic acid (10 mL). The phases were separated and the aqueous phase was washed three times with ethyl acetate (3x 10 mL). The combined organic extracts were washed with an aqueous Na_2CO_3-solution (5 %), and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (petroleum ether/ ethyl acetate= 3:1) to yield the title compound **2c** (29.5 mg, 0.106 mmol, 63 %) along with the starting alcohol **11** (4 mg) and aldehyde **1c** (5 mg).

Under the same conditions (*R*)-3,7-dimethyloct-6-en-1-ol (**12**) and (*Z*)-non-6-en-1-ol (**13**) gave products **2d** (62%) and **2e** (53%), respectively.

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-one (**14**): **2h** (34 mg, 0.08 mmol, 1 eq.) was dissolved in CH_2Cl_2 (0.8 mL) and cooled to 0°C. Then, *m*CPBA (70%, 33 mg, 0.13 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 2 h at 0°C. The reaction was terminated by addition of a saturated solution of $Na_2S_2O_3$ and stirring was continued for additional 60 min at rt. The phases were separated and the aqueous phase was washed three times with CH_2Cl_2 followed by ethyl acetate. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material

was purified by column chromatography (silica, petroleum ether / ethyl acetate= 5:1) to yield the title compound **14** (17.6 mg, 0.07 mmol; 88%) as a yellowish oil. $[\alpha]_D^{20}$= -46.0 (*c*= 1.2, $CDCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 7.46-7.27 (m, 5H, aromatic H), 5.04 (s, 1H, C*H*-OTBS), 2.11 (s, 3H, (CO)CH_3), 0.95 (s, 9H, *t*-Bu), 0.09 (s, 3H. Si(CH_3)), -0.0 (s, 3H, Si(CH_3)); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 209.2 (q, C=O), 138.8 (q, C-aromat.), 128.6 (t, C-aromat.), 128.2 (t, C-aromat.), 126.0 (t, C-aromat.), 81.4 (t, C-OTBS), 25.9 (p, t-Bu), 24.1 (p, -(CO)-CH_3), 18.4 (q, $C(CH_3)_2$), -4.8 *(p,* SiCH_3*),* -5.0 (*p,* SiCH_3); HRMS (ESI): m/z: calculated for [M+ Na]$^+$ $C_{15}H_{24}O_2SiNa$ 287.1443; found 287.1443.

(*S*)-1-(*tert*- Butyldimethylsiloxy)-1-phenyl-2-butanone (**15**): **2i** (143 mg, 0.34 mmol, 1 eq.) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Then, *m*CPBA (70%, 126 mg, 0.52 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 1 h at 0°C. The reaction was terminated by addition of a saturated solution of $Na_2S_2O_3$ and stirring was continued for additional 45 min at 0°C. The phases were separated and the aqueous phase was washed with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica, petroleum ether / ethyl acetate= 10:1) to yield the title compound **15** (83 mg, 0.3 mmol; 87%) as a colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 7.43-7.25 (m, 5H, aromatic H), 5.08 (s, 1H, C*H*-OTBS), 2.66 and 2.47 (m, 2H, -(CO)C$H_2$$CH_3$), 0.95 (s, 9H, *t*-Bu), 0.94 (t, *J*= 7.2 Hz, 3H, -(CO)C$H_2$$CH_3$), 0.08 (s, 3H. Si($CH_3$)), -0.01 (s, 3H, Si($CH_3$)); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 211.6 (q, C=O), 139.1 (q, C-aromat.), 128.6 (t, C-aromat.), 128.0 (t, C-aromat.), 126.0 (t, C-aromat.), 81.2 (t, C-OTBS), 29.4 (s, -(CO)$CH_2$$CH_3$), 25.9 (p, tBu), 18.3 (q, $C(CH_3)_2$), 7.5 (p, -(CO)$CH_2$$CH_3$), -4.8 *(p,* Si$CH_3$*),* -5.0 (*p,* Si$CH_3$); RMS(ESI): *m/z*: calculated for $C_{16}H_{27}O_2Si$ [M+H]$^+$: 279.1780, found: 279.1783.

