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Aikaterini Nikolaou, George Kokotos, Victoria Magrioti

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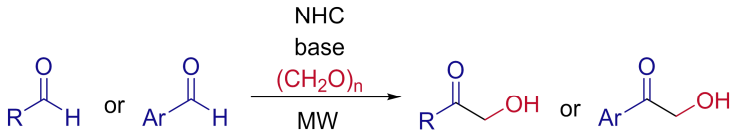
Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis, Athens 15771, Greece



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ABSTRACT

Hydroxymethyl ketones are useful auxiliaries in organic synthesis and are also found in several medicinal agents. N-Heterocyclic carbenes (NHCs) have been used in the literature in order to introduce the hydroxymethyl group into aromatic aldehydes in good yields, but they are not that successful for aliphatic aldehydes. In the present work, the use of microwave irradiation has been efficiently incorporated into this organocatalytic synthesis of aromatic, but more importantly of aliphatic hydroxymethyl ketones that can be used as precursors for medicinally interesting compounds.

* Corresponding author. Tel.: +30-210-727-4497; fax: +30-210-727-4761; e-mail: vmagriot@chem.uoa.gr

1. Introduction

Hydroxymethyl ketones are valuable intermediates as they can be found in some pharmaceutical agents, but they can also be used as useful building blocks for the synthesis of numerous compounds of synthetic or pharmaceutical interest. For instance, the α-hydroxymethyl ketone functionality can be found in antidepressants, HIV-protease inhibitors, selective inhibitors of amyloid-β protein production, agents for the treatment of Alzheimer's disease, antitumor antibiotics and antifungal agents.[1-5] Furthermore, several natural products that present various pharmaceutical properties contain the hydroxymethyl ketone motif.[6-13]

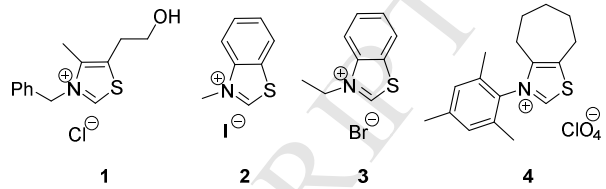
General synthetic methods reported in the literature for the preparation of hydroxymethyl ketones include mostly oxidation or hydrolysis reactions.[5,14-21] More recently, several organocatalytic methods have been published on the α-hydroxylation of carbonyl compounds.[22-26]

N-Heterocyclic carbenes (NHCs) have been demonstrated to be efficient synthetic tools as organocatalysts in various reactions,[27,28] such as benzoin reactions, the Stetter reaction and nucleophilic substitution reactions, etc., due to simple reaction handling, environmental friendliness, low cost and toxicity compared to transition-metal catalysts; and the fact that new synthetic strategies are made possible.[29] In particular, the inversion of the classical reactivity known as umpolung opens up new synthetic pathways. On the other hand, microwave (MW) irradiation is considered to be a more green mode of activation than conventional heating and provides several advantages,[30-33] such as significant acceleration as a result of the more efficient energy transfer to the reaction mixture combined with pressure effects, higher yields under milder reaction conditions and higher product purities. Interestingly enough, the application of microwave technology has not been widely used in organocatalytic reactions, even though prolonged reaction time and heat is used in several cases. In our effort to synthesize hydroxymethyl ketones we decided to use NHCs combined with MW irradiation, as they both seemed promising, in a reaction that involves the formation of a new C-C bond.

2. Results and Discussion

In the present work, a microwave-assisted method catalyzed by NHCs was studied to introduce the hydroxymethyl group in aliphatic and aromatic aldehydes. Recently, Kuhl and Glorius described a strategy based on the NHC catalyzed umpolung reactivity of aromatic aldehydes reacting with paraformaldehyde using several NHC precursors including compounds **1-4** [26] (Scheme 1) by the formation of the Breslow-intermediate, a mechanism recently confirmed by Berkessel *et al.*[34] In that synthetic study, only few examples of the use of an aliphatic aldehyde were described and only afforded the hydroxymethyl ketone in low yields. Since our target was the synthesis of such aliphatic hydroxymethyl ketones, the method had to be somehow modified in order to afford the aliphatic hydroxymethyl ketones successfully.

