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Stereoselective Oxidation of Titanium(IV) Enolates with Oxygen

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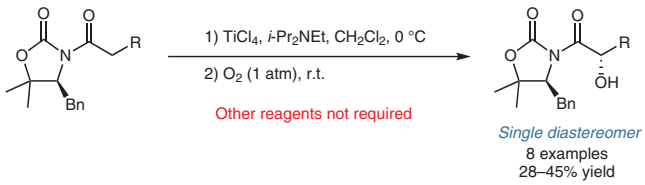

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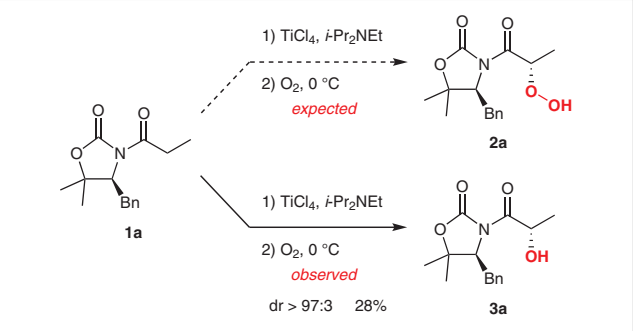
Abstract A novel approach to synthesize enantiomerically pure α-hydroxy carboxylic derivatives is reported. A highly stereoselective oxidation of titanium(IV) enolates from chiral *N*-acyloxazolidinones is performed with oxygen under simple experimental conditions that do not require any reducing steps. The success of this approach depends on the biradical character of titanium(IV) enolates.

Key words stereoselective synthesis, hydroxylation, titanium enolates, chiral auxiliaries, oxygen, radicals

The chemo-, site-, and stereoselective oxidation of the carbon backbone of organic molecules is a formidable challenge that has attracted increasing interest in recent years.[1] It goes without saying that the wide range of functional groups and positions that can be oxidized makes such a synthetic approach very complicated. Hence, the oxidation of metal enolates is an appealing way to tackle such a challenge and gain access to enantiomerically pure α-hydroxy carbonyl or carboxylic compounds in a straightforward manner.[2] Indeed, this ensures site-selective oxidation of the Cα position, both the control of the geometry (*Z* vs *E*) and the π-face differentiation of the enolate enable highly stereocontrolled transformations, and the overall reactivity can be tuned by the appropriate choice of the metal. Traditionally, the stereoselective oxidation of enolates has been carried out with *N*-sulfonyloxaziridines,[2–4] but there is a need for new methods that use environmentally benign oxidants. Molecular oxygen is arguably the most suitable candidate for such an oxidant as it is an abundant reagent that does not produce harmful by-products.[5] However, despite such benefits, it has been scarcely used for the stereoselective hydroxylation of enolates. In pioneering studies, Córdova described the organocatalytic and photosensitized oxidation of cyclohexanones and aldehydes with molecular oxygen.[6] Furthermore, Brigaud established that treating sodium enolates from chiral *N*-acyl trifluoromethylated oxazolidines with molecular oxygen produced α-hydroxy adducts with outstanding diastereoselectivities.[7] In turn, Itoh and Zhao used oxygen for the enantioselective phase transfer catalyzed α-hydroxylation of oxindoles and ketones leading to tertiary alcohols.[8] More recently, Lu has reported a highly efficient hydroxylation of chiral sulfinyl imidates and amidines with oxygen.[9] All of these reported oxidations involve a heterolytic mechanism that provides the corresponding hydroperoxide intermediates, which must be subsequently reduced to the desired α-hydroxy derivatives.

In this context and by taking advantage of both the biradical character of the titanium(IV) enolates[10,11] and our experience of oxidizing them with TEMPO,[12] we aimed to determine whether the reaction of chiral titanium(IV) enolates with triplet molecular oxygen would yield enantiomerically pure α-hydroxylated derivatives through a radical pathway. Thus, we were pleased to observe in exploratory experiments that bubbling a stream of oxygen through a solution of the $TiCl_4$-enolate of (*S*)-4-benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one (**1a**) triggered the desired oxidation at 0 °C (Scheme 1). To our surprise, instead of the expected hydroperoxide **2a**, the hydroxylated derivative **3a** was directly obtained as a single diastereomer with a yield of 28% (Scheme 1).



