Preparation of Acyloins by Cerium-Catalyzed, Direct Hydroxylation of β-Dicarbonyl Compounds with Molecular Oxygen

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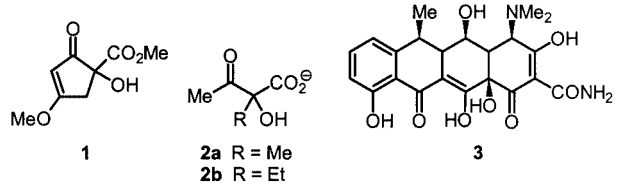
We report the metal-catalyzed α-hydroxylation of a variety of cyclic and acyclic β-dicarbonyl compounds by molecular oxygen. The decisive advantage of this new method is the use of catalytic amounts of the nontoxic cerium salt $CeCl_3 \cdot 7H_2O$ in 2-propanol at ambient temperature. Most of the cyclic substrates **4a**–**4i** give high yields of analytically pure products **5a**–**5i**, and the workup procedure is simple filtration through silica gel. The oxidation of acyclic dicarbonyl compounds **4j**–**4p**, however, is accompanied by side reactions and decomposition, reducing the yields of products **5j**–**5p** significantly. A proposed mechanism is in agreement with experimental results, in particular the observed oxygen uptake.

Introduction

The α-hydroxy-β-dicarbonyl moiety can be found in biologically important compounds such as the cyclopentenoid kjellmanianone (**1**),[1] the biosynthetic precursors of valine and isoleucine [α-acetolactate (**2a**) and α-acetohydroxybutyrate (**2b**)],[2] and tetracycline-type antibiotics such as doxycycline (**3**; Scheme 1).[3] In addition to some other methods of synthesizing this functionality[4] a number of reagents exist for the direct α-hydroxylation of β-dicarbonyl compounds. Examples are the stoichiometric application of $[Pb(OAc)_4]$,[5] the Mimoun reagent (MoO_5·pyridine·HMPA),[6] oxaziridines introduced by Davis[7] and peracids.[8] A sequence of deprotonation, silyl enol ether formation and epoxidation known as Rubottom oxidation[9] can also be applied. The disadvantage of all these methods is the formation of large quantities of by-products. Adam and co-workers were the first to use dimethyl dioxirane (DMD) for the α-oxidation of ketones after deprotonation with LDA or NaHMDS.[10] The corresponding α-hydroxylation of β-dicarbonyl compounds with DMD did not require a stoichiometric amount of strong base. Since acetone is the only by-product formed in these DMD oxidations,[11] this method may be viewed as environmentally sound "green chemistry". The yields can be improved by the application of either KF (supposedly stabilizing the enol tautomer by H-bonding)[12] or catalytic amounts of $[Ni(acac)_2]$.[13] However, with regard to economical and ecological considerations molecular oxygen represents the optimal oxidizing reagent, an issue that has received continuous attention.[14] The metal-catalyzed α-hydroxylation of β-dicarbonyl compounds with O_2 has previously been reported three times. $CoCl_2$,[15] Cs_2CO_3,[16] and $Mn(OAc)_2 \cdot 4H_2O$[17] have been applied as catalytically active compounds. There has been one publication on Mn- and Co-catalyzed radical additions of malonates to olefins in the presence of oxygen yielding γ-hydroxylated products.[18] In this paper we report the application of $CeCl_3 \cdot 7H_2O$ as a catalyst[19] that seems to be superior to the other protocols mentioned above. The advantages, apart from the improved yields, are the use of the inexpensive and nontoxic cerium salt and *i*PrOH as the solvent.



1 **2a** R = Me **2b** R = Et **3**

Scheme 1. Examples of the α-hydroxy-β-dicarbonyl moiety occurring in natural products

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Results and Discussion

Optimization

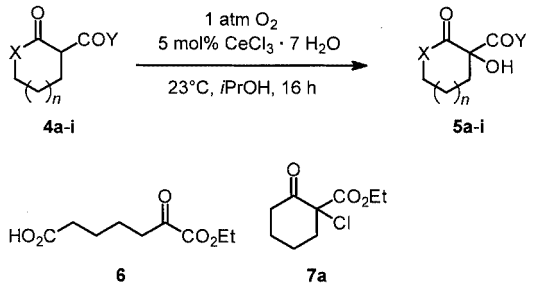
In the course of our combinatorial type of search for new catalysts for C−C bond-forming reactions[20] we observed the formation of α-hydroxylated by-products **5** when treating β-dicarbonyl compounds **4** with catalytic amounts of $CeCl_3 \cdot 7H_2O$ without excluding air. During our search for optimal reaction conditions we recognized that the solubility of oxygen in the reaction mixture seems to be crucial for the success of this transformation. Finally, the optimal solvents turned out to be DMF and *i*PrOH, and the conver-

sion should be run at ambient temperature. Importantly, we found that 1 atm of O_2 was in most cases superior to air. Nevertheless, full conversion of some substrates, for example **4a** or **4c**, can also be achieved with air. Moreover, a slow but continuous stream of O_2 seemed to be required for optimal results. The use of a static reservoir (e.g. a balloon of O_2) sometimes gave irreproducible results. Presumably the slow evaporation of the solvent lowers the partial pressure of O_2 adjacent to the liquid phase. All optimization experiments were performed with compounds **4a** and **4h** as the substrates. With regard to the cerium source, we recommend $CeCl_3 \cdot 7H_2O$, although $(NH_4)_2Ce(NO_3)_6$ or $Ce(OAc)_3 \cdot H_2O$ can also be used in some cases. The use of additives (Brönstedt bases or ligands) never improved the conversion.