At first, the commercially available (**1**, **2**)[26] or easy to synthesize (**3**)[26,35] NHCs (Scheme 1) were used and catalyst **3** turned out to be the most efficient out of the three. As a consequence, catalyst **3** was used in a series of reactions under different experimental conditions, which aimed to optimize the yield. Heptanal was used as starting material since aliphatic substrates were the main scope of this study.



Scheme 1. N-Heterocyclic carbenes used as organocatalysts in this study.

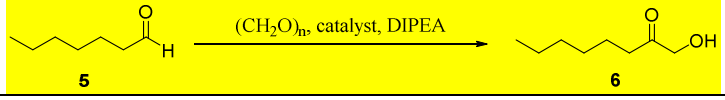
In the literature[26,36,37] the corresponding experimental conditions mentioned heating at 60 °C for 24 h and several ratios of aldehyde:paraformaldehyde:catalyst:base, e.g. 1 mol:2 mol:10 mol%:20 mol%, using various catalysts including structures **1-4**. To study this method, the reaction was tested using a ratio of aldehyde:paraformaldehyde:catalyst:base 1 mol:2 mol:20 mol%:20 mol% via the conventional heating method (Δ), but all three catalysts (**1-3**) afforded the product in low yields, despite the prolonged reaction times (Table 1, Entries 2, 4, 5).

Changes in the molar ratio (Table 1, Entry 3) and also use of microwave irradiation (MW) were studied (Table 1, Entries 10-18) in order to both optimize the yield and minimize the reaction time. Indeed, the new conditions, and especially the use of microwaves, which has never been mentioned in the literature for such a reaction, significantly improved the synthesis of the hydroxymethyl ketones.

After having these promising results with the use of MW irradiation, catalyst **4** was synthesized and examined in the new MW methodology, as it was reported to give higher yields in the conventional heating procedure.[26] The ratio of aldehyde:paraformaldehyde:catalyst:base was also slightly changed when compared to the reported 1 mol:3 mol:10 mol%:20 mol% while incorporating microwave irradiation, and as it turned out catalyst **4** was even more efficient (Table 1, Entries 19-20).

It is essential to point out that using the same molar ratio of the reagents, a yield of 7% in 24 h and 10% in 48 h of 60 °C conventional heating, turned into a yield of 58% in just 1 h and at 100 °C with MW irradiation (Table 1, Entries 8, 9, 20).

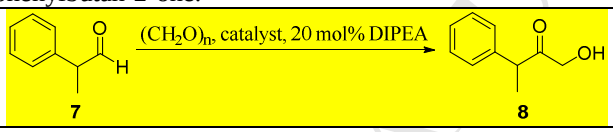
Table 1. Synthesis of 1-hydroxyoctan-2-one.



Entry	Method	Catalyst	$(CH_2O)_n$ (eq)	Catalyst (mol%)	DIPEA (mol%)	Solvent	T/°C	t/h	Yield(%)
1	Δ	**1**	2	10	20	THF	60	48	4
2	Δ	**1**	2	20	20	THF	60	24	20
3	Δ	**1**	2	50	50	THF	60	48	16