Scheme 1 Oxidation of Ti(IV) enolates with molecular oxygen

Titanium(IV) enolates prepared by enolization with $TiCl_3(i\text{-PrO})/i\text{-Pr}_2NEt$ did not add any benefit and milder $TiCl_2(i\text{-PrO})_2$ or $TiCl(i\text{-PrO})_3$ Lewis acids are known to be unable to promote an appropriate enolization of such oxazolidinones.[13,14] In turn, the oxidation of the corresponding sodium or boron enolates using the same conditions was unsuccessful; whereas the oxidation of zirconium(IV) enolates[15] produced the α-hydroxylated adduct **3a** in a yield of 18%. Remarkably, careful analysis of the crude reaction mixtures indicated the generation of low, but significant amounts of the by-products **4** shown in Figure 1.

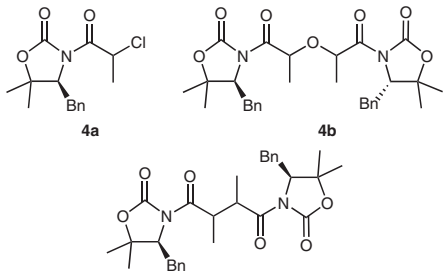


Figure 1 By-products formed in the oxidation of Ti(IV) enolates with oxygen

A comprehensive optimization of the reaction conditions indicated that the oxidation was much more reliable by a simple stirring of the solution containing the titanium(IV) enolate in an oxygen atmosphere at room temperature. Indeed, enolization of **1a** with $TiCl_4/i\text{-Pr}_2NEt$ at 0 °C for 40 minutes in a nitrogen atmosphere and further stirring of the resulting deep red solution under an oxygen atmosphere (1 atm) at room temperature for 3 hours produced the α-hydroxy adduct **3a** in a yield of 45% without consuming all the starting material (see Figure 2). Interestingly, the color of the reacting mixture changed to orange or dark yellow, which facilitated the monitoring of the oxidation.

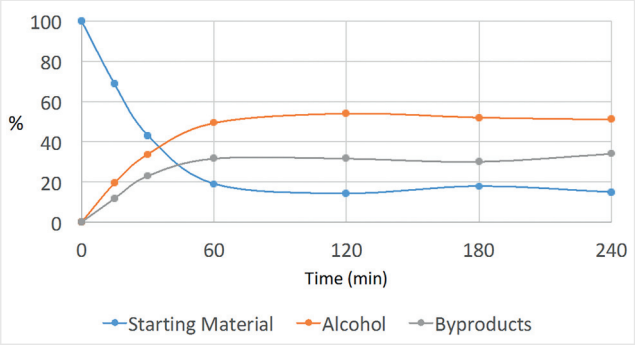
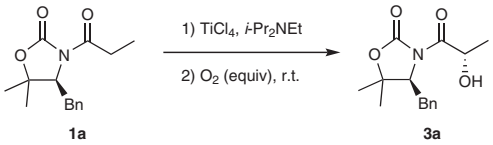


Figure 2 Oxidation of titanium(IV) enolate of **1a** with oxygen

The use of molecular sieves or the addition of a second equivalent of $TiCl_4$ or other reagents, such as $(EtO)_3P$, did not improve the yield. Instead, temperature turned out to be crucial, since the reaction did not progress at all at temperatures lower than –20 °C. Finally, we also examined the influence of the amount of oxygen on the yield of the reaction. Surprisingly, both an excess and 1.3 equivalents of oxygen produced the same yield (Table 1, entries 1 and 2), whereas a substoichiometric amount of oxygen gave **3a** in a 40% yield (entry 3). Such close results hinted that both atoms of the oxygen molecule were incorporated into the oxidized adduct **3a**.

