Stereoselective Aldol Reactions Catalyzed by Acyclic Amino Acids in Aqueous Micelles

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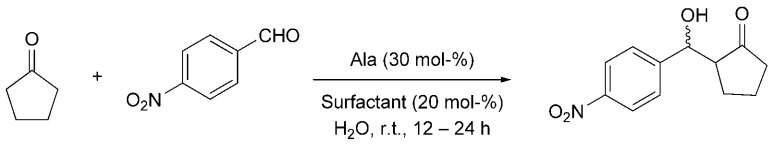
The catalytic properties of all proteinogenic, *acyclic* amino acids for direct aldol reaction in H_2O, assisted by various surfactants, were investigated. The basic and neutral amino acids were shown to be efficient catalysts, giving rise to good-to-excellent yields of adducts (up to 95%), with moderate-to-good diastereoselectivities (up to 86%), L-arginine being the most-effective catalyst. The *syn*/*anti* diastereoisomer ratio could be readily tuned by proper choice of the amino acid used. Also, the range of substrates that underwent the reaction was extended to less-reactive aldehydes carrying electron-donating Br substituents.

1. Introduction. – The aldol reaction is one of the most-important C,C bond forming reactions in synthetic organic chemistry. Catalysts that can promote this reaction include aldolase enzymes [1], *Lewis* acids [2], *Lewis* bases, and small organic molecules [3][4]. Since natural amino acids were shown to be able to catalyze some organic reactions [5], they have been extensively investigated as catalysts, which has created a renaissance in organic synthesis [6]. L-Proline (Pro) and its derivatives have been shown to be efficient catalysts for aldol reactions carried out in both organic or aqueous media [7]. In contrast, *acyclic* amino acids are generally considered as poor catalysts for intermolecular aldol reactions of unmodified ketones and aldehydes [8]. However, *Córdova* and co-workers recently reported that acyclic amino acids, lacking a five-membered ring, are capable of catalyzing direct asymmetric aldol reactions [9][10]. Intrigued by these observations, and in continuation of our studies concerning environmentally benign catalytic reactions [11], we carried out a systematic investigation into the catalytic properties of natural acyclic amino acids in direct aldol reactions in aqueous micelles and compared our results with those obtained for Pro under similar conditions [12].

2. Result and Discussion. – Initial experiments were carried out for the aldol reaction between cyclopentanone (**1**) and 4-nitrobenzaldehyde (**2**) as a model reaction, catalyzed by L-alanine (Ala) in the presence of different surfactants, including anionic, neutral, and cationic types. The results are summarized in *Table 1*. In the presence of sodium dodecyl sulfate (SDS), the desired aldol adduct **3** was obtained in 78% yield (*Table 1*, *Entry 2*), compared to 25% in bulk H_2O (*Entry 8*). Anionic surfactants generally improved the efficiency of the reaction significantly, but not the diastereoselectivity (*Entries 1–4*). In the absence of Ala, basically no reaction took place (*Entry 6*), which

confirmed the role of Ala as catalyst. Both the cationic surfactant cetyl trimethylammonium bromide (CTAB; *Entry 5*) and the neutral surfactant polyoxyethylene sorbitan monooleate (*Tw-20*; *Entry 7*) had an adverse effect on the reaction. In the latter case, this is possibly due to *Tw-20* not being able to form colloidal dispersions with the substrates in H_2O. To examine temperature effects, the model reaction was carried out at 0, 40, and 60°, respectively. The reaction did not proceed at 0° (*Entry 9*); at higher temperature (*Entries 10* and *11*), there was basically no effect on either yield or diastereoselectivity.

Table 1. *The Alanine-Catalyzed Aldol Model Reaction in H_2O as a Function of Micellar Surfactant*



1 **2** **3**

Entry	Surfactant[a])	Time [h]	Yield [%][b])	*syn*/*anti*[c])
1	SDBS	12	76	42:58
2	SDS	12	78	42:58
3	SLS	12	70	44:56
4	SL	24	48	46:54
5	CTAB	24	32	50:50
6[d])	SDS	24	trace	–
7	Tw-20	24	10	38:62
8	None	24	25	50:50
9[e])	SDS	24	trace	–
10[f])	SDS	12	83	40:60
11[g])	SDS	12	80	40:60

[a]) SDS, sodium dodecyl sulfate; SDBS, sodium dodecylbenzene sulfonate; SLS, sodium lauryl sulfonate; SL, sodium laurate; CTAB, cetyl trimethylammonium bromide; *Tw-20*, polyoxyethylene sorbitan monooleate. [b]) After column-chromatographic purification. [c]) Determined by ^{1}H-NMR. [d]) Without Ala. [e]) At 0°C. [f]) At 40°C. [g]) At 60°C.