4	Δ	**2**	2	20	20	THF	60	48	-
5	Δ	**3**	2	20	20	THF	60	96	10
6	Δ	**4**	2	20	20	THF	60	48	22
7	Δ	**4**	2	20	20	DMF	120	48	24
8	Δ	**4**	3	10	20	THF	60	24	7
9	Δ	**4**	3	10	20	THF	60	48	10
10	MW	**1**	2	20	20	-	120	1	19
11	MW	**2**	2	20	20	-	120	1	4
12	MW	**3**	2	20	20	-	120	1	28
13	MW	**3**	2	20	20	DMF	120	1	36
14	MW	**3**	2	20	20	DMF	100	1	36
15	MW	**3**	2	20	20	THF	100	1	36
16	MW	**3**	3	20	20	-	120	1	28
17	MW	**3**	1	20	20	DMF	120	1	27
18	MW	**3**	2	10	20	DMF	120	1	30
19	MW	**4**	2	20	20	THF	100	1	40
20	MW	**4**	3	10	20	THF	100	1	58

Table 2. Synthesis of 1-hydroxy-3-phenylbutan-2-one.



Entry	Method	Catalyst	$(CH_2O)_n$ (eq)	Catalyst (mol%)	Solvent	T/°C	t/h	Yield (%)
1	MW	**3**	2	20	DMF	120	1	31
2	MW	**4**	2	20	DMF	120	1	38
3	MW	**4**	3	10	THF	100	1	63
4	Δ	**4**	3	10	THF	60	24	18

In order to study the application of this methodology on different aliphatic aldehydes, several reaction conditions were tested on 2-phenylpropanal, an aliphatic aldehyde that has a secondary carbon atom next to the carbonyl moiety (Table 2).

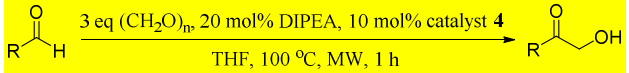
Once again, it was obvious that the microwave assisted reaction conditions, optimized for heptanal, yielded the desired product in far better yield (Table 2, Entry 3) than the corresponding conventional heating reaction conditions (Table 2, Entry 4).

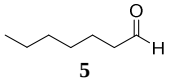
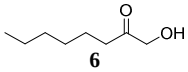
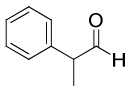
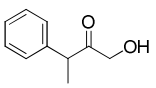
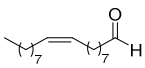
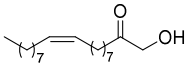
Using the most efficient reagent ratios and conditions with microwave irradiation, the hydroxymethyl ketones shown in Table 3 were successfully synthesized. When compared to the previously reported[26] yield of 57% after 24 h heating, hydroxymethyl ketone **12** was synthesized using our MW methodology in a slightly higher yield, but in the significantly shorter time of just one hour.

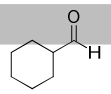
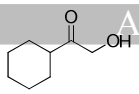
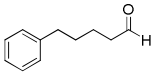
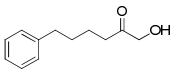
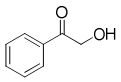
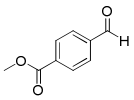
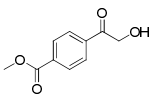
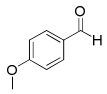
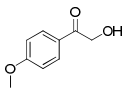
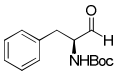
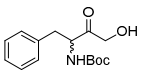
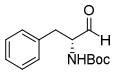
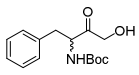
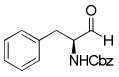
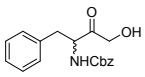
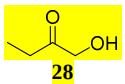
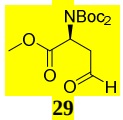
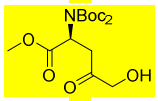
We have to report that, interestingly enough, this methodology did not work as well for aromatic substrates such as compounds **15** and **17**. On the other hand, this green method worked better for *p*-anisaldehyde **19** yielding hydroxymethyl ketone **20** in 45%, while the classic heating method yielded it in just 32%.