Table 1 Influence of the Amount of Oxygen on the Yield of the Reaction

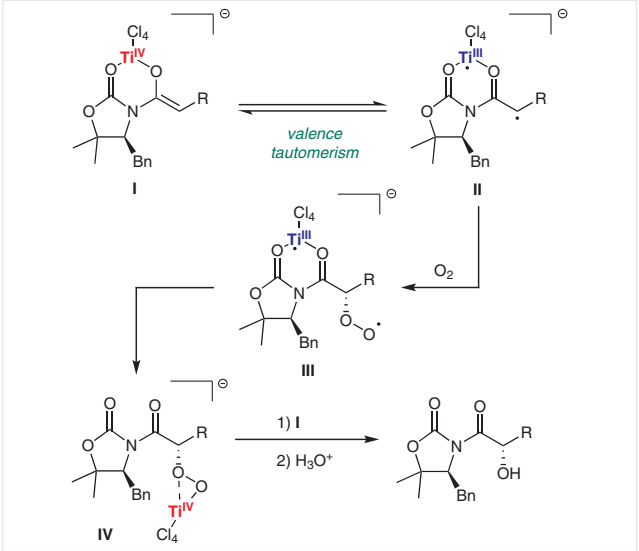


Entry	O_2 (equiv)[a]	Yield (%)[b]
1	excess	45
2	1.3	45
3	0.6	40

[a] Estimated amount of O_2 based on the equivalence 1 mmol ≈ 22.4 mL.
[b] Isolated yields.

Although the underlying mechanism of such α-hydroxylation is still unclear, the abovementioned results suggest that the oxidation of titanium(IV) enolates might be rationalized by considering the biradical character of such species. Indeed, we hypothesized that a radical-like reaction of triplet oxygen with the biradical titanium enolate **II** might trigger the formation of the peroxide **III** shown in Scheme 2. The observed high π-face selectivity may be due to the chelated character of **II**.[16] Taking into account a previous report by Adam,[17] the internal autoxidation of the titanium(III) center of the resulting species might then generate a peroxytitanate intermediate like **IV**, which could be responsible for the further oxidation of a titanium(IV) enolate **I** that is not yet oxidized.[18–20]

Aiming to assess the scope of the reaction, we next applied the optimized reaction conditions to $TiCl_4$-enolates from *N*-acyloxazolidinones **1** containing a wide array of R groups (Scheme 3).[17,18] All these reactions provided in moderate yields a single diastereomer of the corresponding oxygenated adducts, which were easily isolated by column chromatography (Scheme 3). The yields from **1a–d** indicated that the reaction is sensitive to the steric hindrance of the R groups. Otherwise, the benzylic position in **1e** (R: Bn),

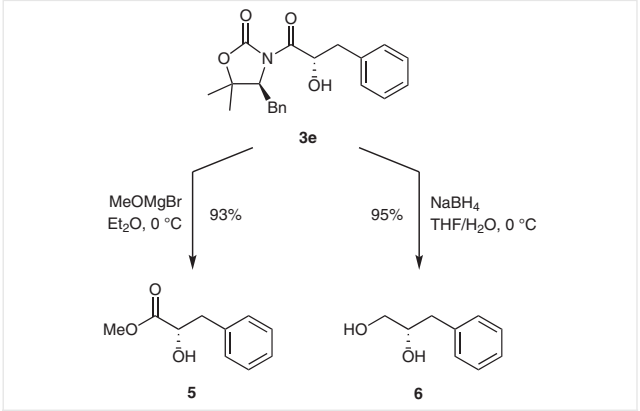


Scheme 2 Mechanistic hypothesis

the double and triple carbon bonds in **1f** and **1g**, respectively, or the ester group in **1h** did not affect the result, which proves the high site-selectivity and chemoselectivity achieved in this oxidation of the Cα position.