The amount of $CeCl_3 \cdot 7H_2O$ applied in our standard procedure was 5 mol %. However, it is worth mentioning that for substrate **4a**, which seems to be the optimal case, full conversion was observed (by GC) within 16 h with 1 mol % catalyst, and even with 0.5 mol % a 77% yield of isolated material **5a** was achieved.

Cyclic Substrates

With our optimized procedure, cyclic substrates **4a**−**4i** generally gave good (**5d**−**5i**) to excellent (**5a**−**5c**) results (Scheme 2). Moreover, at least for compounds **5a**−**5g**, the workup procedure was extraordinarily simple: Filtration through a small pad of SiO_2 separated all metal-containing materials and gave analytically pure products **5a**−**5g** after removal of all volatiles under high vacuum. The ester **5b** was obtained as a mixture of two diastereoisomers (1:1). In the case of the lactams **5d**, **5e** and lactones **5f**, **5g** polar by-products needed to be removed by either filtration through SiO_2 (**5d**, **5e**, **5f**) or chromatography (**5g**). The six-membered ring products **5h** and **5i** seemed to decompose slowly under the reaction conditions and they had to be purified by distillation or chromatography. In the case of **5h** the acid **6** (formation of **6** from **5h** has been reported before)[8,17] was identified as the decomposition product (28%). The chloro compound **7a**[21] was found as a by-product (4%).



Compd.	X	Y	*n*	yield (%)
4a, **5a**	CH_2	OEt	0	99
4b, **5b**	CH_2	O(L-menthyl)	0	99
4c, **5c**	CH_2	OMe	2	96
4d, **5d**	BnN	Me	0	72
4e, **5e**	BnN	Me	1	85
4f, **5f**	O	Me	2	83
4g, **5g**	O	Me	0	78
4h, **5h**	CH_2	OEt	1	59
4i, **5i**	CH_2	Me	1	51

Scheme 2. Cerium-catalyzed α-hydroxylation of cyclic β-dicarbonyl compounds **4a**−**4i**; products **5a**−**5f** were purified by simple filtration through 2 cm of SiO_2, **5g** was chromatographed, and **5h**, **5i** were purified either by chromatography (38 and 46% yield for **5h** and **5i**, respectively) or by Kugelrohr distillation; in the case of **5h** by-products **6** and **7a** were isolated after chromatographic workup in 28 and 4% yield, respectively

In the cases of the lactams **5d** and **5e**, as well as the caprolactone **5f**, the constitution of the product was proved by X-ray single-crystal analysis. Their molecular structures are shown in Figures 1−3.