Furthermore, this method was used in order to synthesize optically active hydroxymethyl ketones **22**, **24**, **26** and **30**, starting from the corresponding *N*-protected α- or β-aminoaldehydes **21**, **23**, **25** and **29**. It should be noted that even though several experiments (Chiral HPLC and NMR analysis of Mosher esters and amides) were conducted to find out whether the final products **22**, **24** and **26** where optically pure, the results were inconclusive. Finally, the *N*-Boc protected α-aminoaldehydes yielded the corresponding hydroxymethyl ketones in higher yields than the *N*-Cbz protected α-amino aldehyde.

Table 3. Hydroxymethyl ketones synthesized by the microwave-assisted method using catalyst **4**.



Entry	Reactant	Product	Yield (%)
1	 **5**	 **6**	58
2	 **7**	 **8**	63
3	 **9**	 **10**	42

4	 **11**	 **12**	59
5	 **13**	 **14**	55
6	 **15**	 **16**	45
7	 **17**	 **18**	32
8	 **19**	 **20**	45
9	 **21**	 **22**	51
10	 **23**	 **24**	48
11	 **25**	 **26**	30
12	 **27**	 **28**	18[a]
13	 **29**	 **30**	50

[a]The low yield is due to the volatility of both starting material and product.

3. Conclusion

To conclude, a new microwave-assisted method has been developed, which allows the synthesis of both aliphatic and aromatic hydroxymethyl ketones via NHC organocatalysis starting from the corresponding aldehydes. In this method, thiazolium catalyst **4** proved to be the most efficient and the optimal conditions were 1 mol:3 mol:10 mol%:20 mol% of aldehyde:paraformaldehyde:catalyst:base in THF at 100 °C for 1 h. It is important to note that by using this procedure, one can synthesize aliphatic hydroxymethyl ketones in good yields, something not reported in the past.

4. Experimental

4.1. General

Melting points were determined on a Buchi 530 apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian Mercury spectrometer (^{1}H NMR recorded at 200 MHz, ^{13}C NMR recorded at 50 MHz) and were recorded in chloroform ($CDCl_3$), using the $CHCl_3$ residual peak as the ^{1}H internal reference (7.27 ppm); and the central peak of $CDCl_3$ at 77.0 ppm for ^{13}C NMR. Thin layer chromatography (TLC) plates (silica gel 60 F_{254}) and silica gel 60 (230-400 mesh) for flash column chromatography were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid, in EtOH stain. Tetrahydrofuran and DMF were dried by standard procedures and stored over molecular sieves. All other solvents and chemicals were reagent grade and used without further purification. All the products gave satisfactory elemental analysis results.

4.2. General procedure for the microwave-assisted synthesis of hydroxymethylketones from the corresponding aldehydes

To a solution of the aldehyde (1 mmol) in dry THF (0.29 mL) in the appropriate MW vial was added paraformaldehyde (3 mmol, 90 mg), catalyst **4** (0.1 mmol, 37 mg) and diisopropylethylamine (0.2 mmol, 26 mg, 35 µL). The vial was flushed with argon and then inserted in the MW apparatus for 1 h, under stirring at 100 °C (max temperature) and at 50 Watts (max energy). After 1 h, the solvent was evaporated under reduced pressure, H_2O (15 mL) and CH_2Cl_2 (15 mL) were added to the mixture and the layers separated. The aqueous layer was extracted twice with CH_2Cl_2 (15 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the final product obtained after flash column chromatography using the appropriate eluent.

*4.2.1. 1-Hydroxyoctan-2-one[38] (**6**)*

Yield 58% (146 mg); Yellow oil; Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 9/1 to 7/3; δ_H (200 MHz, $CDCl_3$) 4.21 (2H, s, C$\underline{H_2}$OH), 3.05 (1H, s, OH), 2.38 (2H, t, *J* 8.0 Hz, CH_2), 1.80-1.50 (2H, m, CH_2), 1.40-1.10 (6H, m, CH_2), 0.85 (3H, t, *J* 6.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 209.9, 68.0, 38.3, 31.4, 28.7, 23.6, 22.3, 13.9; m/z (ESI) (%) 145.3 [$(M+H)^+$, 52].