Finally, the smooth removal of the chiral auxiliary from model adduct **3e**, following reported procedures,[21] generated excellent yields of up to 95% of the α-hydroxy ester **5** and 1,2-diol **6** (Scheme 4). This also enabled the *S*-configuration of the α-stereocenter to be established.

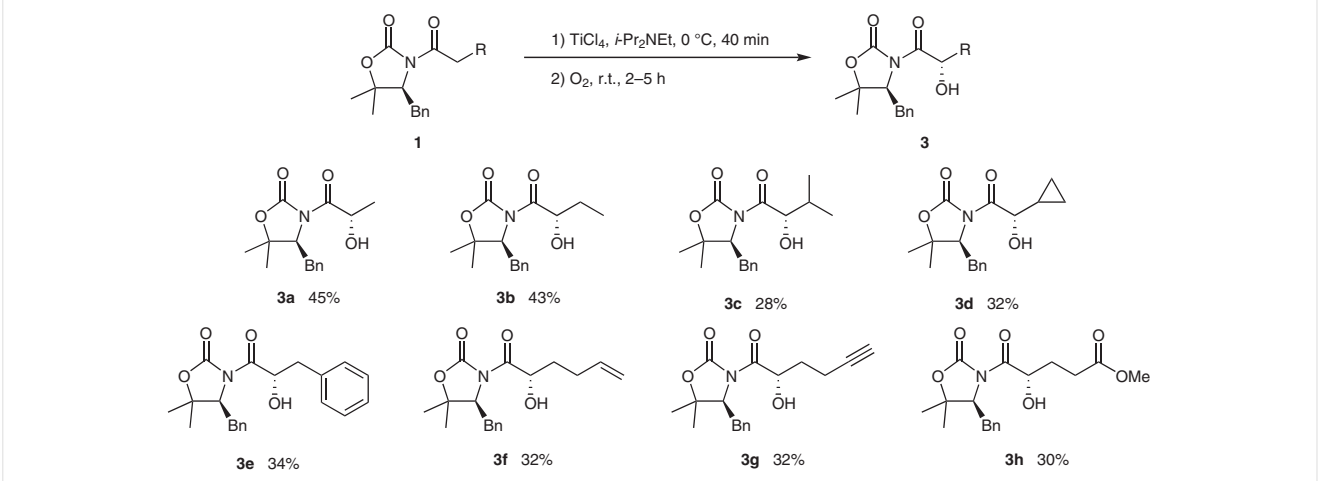
In summary, we have reported a novel stereoselective approach of synthesizing α-hydroxy carboxylic derivatives based on the oxidation of titanium(IV) enolates from chiral acyl oxazolidinones with environmentally friendly oxygen using simple experimental conditions. This transformation produces moderate yields, but in a highly selective manner,



Scheme 4 Removal of the chiral auxiliary

of the corresponding α-hydroxy adducts, which can then be easily converted into enantiomerically pure and synthetically useful intermediates. Importantly, the isolation of the α-hydroxy adducts does not require any additional reducing agent, suggesting that the overall reaction involves an internal redox step that is probably linked to the biradical character of titanium(IV) enolates.

Unless otherwise stated, reactions were conducted in oven-dried glassware under an inert atmosphere of N_2 with anhydrous solvents. The solvents and reagents were dried and purified, when necessary, according to standard procedures. All commercial reagents were used as received. Column chromatography were carried out under low pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Analytical TLC were carried out on Merck silica gel 60 F254 plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid or *p*-anisaldehyde. R_f values are approximate. Melting points were determined with a Stuart Scientific SMP10 or a Gallenkamp apparatus and are uncorrected. Specific rotations ([α]) were determined at 589 nm and at 20 °C on a PerkinElmer 241 MC polarimeter. IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Nicolet



Scheme 3 Oxidation of *N*-acylated oxazolidinones **1**

6700 FT-IR Thermo Scientific spectrophotometer and only the more representative frequencies are reported. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ 0.00 for ^{1}H NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR); data are reported as follows: integration, peak multiplicity (standard abbreviations) with coupling constants measured in Hz; when necessary, 2D techniques (COSY and HSQC) were also used to assist with structure elucidation. High-resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