(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-phenylhexan-3-one (**16**): **2k** (148 mg, 0.34 mmol, 1 eq.) was dissolved in CH_2Cl_2 (25 mL) and cooled to 0°C. Then, *m*CPBA (70%, 128 mg, 0.52 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 1 h at 0°C. The reaction was terminated by addition of a saturated solution of $Na_2S_2O_3$ and stirring was continued for additional 20 min at rt. The phases were separated and the aqueous phase was washed with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica, petroleum ether / ethyl acetate= 10:1) to yield the title compound **16** (89 mg, 0.29 mmol; crude 85%) as a colorless oil. The ketone was directly used for the next step.

(3*S*,5*R*,6*R*)-3-((tert-Butyldimethylsilyl)oxy)-6-hydroxy-5,7-dimethyl-1-phenyloct-7-en-4-one (17): Ketone **16** (89 mg, 0.29 mmol, 1 eq.) described above was dissolved in CH_2Cl_2 (3 mL) and cooled to 678°C. Then, $TiCl_4$ (0.34 mL, 1M in CH_2Cl_2, 0.34 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 5 minutes at -78°C. Then, diisopropylethyl amine (DIPEA, 66 μL, 0.40 mmol, 1.4 eq.) was added and the solution was stirred for 1.5 h at -78°C. Methacroleine (71 mL, 0.86 mmol, 3 eq.) was added and the reaction mixture was stirred for 12 h at -40°C. The reaction was terminated by addition of an aqueous NH_4Cl-solution and stirring was continued at rt for 2 h. The phases were separated and the aqueous phase was washed three times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica, petroleum ether / ethyl acetate= 10:1) to yield the title compound **17** (65 mg, 0.17 mmol; 60%) as a colorless oil.
$[\alpha]_D^{20}$= +10.7 (*c*= 1 $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ= 7.31-7.27 (m, 2H, aromatic H), 7.22-7.17 (m, 3H, aromatic H); 5.14 and 4.97 (2s, 1H, H-8), 4.34 (t, *J*= 0.7 Hz, 1H; H-6), 4.21 (t, *J*= 6.0 Hz, 1H, H-3), 3.23 (dq, *J*= 2.4, 7.2 Hz, 1H, H-5), 2.66 (t, *J*= 8.2 Hz, 2H, H-1), 2.03-1.96 (m, 2H, H-2), 1.68 (s, 3H, H-9), 1.07 (d, *J*= 7.1 Hz, 3H, H-10), 0.96 (s, 9H, *t*-Bu), 0.1 (s, 3H. Si(CH_3)), 0.08 (s, 3H, Si(CH_3)); ^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): δ= 219.0 (q, C-4), 143.1 (q, C-7), 141.4 (q, aromat. H), 128.7 (t, C-aromat.), 128.5 (t, C-aromat.), 126.3 (t, C-aromat.), 112.1 (s, C-8), 78.1 (t, C-3), 77.2 (t, C-6), 73.3 (s, C-5), 42.1 (s, C-2), 37.0 (s, C-1), 31.6, 25.9 (p, tBu), 19.9 (p, C-9), 18.2 (q, $C(CH_3)_2$), 9.6 (C-10), -4.6 *(p,* SiCH_3*),* -4.7 (*p,* SiCH_3); HRMS (ESI): m/z: calculated for [M+ Na]$^+$ $C_{22}H_{36}O_3SiNa$ 399.2334; found 399.2331.

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Graphical Abstract

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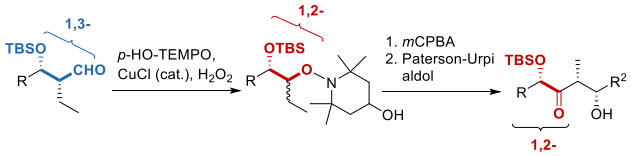

Key words: aldol reaction, deformylation, oxidation, polyketides, TEMPO

Supporting Information

The supporting information provides copies of ^{1}H- and ^{13}C-NMR spectra.

Graphical abstract:

The TEMPO-mediated oxidative deformylation of aldehydes was further developed for the preparation of chiral backbones with 1,2-oxo functionalization found in polyketide antibiotics.