Based upon the above results, SDS was chosen for further experiments. A range of natural amino acids were then screened as potential catalysts in the model aldol reaction of **1** and **2** at room temperature, and the results are collected in *Table 2*. Neutral and basic amino acids showed the best catalytic properties, with moderate-to-good yields of **3**. Unfortunately, there was no significant enantioselectivity with Ala (*Table 2*, *Entry 4*). When L-leucine (Leu) or L-isoleucine (Ile) were employed, the desired aldol product **3** was obtained in a diastereoisomer excess (de) of 28%, in favor of the *anti* isomers, and in high yield (92–94%; *Entries 6* and *7*). When employing L-arginine (Arg), L-histidine (His), and L-lysine (Lys) as catalysts (*Entries 17–19*), the *syn* isomers of **3** were obtained in 30% de, and in yields of up to 98%. The amino acids L-tyrosine (Tyr), L-glutamate (Glu), and L-aspartate (Asp) gave rise to only 20% of **3** after 24 h (*Entries 14–16*), the *anti* adducts being the major isomers in each case. Interestingly,

Table 2. *Results of the Amino Acid Catalyzed Aldol Model Reaction between* **1** *and* **2** (see *Table 1*) *in Aqueous Micellar Sodium Dodecyl Sulfate* (SDS) *Solution.* Conditions: H_2O, r.t., with 20 and 30 mol-% of SDS and amino acid, resp., relative to the aldehyde.

Entry	L-Amino acid	Time [h]	Yield [%][a])	*syn*/*anti*[b])
1	Glycine	24	60	40:60
2	Serine	24	56	42:58
3	Threonine	24	80	38:62
4	Alanine	12	78	42:58[c])
5	Valine	12	85	36:64
6	Leucine	12	92	36:64
7	Isoleucine	12	94	36:64
8	Cysteine	24	68	40:60
9	Glutamine	24	72	40:60
10	Asparagine	24	70	40:60
11	Methionine	12	85	35:65
12	Phenylalanine	12	78	38:62
13	Tryptophan	8	86	38:62
14	Tyrosine	24	20	25:75
15	Glutamate	24	20	38:62
16	Aspartate	24	20	40:60
17	Arginine	6	98	65:35
18	Histidine	12	95	58:42
19	Lysine	8	94	65:35
20	Sulfamic acid[d])	24	trace	trace

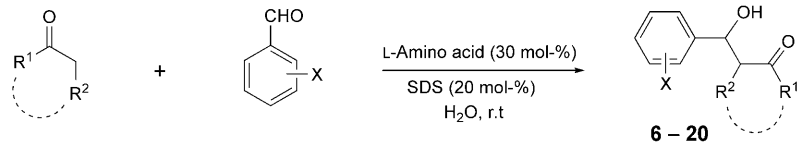
[a]) After column-chromatographic purification. [b]) Determined by ^{1}H-NMR. [c]) The enantiomeric excess (ee) was 13% and 7% for the *syn* and *anti* isomers, resp., as determined by HPLC (*Daicel Chiralpak AS-PH*). [d]) In H_2O mainly present as $NH_3^+SO_3^-$.

sulfamic acid ($H_3N^+SO_3^-$), a zwitter-ionic compound in H_2O, was not able to trigger the reaction (*Entry 20*).

The results listed above suggest that both basic and neutral acyclic amino acids catalyze direct aldol reactions in aqueous SDS micelles effectively, with Arg and Ile showing the best results. Hence, in the next step, we decided to investigate the scope of Arg- and Ile-catalyzed aldol reactions of different substrates. The results are summarized in *Table 3*. With these two catalysts, excellent yields of up to 98% were achieved for the condensation of the ketones **4** with the aromatic aldehydes **5** bearing electron-withdrawing groups (*Table 3*, *Entries 1–5*, *8*, *9*, *12*, *14*, and *16–19*). For the less-active aromatic aldehydes, a longer reaction time was required to obtain comparable yields (*Entries 6*, *7*, *10*, *11*, and *15*).