Acylation of the Chiral Auxiliary (*S*)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one; General Procedure

A 2.5 M solution of *n*-BuLi in hexanes (2.2 mL, 5.5 mmol) was added dropwise to a solution of (*S*)-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one[22] (1.03 g, 5.0 mmol) in THF (25 mL) at –78 °C under N_2. The solution was stirred for 15 min and the corresponding acyl chloride (6.5 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 20 min, allowed to warm to r.t., stirred for 2 h, and quenched with sat. aq NH_4Cl (20 mL). The volatiles were removed and the resulting mixture was partitioned between H_2O and EtOAc (20 mL each), and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography to give the respective acylated chiral auxiliary **1a–h**[23] in yields higher than 90%.

Direct Oxidation of 1; General Procedure

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of respective **1a–h** (0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. The reaction flask was purged with H_2SO_4-dried O_2 for 5 min at 0 °C and stirring was continued at r.t. for 2–5 h under an O_2 atmosphere. The reaction was quenched by the addition of a sat. aq NH_4Cl (2 mL) at r.t. with vigorous stirring. The mixture was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was analyzed by ^{1}H NMR and purified by column chromatography to afford a single diastereomer of the corresponding hydroxylated compound **3a–h**.

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxypropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3a)

Prepared according to the General Procedure from (*S*)-4-benzyl-*N*-propanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (**1a**; 131 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 62 mg (0.22 mmol, 45%) of **3a** as a white solid; mp 45–47 °C; $[\alpha]_D^{20}$ –36.5 (*c* 1.1, $CHCl_3$); R_f = 0.20 (hexanes–EtOAc, 80:20).

IR (ATR): 3451, 2982, 2930, 1771, 1694, 1392, 1354, 1275, 1100 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 5.04 (1 H, quint, *J* = 6.9 Hz), 4.49 (1 H, dd, *J* = 9.5, 3.8 Hz), 3.74 (1 H, d, *J* = 6.9 Hz), 3.18 (1 H, dd, *J* = 14.5, 3.8 Hz), 2.93 (1 H, dd, *J* = 14.5, 9.5 Hz), 1.42 (3 H, d, *J* = 6.9 Hz), 1.40 (3 H, s), 1.39 (3 H, s).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.2, 152.7, 136.5, 129.0, 128.7, 126.9, 83.7, 67.2, 64.0, 35.1, 28.6, 22.2, 19.7.

HRMS (+ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}NO_4$: 278.1387; found: 278.1392.

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxybutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3b)

Prepared according to the General Procedure from (*S*)-4-benzyl-*N*-butanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (**1b**; 137 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 63 mg (0.22 mmol, 43%) of **3b** as a white solid; mp 67–68 °C; $[\alpha]_D^{20}$ –30.7 (*c* 1.0, $CHCl_3$); R_f = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3412, 2967, 2927, 2874, 1770, 1672, 1352 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 4.95 (1 H, td, *J* = 7.6, 3.8 Hz), 4.47 (1 H, dd, *J* = 9.6, 3.6 Hz), 3.44 (1 H, d, *J* = 7.6 Hz), 3.20 (1 H, dd, *J* = 14.5, 3.6 Hz), 2.93 (1 H, dd, *J* = 14.5, 9.6 Hz), 1.91–1.81 (1 H, m), 1.68–1.57 (1 H, m), 1.39 (3 H, s), 1.39 (3 H, s), 1.03 (3 H, t, *J* = 7.4 Hz).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.0, 152.4, 136.6, 129.0, 128.7, 126.9, 83.5, 71.8, 64.0, 35.0, 28.5, 27.3, 22.1, 9.4.

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{21}NO_4Na$: 314.1363; found: 314.1373.