*4.2.2. 1-Hydroxy-3-phenylbutan-2-one[26] (**8**)*

Yield 63% (182 mg); Yellow oil; Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 9/1 to 7/3; δ_H (200 MHz, $CDCl_3$) 7.50-7.00 (5H, m, arom), 4.20 (2H, s, C$\underline{H_2}$OH), 3.77 (1H, q, *J* 4.0 Hz, CH), 2.88 (1H, s, OH), 1.48 (3H, d, *J* 4.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 210.0, 139.3, 129.1, 127.7, 127.6, 66.8, 49.1, 17.1; m/z (ESI) (%) 165.2 [$(M+H)^+$, 48].

*4.2.3. (Z)-1-Hydroxynonadec-10-en-2-one (**10**)*

Yield 42% (210 mg); White solid; mp. 35-38 °C; Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 9/1; R_f (20% AcOEt/PE) 0.48; ν_{max}(KBr) 3400, 2922, 1722, 1463, 1406, 1378, 1075 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.50-5.20 (2H, m, CH), 4.20 (2H, s, C$\underline{H_2}$OH), 3.20 (1H, s, OH), 2.36 (2H, t, *J* 6.0 Hz, $CH_2C\underline{H_2}CO$), 2.10-1.80 (4H, m, 2x$C\underline{H_2}CH$), 1.70-1.40 (2H, m, CH_2), 1.40-1.00 (20H, m, CH_2), 0.84 (3H, t, *J* 6.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 209.8, 129.9, 129.5, 68.0, 38.3, 31.8, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 29.0, 27.1, 27.0, 25.5, 23.6, 22.6, 14.0; m/z (ESI) (%) 295.4 [$(M-H)^-$, 100]; HRMS (EI): MH^-, found 295.2649. $C_{19}H_{36}O_2$ requires 295.2643.

*4.2.4. 1-Cyclohexyl-2-hydroxyethan-1-one[26] (**12**)*

Yield 57% (143 mg); Yellow oil; Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 8/2 to 7/3; δ_H (200 MHz, $CDCl_3$) 4.26 (2H, s, C$\underline{H_2}$OH), 3.38 (1H, s, OH), 2.50-2.20 (1H, m, CH), 2.00-1.50 (4H, m, CH_2), 1.50-1.10 (6H, m, CH_2); δ_C (50 MHz, $CDCl_3$) 212.7, 66.4, 47.0, 28.8, 25.8, 25.4; m/z (ESI) (%) 143.3 [$(M+H)^+$, 57].

*4.2.5. 1-Hydroxy-6-phenylhexan-2-one[39] (**14**)*

Yield 55% (150 mg); Yellow oil; Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 9/1 to 7/3; δ_H (200 MHz, $CDCl_3$) 7.50-7.00 (5H, m, arom), 4.21 (2H, s, C$\underline{H_2}$OH), 3.16 (1H, s, OH), 2.62 (2H, t, *J* 6.0 Hz, CH_2), 2.41 (2H, t, *J* 6.0 Hz, CH_2), 1.90-1.50 (4H, m, CH_2); δ_C (50 MHz, $CDCl_3$) 209.6, 141.8, 128.3, 125.8, 68.0, 38.1, 35.5, 30.8, 23.2; m/z (ESI) (%) 193.2 [$(M+H)^+$, 51].

*4.2.6. 2-Hydroxy-1-phenylethan-1-one[40] (**16**)*

Yield 45% (110 mg); White solid; mp. 83-85 °C (lit mp 84-85 °C[40]); Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 9/1 to 7/3; δ_H (200 MHz, $CDCl_3$) 7.91 (2H, d, *J* 8.0 Hz, arom), 7.80-7.20 (3H, m, arom), 4.87 (2H, s, C$\underline{H_2}$OH), 3.52 (1H, s, OH); δ_C (50 MHz, $CDCl_3$) 198.4, 134.3, 128.9, 127.6, 65.4; m/z (ESI) (%) 135.0 [$(M-H)^-$, 45].