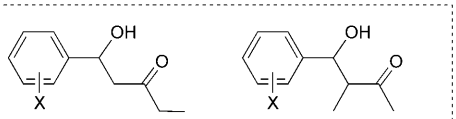
When Arg was used as catalyst, all reactions afforded the corresponding products **6**–**20** in good-to-excellent yields, generally favoring the *syn* isomers, with up to 80% de (see, *e.g.*, *Entry 11*). Interestingly, although Ile had a similar catalytic efficiency as Arg, it favored the *anti* adducts rather than the *syn* adducts, with up to 86% de (see, *e.g.*, *Entry 19*). When a 1:1 mixture (15 mol-% each) of Arg and Ile was used as mixed catalyst (*Entry 3*), the *syn* and *anti* selectivities were nearly cancelled, the reaction affording **6** in only 4% de (*Entry 3*).

Table 3. *Arginine-* vs. *Isoleucine-Catalyzed Aldol Reactions of Different Ketones and Aromatic Aldehydes in Aqueous Micellar SDS Solution*



4a Cyclopentanone
4b Cyclohexanone
4c Acetone
4d Butan-2-one

5a X = 4-NO_2
5b X = 2-NO_2
5c X = 4-Br
5d X = H
5e X = 3-NO_2



17a X = 4-NO_2
18a X = 2-NO_2

17b X = 4-NO_2
18b X = 2-NO_2

Entry	Ketone	Aldehyde	Time [h]	Product(s)	Arg[a])		Ile[a])	
					Yield [%]	*syn*/*anti*	Yield [%]	*syn*/*anti*
1	**4a** (=**1**)	**5a** (=**2**)	6	**6** (=**3**)	98	65:35		
2	**4a** (=**1**)	**5a** (=**2**)	12	**6** (=**3**)			94	36:64
3[b])	**4a** (=**1**)	**5a** (=**2**)	6	**6** (=**3**)	94	52:48		
4	**4a** (=**1**)	**5b**	10	**7**	96	60:40		
5	**4a** (=**1**)	**5b**	16	**7**			90	35:65
6	**4a** (=**1**)	**5c**	48	**8**	83	57:43		
7	**4a** (=**1**)	**5d**	48	**9**	82	72:28	72	45:55
8	**4b**	**5a** (=**2**)	24	**10**	96	62:38	86	13:87
9	**4b**	**5b**	24	**11**	94	60:40	83	10:90
10	**4b**	**5c**	48	**12**	80	60:40		
11	**4b**	**5d**	48	**13**	80	90:10		
12	**4c**	**5a** (=**2**)	12	**14**	95			
13	**4c**	**5a** (=**2**)	36	**14**			65	
14	**4c**	**5b**	24	**15**	90			
15	**4c**	**5d**	48	**16**	50			
16	**4d**	**5a** (=**2**)	24	**17a**	18			
				17b	64	56:44[c])		
17	**4d**	**5b**	24	**18a**	26			
				18b	54	55:45[c])		
18	**4a** (=**1**)	**5e**	24	**19**			91	28:72
19	**4b**	**5e**	24	**20**			82	7:93

[a]) 30 mol-% Amino acid, isolated yields, *syn*/*anti* according to ^{1}H-NMR. [b]) Catalyst: Arg/Ile 1:1 mixture (15 mol-% each). [c]) Determined from ^{1}H-NMR coupling constants [3b][12][13]. For example, in the case of **17b** (*Entry 16*), the signals at δ(H) 5.27 (J = 2.3 Hz) and 4.87 (J = 7.8 Hz) were attributed to the *syn* and *anti* isomers, resp., the one with the smaller coupling constant (2.3 Hz) indicating two adjacent H-atoms on the same side of the ring (*syn*).

In the case of butan-2-one as nucleophile (*Entries 16* and *17*), there are two positions susceptible to deprotonation. Only moderate regio- and stereoselectivities were observed, giving rise to products **17a,b** and **18a,b**, respectively.