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-3-methylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3c)

Prepared according to the General Procedure from (*S*)-4-benzyl-5,5-dimethyl-*N*-(3-methylbutanoyl)-1,3-oxazolidin-2-one (**1c**; 145 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 43 mg (0.14 mmol, 28%) of **3c** as a white solid; mp 65–66 °C; $[\alpha]_D^{20}$ –18.0 (*c* 1.0, $CHCl_3$); R_f = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3430, 2972, 2923, 2869, 1766, 1694, 1672, 1347 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 4.98 (1 H, dd, *J* = 8.3, 3.3 Hz), 4.46 (1 H, dd, *J* = 9.7, 3.5 Hz), 3.21 (1 H, dd, *J* = 14.5, 3.5 Hz), 3.19 (1 H, d, *J* = 8.3 Hz), 2.94 (1 H, dd, *J* = 14.5, 9.7 Hz), 2.12–2.04 (1 H, m), 1.38 (6 H, s), 1.09 (3 H, d, *J* = 6.8 Hz), 0.84 (3 H, d, *J* = 6.8 Hz).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.1, 152.2, 136.6, 129.0, 128.7, 126.9, 83.4, 74.7, 64.2, 35.0, 31.4, 28.4, 22.1, 19.7, 15.1.

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{23}NO_4Na$: 328.1519; found: 328.1529.

(*S*)-4-Benzyl-*N*-[(*S*)-2-cyclopropyl-2-hydroxyacetyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3d)

Prepared according to the General Procedure from (*S*)-4-benzyl-*N*-(2-cyclopropylacetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**1d**; 99 mg, 0.35 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 28 mg (0.11 mmol, 32%) of **3d** as a white solid; mp 106–108 °C; $[\alpha]_D^{20}$ –30.9 (*c* 1.0, $CHCl_3$); R_f = 0.20 (hexanes–EtOAc, 80:20).

IR (ATR): 3404, 2963, 2918, 2851, 1780, 1668, 1352, 1160, 1094 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 4.82 (1 H, dd, *J* = 8.0, 6.1 Hz), 4.49 (1 H, dd, *J* = 9.6, 3.6 Hz), 3.39 (1 H, d, *J* = 8.0 Hz), 3.21 (1 H, dd, *J* = 14.5, 3.6 Hz), 2.95 (1 H, dd, *J* = 14.5, 9.6 Hz), 1.41 (3 H, s), 1.40 (3 H, s), 1.29–1.22 (1 H, m), 0.61–0.39 (4 H, m).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.7, 152.6, 136.6, 129.0, 128.7, 126.9, 83.6, 71.4, 64.2, 35.1, 28.5, 22.1, 13.7, 1.5, 0.9.

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{21}NO_4Na$: 326.1363; found: 326.1359.

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-3-phenylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3e)

Prepared according to the General Procedure from (*S*)-4-benzyl-5,5-dimethyl-*N*-(3-phenylpropanoyl)-1,3-oxazolidin-2-one (**1e**; 168 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 60 mg (0.17 mmol, 34%) of **3e** as a white solid; mp 98–99 °C; $[\alpha]_D^{20}$ –17.3 (*c* 1.0, $CHCl_3$); R_f = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3425, 3056, 3025, 2994, 2972, 2914, 1792, 1677, 1352, 1330, 1094 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.23 (10 H, m), 5.28 (1 H, td, *J* = 7.9, 4.0 Hz), 4.46 (1 H, dd, *J* = 9.7, 3.7 Hz), 3.46 (1 H, d, *J* = 7.9 Hz), 3.20 (1 H, dd, *J* = 14.2, 3.7 Hz), 3.16 (1 H, dd, *J* = 13.8, 4.0 Hz), 2.92 (1 H, dd, *J* = 14.2, 9.7 Hz), 2.88 (1 H, dd, *J* = 13.8, 7.9 Hz), 1.40 (3 H, s), 1.37 (3 H, s).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.2, 152.4, 136.7, 136.5, 129.5, 129.0, 128.7, 128.3, 126.9, 126.7, 83.5, 71.7, 64.0, 40.2, 35.0, 28.5, 22.2.