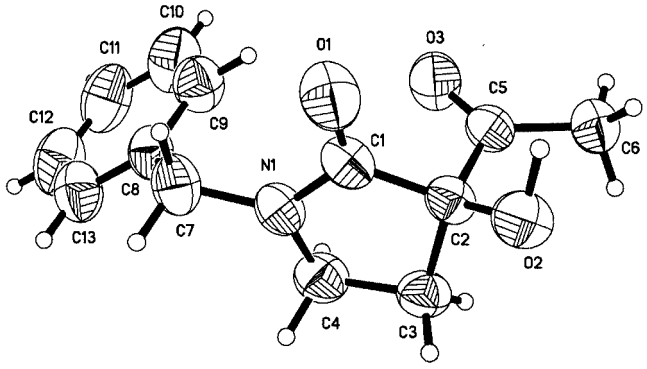


Figure 1. Molecular structure of the α-hydroxylated butyrolactam **5d**

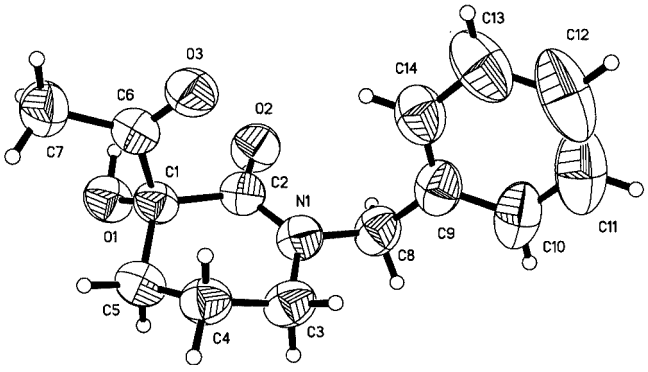


Figure 2. Molecular structure of the α-hydroxylated valerolactam **5e**

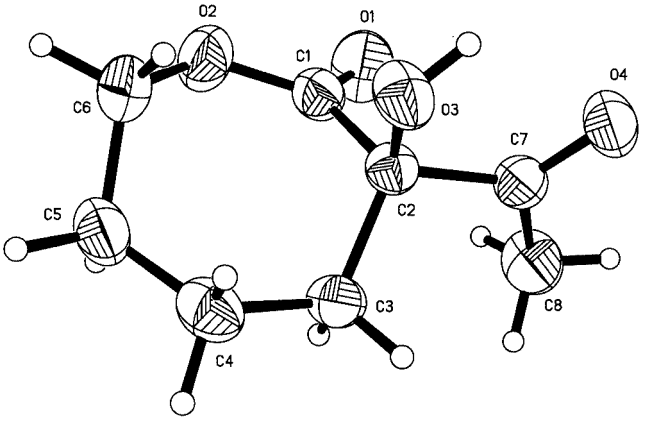
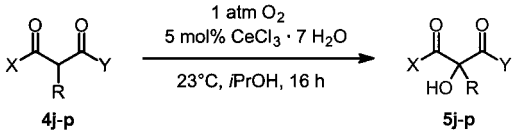


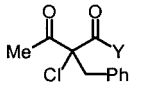
Figure 3. Molecular structure of the α-hydroxylated caprolactone **5f**

Acyclic Substrates

Investigation of acyclic substrates showed that only the β-oxo esters **4j**−**4o** and the β-diketone **4p** with an α-alkyl substituent gave isolable α-hydroxylated products **5j**−**5p** (Scheme 3). As shown in Scheme 3, the yields (30−44%) are moderate, in the case of the α-isopropyl ester **5m** even low. This low yield might be due to a steric effect. For two of the substrates (**4o**, **4p**), the α-chlorinated by-products **7b**[22] and **7c**[19] were separated and isolated by column chromatography.



4j-p **5j-p**



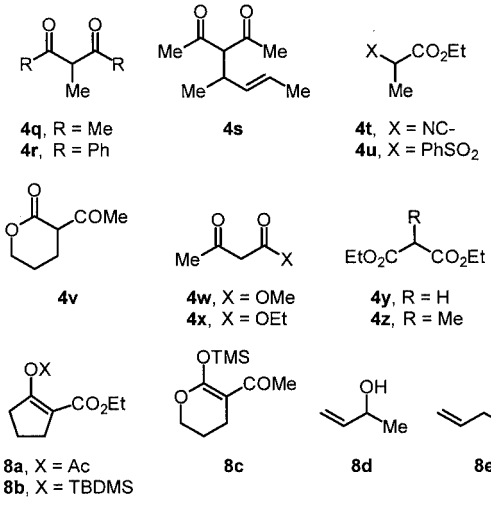
7b, Y = OEt
7c, Y = Me

Compd.	X	Y	R	yield (%)
4j, **5j**	Me	OEt	Me	29
4k, **5k**	Me	OEt	Et	32
4l, **5l**	Me	OEt	Bu	45
4m, **5m**	Me	OEt	*i*Pr	13
4n, **5n**	Ph	OEt	Me	30
4o, **5o**	Me	OEt	CH_2Ph	30
4p, **5p**	Me	Me	CH_2Ph	44

Scheme 3. Cerium-catalyzed α-hydroxylation of acyclic β-dicarbonyl compounds **4j**−**4p**; products **5j**−**5p** were purified by chromatography; in the case of **5o** and **5p** by-products **7b** and **7c** were isolated in 14 and 7%, respectively; starting materials **4m** (63%), **4n** (16%) and **4o** (42%) were recovered

Other Substrates

The diketones **4q**−**4s** as well as the cyano ester **4t** and the sulfone **4u** (Scheme 4) showed no conversion under the reaction conditions. In contrast, the dicarbonyl compounds **4v**−**4z** gave unspecified reaction mixtures, and the corresponding α-hydroxylated compounds **5v**−**5z** were only detectable in trace amounts by GC-MS.



4q, R = Me
4r, R = Ph

4s

4t, X = NC-
4u, X = $PhSO_2$

4v

4w, X = OMe
4x, X = OEt

4y, R = H
4z, R = Me

8a, X = Ac
8b, X = TBDMS

8c **8d** **8e**

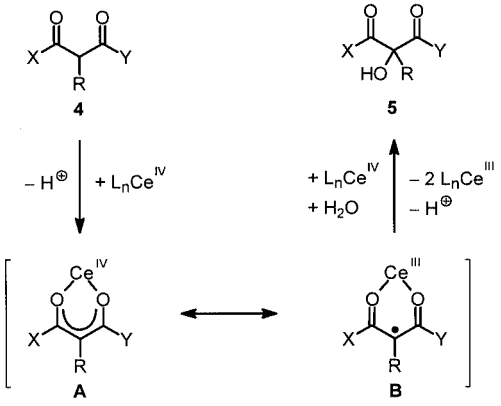
Scheme 4. Substrates either giving no conversion (**4q**−**4u**, **8a**−**8e**) or decomposing under the reaction conditions (**4v**−**4z**)

We utilized the enol acetate **8a** as well as the silyl enol ethers **8b**, **8c** as substrates hoping to find isolable intermediates of the oxidation. Unfortunately, we detected no conversion for compounds **8a**−**8c**, the allylic alcohol **8d** or the ether **8e**.