*4.2.7. Methyl 4-(2-hydroxyacetyl)benzoate[26] (**18**)*

Yield 32% (110 mg); White solid; mp. 154-156 °C; Flash column chromatography eluent: CH_2Cl_2 / MeOH 98/2; δ_H (200 MHz, $CDCl_3$) 8.16 (2H, d, *J* 8.0 Hz, arom), 7.98 (2H, d, *J* 8.0 Hz, arom), 4.92 (2H, s, C$\underline{H_2}$OH), 3.96 (3H, s, OCH_3), 3.42 (1H, s, OH); δ_C (50 MHz, $CDCl_3$) 214.5, 168.1, 130.4, 130.1, 128.2, 127.6, 65.8, 52.6; m/z (ESI) (%) 195.1 [$(M+H)^+$, 55].

*4.2.8. 2-Hydroxy-1-(4-methoxyphenyl)ethan-1-one[41] (**20**)*

Yield 45% (130 mg); Yellow solid; mp. 95-97 °C (lit mp 98.5-100.5 °C[41]); Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 9/1 to 7/3; δ_H (200 MHz, $CDCl_3$) 7.89 (2H, d, *J* 8.0 Hz, arom), 6.96 (2H, d, *J* 8.0 Hz, arom), 4.81 (2H, s, C$\underline{H_2}$OH), 3.87 (3H, s, OCH_3), 3.51 (1H, s, OH); δ_C (50 MHz, $CDCl_3$) 196.7, 164.3, 132.2, 130.0, 114.1, 64.9, 55.5; m/z (ESI) (%) 167.3 [$(M+H)^+$, 70].

*4.2.9. tert-Butyl (4-hydroxy-3-oxo-1-phenylbutan-2-yl)carbamate (**22**)*

Yield 51% (270 mg); Yellow solid; mp. 96-98 °C; $[\alpha]_D^{20}$ -1.2 (*c* 0.5, $CHCl_3$). Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 8/2 to 6/4; R_f (50% AcOEt/PE) 0.58; ν_{max}(KBr) 3446, 3366, 2967, 2929, 1727, 1680, 1515, 1171 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.50-7.00 (5H, m, arom), 5.12 (1H, d, *J* 7.4 Hz, NH), 5.30-4.90 (1H, m, CH), 4.27 (1H, d, *J* 20.0 Hz, C$\underline{H}$HOH), 4.11 (1H, d, *J* 20.0 Hz, CH$\underline{H}$OH), 3.40-2.60 (3H, m, OH, C$\underline{H_2}$Ph), 1.38 (9H, s, $C(CH_3)_3$); δ_C (50 MHz, $CDCl_3$) 209.4, 155.2, 135.6, 129.0, 128.8, 127.2, 80.3, 67.2, 57.8, 37.4, 28.1; m/z (ESI) (%) 280.0 [$(M+H)^+$, 100]; HRMS (EI): MH^-, found 278.1390. $C_{15}H_{21}NO_4$ requires 278.1398.