3. Conclusions. – Our results reveal a novel application of natural acyclic amino acids as organic catalysts for stereoselective direct aldol reactions in H_2O. Both basic and neutral amino acids are able to stereoselectively catalyze the reaction between ketones and aldehydes in aqueous anionic micelles. Notably, the catalytic efficiency of acyclic amino acids, especially Arg and Ile, is much higher than that of L-proline [12]. For instance, the aldol reaction between 2-nitrobenzaldehyde and cyclopentanone was reported to take 168 h with Pro as catalyst [12], affording the corresponding adduct in 44% yield, and in favor of the *anti* isomers. However, the same reaction catalyzed by Arg was complete within 10 h, giving rise to 96% yield, with the *syn* isomers being favored.

Our synthetic protocol benefits from the following advantages: *1*) the catalysts are naturally abundant and inexpensive, *2*) the reaction is environmentally highly benign, *3*) good-to-excellent yields can be achieved at room temperature in relatively short time, and *4*) the diastereoselectivity (*syn vs. anti* adducts) can be readily controlled by proper choice of the amino acid. Finally, and most importantly, compared with Pro [12], we were able to extend the scope of the reaction in terms of substrate from highly to much less reactive aromatic aldehydes carrying electron-donating groups such as Br.

Experimental Part

General. All reagents were commercially available and used as received. Anal. HPLC: *Daicel Chiralpak AS-PH* column, eluting with hexane/i-PrOH 82 : 18 at a flow rate of 1 ml/min, UV detection at 254 nm; retention times (t_R) in min. ^{1}H-NMR Spectra were recorded on a *Varian Unity-Nova* 300-MHz spectrometer in $CDCl_3$ at r.t.; δ in ppm rel. to Me_4Si, J in Hz. Mass spectra were recorded on a *Shimadzu LC/MS-2010A* apparatus; in m/z. All compounds were characterized by NMR and MS, and selected anal. data are presented below.

General Procedure for the Amino Acid Catalyzed Aldol Reaction. To a soln. of SDS (0.1 mmol) and the appropriate L-amino acid (0.15 mmol) in H_2O (1 ml) is added a soln. of the ketone (4.5 mmol) and the aldehyde (0.5 mmol). The mixture is stirred at r.t., the progress of the reaction being monitored by TLC. The mixture is quenched with sat. aq. $NaHCO_3$ soln., and then extracted with AcOEt (3×20 ml). The combined org. layers are washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield the crude product, which is purified by column chromatography (SiO_2, 100–200 mesh; hexane/AcOEt).

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentan-1-one (**3**=**6**; *Table 2*, *Entry 4*). HPLC (*syn* isomers): t_R 10.70 (major), 31.37 (minor); 13% ee. HPLC (*anti* isomers): t_R 12.47 (minor), 17.14 (*major*); 7% ee. ^{1}H-NMR ($CDCl_3$; *syn* isomers): 8.19 (*dd*, J=6.8, 8.8, 2 arom. H); 7.50 (*dd*, J=3.2, 8.3, 2 arom. H); 5.41 (*d*, J=1.3, OCH); 1.51–2.51 (br. *m*, 7 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 8.19 (*dd*, J=6.8, 8.8, 2 arom. H); 7.50 (*dd*, J=3.2, 8.3, 2 arom. H); 4.84 (*d*, J=9.0, OCH); 1.51–2.51 (br. *m*, 7 H). ESI-MS: 258.3 ($[M+Na]^+$).

2-[Hydroxy(2-nitrophenyl)methyl]cyclopentan-1-one (**7**; *Table 3*, *Entry 4*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 7.77–8.00 (*m*, 2 arom. H); 7.61–7.66 (*m*, 1 arom. H); 7.39–7.45 (*m*, 1 arom. H); 5.89 (*d*, J=2.8, OCH); 1.68–2.72 (br. *m*, 7 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 7.77–8.00 (*m*, 2 arom. H); 7.61–7.66 (*m*, 1 arom. H); 7.39–7.45 (*m*, 1 arom. H); 5.42 (*d*, J=8.5, OCH); 1.68–2.72 (br. *m*, 7 H). ESI-MS: 258.1 ($[M+Na]^+$).