Mechanistic Rationale

From a mechanistic point of view, we propose the in situ oxidation of Ce^{III} to Ce^{IV} by O_2. According to Equation (1) in Scheme 5, 2 equiv. of Ce^{III} require 1 equiv. of 1/2 O_2. We further assume the formation of Ce^{IV} diketonate complexes **A** in the reaction mixture. Species **A** could undergo intramolecular electron transfer (ligand-to-metal charge transfer) giving a radical species **B**. At least formally, species **B** is oxidized by a second equivalent of Ce^{IV} and hydrated to give products **5**. Although the details of the conversion of **B** to **5** remain unclear, this proposal is in accordance with the stoichiometry in Equation (1), and it is experimentally supported by the average oxygen uptake, calculated from the mass difference to be 1.15 equiv. of 1/2 O_2 per equivalent of dicarbonyl compound **4a**, if 5 mol % Ce^{III} catalyst is used. Application of 10 mol % catalyst results in an uptake of 1.22 equiv. of oxygen and 50 mol % catalyst in an uptake of 1.37 equiv. of oxygen per equivalent of ester **4a**. This stoichiometry per se excludes the oxidation of any co-substrate, such as the solvent *i*PrOH, to give acetone.

$$2\ H^{\oplus} + 2\ Ce^{III} + \tfrac{1}{2}\ O_2 \longrightarrow H_2O + 2\ Ce^{IV} \quad \text{eq. (1)}$$

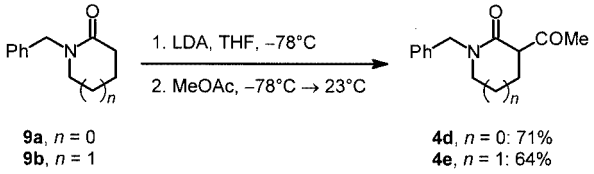


Scheme 5. Mechanistic proposal for the cerium-catalyzed α-oxidation of β-dicarbonyl compounds

The outline shown in Scheme 5 is further supported by the fact that an alkyl group (R ≠ H) seems to be required for chemoselective conversion of the substrates, since the electron-deficient intermediate **B** is stabilized by hyperconjugation. Moreover, the formation of chloro compounds **7a**−**7c** as by-products can be rationalized from intermediate **B**.

Synthesis of α-Acetyllactams

The preparation of α-acetyllactams appears to be considerably simpler than the formation of the corresponding lactones, which we reported recently.[23] The parent lactams **9a**, **9b** (Scheme 6) are deprotonated with LDA in THF at −78 °C followed by addition of MeOAc and warming of the reaction mixture to ambient temperature. The use of AcCl and Ac_2O as acylating reagents results in significantly lower yields.



9a, *n* = 0
9b, *n* = 1

4d, *n* = 0: 71%
4e, *n* = 1: 64%

Scheme 6. Synthesis of α-acetyllactams **4d**, **4e** by deprotonation of lactams **9a**, **9b** followed by treatment with MeOAc

Conclusion

Cerium(III) chloride heptahydrate is a readily available and nontoxic catalyst for the α-hydroxylation of β-dicarbonyl compounds. The oxidant is molecular oxygen and the solvent 2-propanol. With regard to economical and ecological considerations both are ideal. For most cyclic substrates **4a**−**4i**, ranging from β-oxo esters, β-oxolactones and β-oxolactams to β-dicarbonyl compounds, quantitative conversion combined with complete chemoselectivity is achieved, resulting in a very simple workup procedure: Filtration of the reaction mixture through SiO_2 removes all metal-containing materials and yields analytically pure products. Unfortunately, for acyclic substrates **4j**−**4p** the chemoselectivity is significantly lower. Only β-oxo esters and β-diketones bearing an α-alkyl substituent give products with yields up to 50% after chromatography. For a number of other substrates either no conversion (**4q**−**4u**, **8a**−**8e**) or the formation of very complex reaction mixtures (**4v**−**4z**) is observed. We propose a mechanism for the α-hydroxylation which is in accordance with the stoichiometry calculated from the oxygen uptake during the reaction.