HRMS (+ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}NO_4$: 354.1700; found: 354.1705.

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-5-hexenoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3f)

Prepared according to the General Procedure from (*S*)-4-benzyl-*N*-(5-hexenoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**1f**; 150 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 51 mg (0.16 mmol, 32%) of **3f** as a white solid; mp 90–92 °C; $[\alpha]_D^{20}$ –15.1 (*c* 1.0, $CHCl_3$); R_f = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3448, 2994, 2972, 2940, 2990, 2851, 1766, 1703, 1361, 1281 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 5.84–5.75 (1 H, m), 5.07 (1 H, dq, *J* = 17.1, 1.6 Hz), 5.01–4.95 (2 H, m), 4.47 (1 H, dd, *J* = 9.6, 3.7 Hz), 3.52 (1 H, d, *J* = 7.6 Hz), 3.19 (1 H, dd, *J* = 14.5, 3.7 Hz), 2.93 (1 H, dd, *J* = 14.5, 9.6 Hz), 2.29–2.24 (2 H, m), 1.94–1.85 (1 H, m), 1.71–1.62 (1 H, m), 1.40 (3 H, s), 1.39 (3 H, s).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.9, 152.4, 137.5, 136.6, 129.0, 128.7, 126.9, 115.3, 83.5, 70.2, 64.0, 35.0, 33.1, 29.4, 28.5, 22.1.

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{23}NO_4Na$: 340.1519; found: 340.1532.

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-5-hexynoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3g)

Prepared according to the General Procedure from (*S*)-4-benzyl-*N*-(5-hexynoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**1g**; 149 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 51 mg (0.16 mmol, 32%) of **3g** as a white solid; mp 106–108 °C; $[\alpha]_D^{20}$ –16.4 (*c* 1.0, $CHCl_3$); R_f = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3466, 3292, 2949, 2918, 1761, 1699, 1352, 1107 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 4.99 (1 H, ddd, *J* = 8.6, 7.1, 3.6 Hz), 4.49 (1 H, dd, *J* = 9.4, 3.9 Hz), 3.77 (1 H, d, *J* = 7.1 Hz), 3.18 (1 H, dd, *J* = 14.5, 3.9 Hz), 2.93 (1 H, dd, *J* = 14.5, 9.4 Hz), 2.42 (2 H, td, *J* = 7.3, 2.6 Hz), 2.10–2.01 (1 H, m), 1.97 (1 H, t, *J* = 2.6 Hz), 1.87–1.78 (1 H, m), 1.41 (3 H, s), 1.40 (3 H, s).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.9, 152.6, 136.4, 129.0, 128.7, 126.9, 83.7, 83.3, 69.5, 68.9, 64.0, 35.0, 32.1, 28.6, 22.2, 14.4.

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{21}NO_4Na$: 338.1363; found: 338.1377.

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-5-methoxy-5-oxopentanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3h)

Prepared according to the General Procedure from (*S*)-4-benzyl-*N*-(5-methoxy-5-oxopentanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**1h**; 166 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 53 mg (0.15 mmol, 30%) of **3h** as a white solid; mp 91–93 °C; $[\alpha]_D^{20}$ –21.0 (*c* 1.0, $CHCl_3$); R_f = 0.20 (hexanes–EtOAc, 80:20).

IR (ATR): 3466, 2972, 2918, 2851, 1757, 1703, 1352, 1245 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 4.97 (1 H, td, *J* = 7.8, 3.9 Hz), 4.48 (1 H, dd, *J* = 9.5, 3.8 Hz), 3.68 (3 H, s), 3.68 (1 H, d, *J* = 7.8 Hz), 3.18 (1 H, dd, *J* = 14.5, 3.8 Hz), 2.92 (1 H, dd, *J* = 14.5, 9.5 Hz), 2.61–2.47 (2 H, m), 2.18–2.10 (1 H, m), 2.00–1.91 (1 H, m), 1.42 (3 H, s), 1.40 (3 H, s).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.1, 173.6, 152.6, 136.5, 128.9, 128.7, 126.9, 83.7, 69.6, 63.9, 51.6, 35.0, 29.4, 28.5 (2 ×), 22.2.