*4.2.10. tert-Butyl (4-hydroxy-3-oxo-1-phenylbutan-2-yl)carbamate (**24**)*

Yield 48% (160 mg); Yellow solid; mp. 96-98 °C; $[\alpha]_D^{20}$ +0.8 (*c* 1.0, $CHCl_3$). Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 8/2 to 6/4; R_f (50% AcOEt/PE) 0.58; ν_{max}(KBr) 3446, 3366, 2967, 2929, 1727, 1680, 1515, 1171 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.50-7.00 (5H, m, arom), 5.12 (1H, d, *J* 7.4 Hz, NH), 5.30-4.90 (1H, m, CH), 4.27 (1H, d, *J* 20.0 Hz, C$\underline{H}$HOH), 4.11 (1H, d, *J* 20.0 Hz, CH$\underline{H}$OH), 3.40-2.60 (3H, m, OH, C$\underline{H_2}$Ph), 1.38 (9H, s, $C(CH_3)_3$); δ_C (50 MHz, $CDCl_3$) 209.4, 155.2, 135.6, 129.0, 128.8, 127.2, 80.3, 67.2, 57.8, 37.4, 28.1; m/z (ESI) (%) 280.0 [$(M+H)^+$, 100]; HRMS (EI): MH^-, found 278.1393. $C_{15}H_{21}NO_4$ requires 278.1398.

*4.2.11. Benzyl (4-hydroxy-3-oxo-1-phenylbutan-2-yl)carbamate[42] (**26**)*

Yield 30% (70 mg); Yellow solid; mp. 112-114 °C (lit mp 76.5-77.5 °C[42]); $[\alpha]_D^{20}$ -2.9 (*c* 1.0, $CHCl_3$). Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 8/2 to 6/4; δ_H (200 MHz, $CDCl_3$) 7.60-6.90 (10H, m, arom), 5.48 (1H, d, *J* 8.0 Hz, NH), 5.04 (2H, s, OC$\underline{H_2}$Ph), 4.70-4.50 (1H, m, CH), 4.30-4.00 (2H, m, C$\underline{H_2}$OH), 3.43-2.70 (3H, m, OH, C$\underline{H_2}$Ph); δ_C (50 MHz, $CDCl_3$) 208.9, 155.8, 135.9, 135.3, 129.0, 128.8, 128.5, 128.2, 128.0, 127.2, 67.2, 67.1, 57.4, 37.5; m/z (ESI) (%) 331.1 [$(M+NH_4)^+$, 55, 314.2 [$(M+H)^+$, 35].

*4.2.12. 1-Hydroxybutan-2-one[43] (**28**)*

Yield 18% (55 mg); Yellow oil; Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 8/2 to 6/4; δ_H (200 MHz, $CDCl_3$) 4.20 (2H, s, C$\underline{H_2}$OH), 3.23 (1H, s, OH), 2.39 (2H, q, *J* 8.0 Hz, C$\underline{H_2}$$CH_3$), 1.07 (3H, t, *J* 8.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 210.3, 67.6, 31.5, 7.4; m/z (ESI) (%) 87.2 [$(M-H)^-$, 100].

*4.2.13. Methyl (R)-2-((bi-tert-butoxycarbonyl)amino)-5-hydroxy-4-oxopentanoate (**30**)*

Yield 50% (180 mg); Yellow solid; mp. 108-110 °C; $[\alpha]_D^{20}$ -69.4 (*c* 1, $CHCl_3$). Flash column chromatography eluent: petroleum ether (b.p. 40-60 °C) / ethyl acetate 8/2 to 6/4; R_f (50% AcOEt/PE) 0.52; ν_{max}(KBr) 3472, 2973, 1744, 1727, 1707, 1480, 1458, 1369, 1100, 1037, 1021 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.60-5.40 (1H, m, CH), 4.42-4.14 (2H, m, C*H*$_2$OH), 3.66 (3H, s, OCH_3), 3.38 (1H, dd, *J* 18.0, 8.0 Hz, C$\underline{H}$H), 3.04 (1H, s, OH), 2.59 (1H, dd, *J* 18.0, 6.0 Hz, CH$\underline{H}$), 1.45 (18H, s, Boc); δ_C (50 MHz, $CDCl_3$) 206.2, 170.3, 151.6, 83.7, 68.2, 54.09, 52.6, 39.3, 27.8; m/z (ESI) (%) 360.3 [$(M-H)^-$, 100]; HRMS (EI): MH^-, found 360.1656. $C_{16}H_{27}NO_8$ requires 360.1664.

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