Experimental Section

General: Starting materials **4a**, **4c**, **4g**−**4i**, **4q**, **4w**−**4y**, **8d**, and **8e** are commercially available. The following compounds were prepared according to literature procedures: **4b**,[24] **4f**, **4v**, **8c**,[23] **4j**, **4k**,[25] **4l**,[26] **4m**,[27] **4n**,[28] **4o**,[29] **4p**,[30] **4r**,[31] **4s**,[32] **4t**,[33] **4u**,[34] **4z**,[35] **8a**,[36] **8b**,[37] **9a**,[38] and **9b**.[39] Column chromatography was carried out using Merck SiO_2 60 with hexanes (PE, b.p. 40−60 °C), and EtOAc (EA) as eluents. LDA (2.0 M in THF/heptane/ethylbenzene) was purchased from Aldrich Chemical Co. ^{13}C NMR multiplicities were determined with DEPT experiments.

α-Acetyl-*N*-benzyl-γ-butyrolactam (4d): A solution of pyrrolidone **9a** (8.77 g, 50.0 mmol) in anhydrous THF (30 mL) was added at −78 °C within 4 h (syringe pump) to a solution of LDA (50.0 mmol, 25.0 mL, 2.0 M) in THF (25 mL). Subsequently, a solution of anhydrous MeOAc (7.98 mL, 7.41 g, 100 mmol) in THF (10 mL) was added within 2 h at −78 °C. The mixture was allowed to warm to 23 °C (16 h), and poured into cold (ice/water bath) hydrochloric acid (25 mL, 2 M). The aqueous layer was separated and extracted with CH_2Cl_2 (1 × 60 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed under vacuum, and the crude product chromatographed on SiO_2 (PE/EA, 1:1, R_f = 0.27) to furnish compound **4d** as a colorless oil (7.72 g, 35.5 mmol, 71%). ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.00−2.08 (m, 1 H), 2.45 (s, 3 H), 2.52−2.59 (m, 1 H), 3.21−3.26 (m, 1 H), 3.32−3.37 (m, 1 H), 3.67−3.70 (m, 1 H), 4.43 (d, *J* = 14.7 Hz, 1 H), 4.51 (d, *J* = 14.7 Hz, 1 H), 7.23−7.38 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 19.4 (CH_2), 30.0 (CH), 44.8 (CH_2), 47.0 (CH_2), 55.7 (CH_3), 127.6 (CH), 127.9 (CH), 128.6 (CH), 135.1 (C), 169.7 (CO), 203.6 (CO) ppm. IR (neat): $\tilde{\nu}$ = 2920 (m), 1720 (vs), 1680 (vs), 1490 (s), 1450 (s), 1430 (s), 1350 (s) cm^{-1}. HRMS (70 eV, EI): calcd. 217.1103 for $C_{13}H_{15}NO_2$, found 217.1102 [M^+]. $C_{13}H_{15}NO_2$ (217.26): calcd. C 71.87, H 6.96, N 6.45; found C 71.43, H 7.00, N 6.45.

α-Acetyl-*N*-benzyl-δ-valerolactam (4e): According to the procedure described for **4d**, *N*-benzylvalerolactam **9b** (7.80 g, 41.2 mmol) was converted into crude **4e** by adding LDA (20.6 mL, 41.2 mmol, 2.0 M) and MeOAc (6.50 mL, 6.03 g, 82.0 mmol). Purification by chromatography (SiO_2, PE/EA, 1:1, R_f = 0.21) gave compound **4e** as a yellow oil (6.09 g, 26.4 mmol, 64%). ^1H NMR ($CDCl_3$, 500 MHz), mixture of keto and enol tautomer (ratio 1:2); **Keto Form:** δ = 1.67−1.76 (m, 1 H), 1.83−1.92 (m, 2 H), 2.08−2.16 (m, 1 H), 2.37 (s, 3 H), 3.17−3.26 (m, 2 H), 3.54−3.60 (m, 1 H), 4.53 (d, *J* = 14.6 Hz, 1 H), 4.66 (d, *J* = 14.6 Hz, 1 H), 7.23−7.36 (m, 5 H) ppm; **Enol Form:** δ = 1.76−1.82 (m, 2 H), 1.95 (s, 3 H), 2.37−2.42 (m, 2 H), 3.22 (t, *J* = 5.7 Hz, 2 H), 4.60 (s, 2 H), 7.23−7.36 (m, 5 H), 14.96 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) ppm: **Keto Form:** δ = 21.4 (CH_2), 24.1 (CH_2), 30.6 (CH_3), 47.6 (CH_2), 50.8 (CH_2), 56.0 (CH), 127.9 (CH), 128.4 (CH), 129.1 (CH), 137.2 (C), 167.0 (C), 206.3 (C) ppm; **Enol Form:** δ = 19.0 (CH_3), 23.02 (CH_2), 24.6 (CH_2), 47.7 (CH_2), 50.2 (CH_2), 96.1 (C), 127.7 (CH), 128.2 (CH), 129.0 (CH), 137.7 (C), 169.7 (C), 170.9 (C) ppm. IR (neat): $\tilde{\nu}$ = 2920 (m), 2840 (m), 1720 (vs), 1640 (vs) cm^{-1}. MS (70 eV, EI): *m/z* (%) = 231 (96) [M^+], 216 (10), 188 (70), 91 (100). $C_{14}H_{17}NO_2$ (231.29): calcd. C 72.70, H 7.41, N 6.06; found C 72.75, H 7.45, N 6.04.