HRMS (+ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{23}NO_6Na$: 372.1418; found: 372.1430.

Methyl (*S*)-2-Hydroxy-3-phenylpropanoate (5)

A 3.0 M solution of MeMgBr in Et_2O (103 µL, 0.31 mmol) was added to MeOH (1.0 mL) and stirred at 0 °C for 10 min. Then, a solution of **3e** (0.53 g, 0.15 mmol) in 3:1 CH_2Cl_2–MeOH (1.5 mL) was added to the former suspension at 0 °C under N_2 and the resultant mixture was stirred for 5 min. The reaction was quenched with 10% w/w aq $NaHSO_3$ (1 mL) and concentrated in vacuo. The residue was partitioned between 10% w/w aq $NaHSO_3$ (10 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (hexanes–EtOAc, 85:15) afforded 31 mg (0.15 mmol, 99% recovery) of (*S*)-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one and 25 mg (0.14 mmol, 93%) of **5** as a white solid; mp 47–48 °C; $[\alpha]_D^{20}$ –13.1 (*c* 1.1, CH_2Cl_2) {Lit.[4a] $[\alpha]_D^{20}$ –13.7 (*c* 1.1, CH_2Cl_2)}.

IR (ATR): 3271, 3018, 2945, 2838, 1748, 1726, 1425, 1273, 1251, 1087 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.20 (5 H, m), 4.45 (1 H, ddd, *J* = 6.8, 6.1, 4.4 Hz), 3.77 (3 H, s), 3.12 (1 H, dd, *J* = 13.9, 4.4 Hz), 2.96 (1 H, dd, *J* = 13.9, 6.8 Hz), 2.74 (1 H, d, *J* = 6.1 Hz).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.5, 136.3, 129.4 (2 ×), 128.4 (2 ×), 126.9, 71.2, 52.4, 40.5.

HRMS (+ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}NO_3$: 198.1125; found: 198.1116.

(*S*)-3-Phenyl-1,2-propanediol (6)

A solution of **3e** (53 mg, 0.15 mmol) in THF (1 mL) was added to a solution of $NaBH_4$ (34 mg, 0.9 mmol) in THF–H_2O (3:1, 2.2 mL) at 0 °C under N_2 and the resultant mixture was stirred at 0 °C for 50 min. The reaction was quenched by dropwise addition of aq 2 M HCl/brine solution until bubbling ceased. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (10 mL) and the brine layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes–EtOAc, from 40:60 to 20:80) afforded 30 mg (0.15 mmol, 97% recovery) of (S)-benzyl-

5,5-dimethyl-1,3-oxazolidin-2-one and 21 mg (0.14 mmol, 95%) of (*S*)-3-phenyl-1,2-propanediol (**6**) as a clear colorless oil; $[\alpha]_D^{20}$ –18.3 (*c* 1.3, $CHCl_3$) {Lit.[6a] $[\alpha]_D^{20}$ –18.6 (*c* 1.3, $CHCl_3$)}; R_f = 0.20 (hexanes–EtOAc, 85:15).

IR (ATR): 3221, 3024, 2917, 2850, 1495, 1451, 1070, 1036 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (5 H, m), 3.95–3.89 (1 H, m), 3.66 (1 H, dd, *J* = 11.2, 2.7 Hz), 3.49 (1 H, dd, *J* = 11.2, 7.0 Hz), 2.80–2.70 (2 H, m), 2.39 (2 H, br s).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.7, 129.3 (2 ×), 128.6 (2 ×), 126.6, 73.0, 66.0, 39.8.

HRMS (+ESI): *m/z* $[M + NH_4]^+$ calcd for $C_9H_{16}NO_2$: 170.1176; found: 170.1176.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609966.

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