General Procedure for the Cerium-Catalyzed α-Hydroxylation: The β-dicarbonyl compound **4** (1 equiv.) was added to a suspension of $CeCl_3 \cdot 7H_2O$ (0.05 equiv.) in *i*PrOH (ca. 3 M). The flask was evacuated twice to ca. 500 mbar, each time flushed with O_2, and the mixture was then stirred for 16 h while a slow stream of O_2 (ca. 50 $cm^3\ h^{-1}$) was passed through.

Workup Procedure A: The mixture was filtered through ca. 2 cm of SiO_2 (washing with EA or CH_2Cl_2). All volatiles were removed from the filtrate under high vacuum to yield the α-hydroxylated products **5**.

Workup Procedure B: The solvents were evaporated and the residue submitted to column chromatography (SiO_2, PE/EA) to yield the products **5**.

Workup Procedure C: The solvents were evaporated and the residue submitted to Kugelrohr distillation under vacuum to yield the products **5**.

Ethyl 1-Hydroxy-2-oxo-1-cyclopentanecarboxylate (5a): According to the General Procedure, **4a** (260 mg, 1.66 mmol) and

$CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5a** after Workup A as a colorless liquid (282 mg, 1.64 mmol, 99%). All data are in accordance with the literature.[17]

L-Menthyl 1-Hydroxy-2-oxo-1-cyclopentanecarboxylate (5b): According to the General Procedure, **4b** (202 mg, 0.758 mmol) and $CeCl_3 \cdot 7\,H_2O$ (15 mg, 0.040 mmol) in *i*PrOH (0.5 mL) were converted to yield **5b** after Workup A as a colorless liquid (211 mg, 0.747 mmol, 99%). All data are in accordance with the literature.[19]

Methyl 1-Hydroxy-2-oxo-1-cycloheptanecarboxylate (5c): According to the General Procedure, **4c** (274 mg, 1.61 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5c** after Workup A as a colorless liquid (287 mg, 1.54 mmol, 96%). All data are in accordance with the literature.[17]

α-Acetyl-*N*-benzyl-α-hydroxy-γ-butyrolactam (5d): According to the General Procedure, **4d** (328 mg, 1.51 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5d** after Workup A as a colorless crystalline solid (255 mg, 1.09 mmol, 72%). M.p. 84.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.10 (ddd, *J* = 13.5, *J* = 8.8, *J* = 7.8 Hz, 1 H), 2.30 (s, 3 H), 2.44 (ddd, *J* = 13.5, *J* = 6.9, *J* = 3.7 Hz, 1 H), 3.27−3.35 (m, 2 H), 4.44 (d, *J* = 14.7 Hz, 1 H), 4.57 (d, *J* = 14.7 Hz, 1 H), 5.07 (br. s, 1 H), 7.19−7.36 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 25.47 (CH_3), 31.27 (CH_2), 43.87 (CH_2), 47.77 (CH_2), 84.03 (C), 128.29 (CH), 128.47 (CH), 129.23 (CH), 135.67 (CH), 172.21 (C), 208.21 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3260 (br, s), 1714 (s), 1676 (s) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 233 (5) [M$^+$], 217 (67), 191 (17), 174 (90), 91 (100). $C_{13}H_{15}NO_3$ (233.26): calcd. C 66.94, H 6.48, N 6.00; found C 67.20, H 6.53, N 5.90.

α-Acetyl-*N*-benzyl-α-hydroxy-δ-valerolactam (5e): According to the General Procedure, **4e** (358 mg, 1.55 mmol) and $CeCl_3 \cdot 7\,H_2O$ (29 mg, 0.078 mmol) in *i*PrOH (0.5 mL) were converted to yield **5e** after Workup A as a colorless crystalline solid (327 mg, 1.32 mmol, 85%). M.p. 102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.83−1.99 (m, 3 H), 2.17−2.28 (m, 1 H), 2.30 (s, 3 H), 3.21−3.35 (m, 2 H), 4.50 (d, *J* = 14.7 Hz, 1 H), 4.59 (s, 1 H), 4.75 (d, *J* = 14.7 Hz, 1 H), 7.26−7.38 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 18.62 (CH_2), 24.59 (CH_3), 30.67 (CH_2), 47.06 (CH_2), 50.71 (CH_2), 79.40 (C), 127.68 (CH), 127.96 (CH), 128.77 (CH), 136.19 (C), 169.13 (C), 208.12 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3316 (br, s), 2940 (m), 2875 (m), 1716 (s), 1622 (vs) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 247 (2) [M$^+$], 230 (17), 204 (99), 91 (100). $C_{14}H_{17}NO_3$ (247.29): calcd. C 68.00, H 6.93, N 5.66; found C 67.91, H 6.95, N 5.48.

α-Acetyl-α-hydroxy-ε-caprolactone (5f): According to the General Procedure, **4f** (250 mg, 1.60 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5f** after Workup A as a colorless crystalline solid (227 mg, 1.32 mmol, 83%). M.p. 70−72 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.74−1.88 (m, 3 H), 1.94−2.06 (m, 2 H), 2.09−2.17 (m, 1 H), 2.39 (s, 3 H), 4.27 (ddd, *J* = 12.3, *J* = 6.9, *J* = 2.0 Hz, 1 H), 4.60 (s, 1 H), 4.79 (ddd, *J* = 12.2, *J* = 9.4, *J* = 1.4 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 22.81 (CH_2), 24.98 (CH_3), 29.07 (CH_2), 32.28 (CH_2), 69.94 (CH_2), 82.35 (C), 172.43 (C), 204.94 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3443 (br, vs), 2974 (m), 2943 (s), 1703 (br, vs) cm^{-1}. MS (CH_4, CI): *m*/*z* (%) = 173 (21) [MH$^+$], 155 (15), 130 (49), 127 (100). $C_8H_{12}O_4$ (172.18): calcd. C 55.81, H 7.02; found C 55.81, H 6.98.

α-Acetyl-α-hydroxy-γ-butyrolactone (5g): According to the General Procedure, **4g** (208 mg, 1.62 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5g** after Workup B (PE/EA, 1:1, R_f = 0.26) as a yellow oil (183 mg, 1.27 mmol, 78%). All data are in accordance with the literature.[12]

Ethyl 1-Hydroxy-2-oxo-1-cyclohexanecarboxylate (5h): According to the General Procedure, **4h** (1.089 g, 6.380 mmol) and $CeCl_3 \cdot 7\,H_2O$ (119 mg, 0.320 mmol) in *i*PrOH (2.0 mL) were converted to yield **5h** after Workup C (110−180 °C/2 mbar) as a colorless liquid (696 mg, 3.74 mmol, 59%). All data are in accordance with the literature.[17]

2-Acetyl-2-hydroxycyclohexanone (5i): According to the General Procedure, **4i** (1.051 g, 7.498 mmol) and $CeCl_3 \cdot 7\,H_2O$ (140 mg, 0.376 mmol) in *i*PrOH (2.4 mL) were converted to yield **5i** after Workup C (60−160 °C/2 mbar) as a colorless liquid (592 mg, 3.79 mmol, 51%). All data are in accordance with the literature.[9d]

Ethyl 2-Hydroxy-2-methyl-3-oxobutanoate (5j): According to the General Procedure, **4j** (235 mg, 1.62 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5j** after Workup B (PE/EA, 5:1, R_f = 0.19) as a colorless liquid (75 mg, 0.47 mmol, 29%). All data are in accordance with the literature.[15]

Ethyl 2-Ethyl-2-hydroxy-3-oxobutanoate (5k): According to the General Procedure, **4k** (255 mg, 1.61 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5k** after Workup B (PE/EA, 10:1, R_f = 0.13) as a colorless liquid (89 mg, 0.51 mmol, 32%). All data are in accordance with the literature.[4b]

Ethyl 2-Acetyl-2-hydroxyhexanoate (5l): According to the General Procedure, **4l** (302 mg, 1.62 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5l** after Workup B (PE/EA, 10:1, R_f = 0.14) as a colorless liquid (149 mg, 0.737 mmol, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (t, *J* = 7.1 Hz, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.16−1.40 (m, 4 H), 1.85−1.96 (m, 1 H), 2.04−2.23 (m, 1 H), 2.29 (s, 3 H), 4.17 (s, 1 H), 4.21−4.36 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 13.87 (CH_3), 14.06 (CH_3), 22.69 (CH_2), 24.68 (CH_3), 25.22 (CH_2), 34.94 (CH_2), 62.58 (CH_2), 84.24 (C), 171.02 (C), 205.11 (C) ppm. IR (neat): $\tilde{\nu}$ = 3493 (br, s), 2961 (s), 2933 (s), 1749 (s), 1719 (vs) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 202 (1) [M$^+$], 160 (100), 85 (64), 43 (27). $C_{10}H_{18}O_4$ (202.24): calcd. C 59.39, H 8.97; found C 59.30, H 8.99.

Ethyl 2-Hydroxy-2-isopropyl-3-oxobutanoate (5m): According to the General Procedure, **4m** (274 mg, 1.59 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5m** after Workup B (PE/EA, 10:1, R_f = 0.16) as a colorless liquid (40 mg, 0.21 mmol, 13%). In a first fraction (R_f = 0.21) starting material **4m** (174 mg, 1.01 mmol, 63%) was recovered. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.80 (d, *J* = 6.7 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 2.32 (s, 3 H), 2.72 (sept, *J* = 6.8 Hz, 1 H), 4.10 (s, 1 H), 4.22−4.33 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 14.09 (CH_3), 15.97 (CH_3), 16.80 (CH_3), 25.18 (CH), 33.77 (CH_3), 62.59 (CH_2), 87.79 (C), 170.84 (C), 205.83 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3482 (br, s), 2972 (s), 1721 (vs), 1261 (s), 1177 (s), 1155 (s) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 189 (10) [MH$^+$], 171 (13), 146 (34), 115 (72), 71 (100), 43 (90). $C_9H_{16}O_4$ (188.22): calcd. C 57.43, H 8.57; found C 57.63, H 8.52.

Ethyl 2-Hydroxy-2-methyl-3-oxo-3-phenylpropanoate (5n): According to the General Procedure, **4n** (270 mg, 1.31 mmol) and $CeCl_3 \cdot 7\,H_2O$ (20 mg, 0.054 mmol) in *i*PrOH (0.5 mL) were converted to yield **5n** after Workup B (toluene/EA, 30:1, R_f = 0.16) as a colorless liquid (87 mg, 0.39 mmol, 30%). In a first fraction (R_f = 0.29) starting material **4n** (43 mg, 0.21 mmol, 16%) was recovered. All data are in accordance with the literature.[19]

Table 1. Crystal data and structure refinement for compounds **5d**−**5f**

	5d	**5e**	**5f**
Empirical formula	$C_{13}H_{15}NO_3$	$C_{14}H_{17}NO_3$	$C_8H_{12}O_4$
M [g mol^{-1}]	233.26	247.29	172.18
Crystal size [mm]	0.3 × 0.15 × 0.10	0.7 × 0.35 × 0.06	0.7 × 0.7 × 0.25
Crystal system	triclinic	monoclinic	monoclinic
Space group	$P\bar{1}$	$C2/c$	$P2_1/c$
a [Å]	6.8367(5)	19.1529(9)	8.5823(9)
b [Å]	9.4094(7)	6.6057(3)	10.2091(6)
c [Å]	10.7287(7)	23.0387(9)	9.9568(9)
α [°]	68.547(6)	90	90
β [°]	80.050(5)	112.938(4)	102.650(7)
γ [°]	77.111(6)	90	90
V [Å^3]	623.00(8)	2684.3(2)	851.21(13)
Z	2	8	4
$\rho_{calcd.}$ [g cm^{-3}]	1.243	1.224	1.344
μ [mm^{-1}]	0.727	0.702	0.913
F(000)	248	1056	368
2Θ range [°]	4.45−65.00	4.17−67.98	5.28−67.98
No. of unique data	2027	2289	1441
No. of data obsd. [$I > 2\sigma(I)$]	1395	1335	1300
No. of parameters refined	159	168	111
$R1$, $wR2$ (all data)	0.0762, 0.2000	0.1198, 0.3304	0.0594, 0.1665
$R1$ (obsd.)	0.0593	0.0956	0.0568
GoF (F^2)	1.118	1.161	1.095
Max./min. electron density [e·Å^{-3}]	0.207/−0.221	0.473/−0.289	0.242/−0.235

Ethyl 2-Benzyl-2-hydroxy-3-oxobutanoate (5o): According to the General Procedure, **4o** (351 mg, 1.59 mmol) and $CeCl_3 \cdot 7\,H_2O$ (30 mg, 0.081 mmol) in *i*PrOH (0.5 mL) were converted to yield **5o** after Workup B (PE/EA, 10:1, R_f = 0.18) as a colorless liquid (112 mg, 0.47 mmol, 30%). In a first fraction (R_f = 0.38) by-product **7b** was recovered as a colorless liquid (55 mg, 0.22 mmol, 14%) and in a second fraction (R_f = 0.19) starting material **4o** (147 mg, 0.667 mmol, 42%). All data are in accordance with the literature.[19]

3-Benzyl-3-hydroxy-2,4-pentanedione (5p): According to the General Procedure, **4p** (126 mg, 0.662 mmol) and $CeCl_3 \cdot 7\,H_2O$ (15 mg, 0.040 mmol) in *i*PrOH (0.35 mL) were converted to yield **5p** after Workup B (PE/EA, 5:1, R_f = 0.34) as a colorless liquid (60 mg, 0.29 mmol, 44%). In a first fraction (R_f = 0.47) by-product **7c** was separated as a colorless liquid (11 mg, 0.049 mmol, 7%). All data are in accordance with the literature.[19]

X-ray Structure Determinations: Crystallographic data for compounds **5d**, **5e**, and **5f** are given in Table 1. The intensities were measured with a Siemens P4 diffractometer (Cu-K_α, λ = 1.54178 Å) at 293 K. The structures were solved by using direct methods and refined against F^2 for all observed reflections. CCDC-190172 (**5d**), -190174 (**5e**), and -190173 (**5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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