2-[(4-Bromophenyl)(hydroxy)methyl]cyclopentan-1-one (**8**; *Table 3*, *Entry 6*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 7.27–7.54 (*m*, 3 arom. H); 7.17–7.21 (*m*, 2 arom. H); 5.22 (*d*, J=2.7, OCH); 1.44–2.42 (br. *m*, 7 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 7.27–7.54 (*m*, 3 arom. H); 7.17–7.21 (*m*, 2 arom. H); 4.67 (*d*, J=9.0, OCH); 1.44–2.42 (br. *m*, 7 H). ESI-MS: 291.3 ($[M+Na]^+$).

2-[Hydroxy(phenyl)methyl]cyclopentan-1-one (**9**; *Table 3*, *Entry 7*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 7.23–7.34 (*m*, 5 arom. H); 5.30 (*d*, *J* = 2.9, OCH); 1.64–2.46 (br. *m*, 7 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 7.23–7.34 (*m*, 5 arom. H); 4.71 (*d*, *J* = 9.1, OCH); 1.64–2.46 (br. *m*, 7 H). ESI-MS: 213.1 ($[M+Na]^+$).

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one (**10**; *Table 3*, *Entry 8*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 8.18 (*dd*, *J* = 7.1, 8.7, 2 arom. H); 7.48 (*dd*, *J* = 2.5, 8.3, 2 arom. H); 5.47 (*d*, *J* = 1.2, OCH); 1.35–2.64 (br. *m*, 9 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 8.18 (*dd*, *J* = 7.1, 8.7, 2 arom. H); 7.48 (*dd*, *J* = 2.5, 8.3, 2 arom. H); 4.90 (*d*, *J* = 8.4, OCH); 1.35–2.64 (br. *m*, 9 H). ESI-MS: 272.35 ($[M+Na]^+$).

2-[Hydroxy(2-nitrophenyl)methyl]cyclohexan-1-one (**11**; *Table 3*, *Entry 9*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 7.74–8.00 (*m*, 2 arom. H); 7.60–7.66 (*m*, 1 arom. H); 7.39–7.45 (*m*, 1 arom. H); 5.96 (*d*, *J* = 1.8, OCH); 1.56–2.92 (br. *m*, 9 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 7.74–8.00 (*m*, 2 arom. H); 7.60–7.66 (*m*, 1 arom. H); 7.39–7.45 (*m*, 1 arom. H); 5.45 (*d*, *J* = 7.2, OCH); 1.56–2.92 (br. *m*, 9 H). ESI-MS: 272.32 ($[M+Na]^+$).

2-[Hydroxy(4-bromophenyl)methyl]cyclohexan-1-one (**12**; *Table 3*, *Entry 10*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 7.46 (*dd*, *J* = 5.0, 8.4, 2 arom. H); 7.18 (*dd*, *J* = 3.7, 8.5, 2 arom. H); 5.33 (*d*, *J* = 1.6, OCH); 1.31–2.60 (br. *m*, 9 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 7.46 (*dd*, *J* = 5.0, 8.4, 2 arom. H); 7.18 (*dd*, *J* = 3.7, 8.5, 2 arom. H); 4.75 (*d*, *J* = 8.6, OCH); 1.31–2.60 (br. *m*, 9 H). ESI-MS: 305.30 ($[M+Na]^+$).

2-[Hydroxy(phenyl)methyl]cyclohexan-1-one (**13**; *Table 3*, *Entry 11*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 7.23–7.38 (*m*, 5 arom. H); 5.38 (*d*, *J* = 2.2, OCH); 1.64–2.46 (br. *m*, 9 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 7.23–7.38 (*m*, 5 arom. H); 4.79 (*d*, *J* = 8.8, OCH); 1.64–2.46 (br. *m*, 9 H). ESI-MS: 227.22 ($[M+Na]^+$).

4-Hydroxy-4-(4-nitrophenyl)butan-2-one (**14**; *Table 3*, *Entry 12*). ^{1}H-NMR ($CDCl_3$): 8.18 (*d*, *J* = 8.8, 2 arom. H); 7.52 (*d*, *J* = 8.3, 2 arom. H); 5.26 (*t*, *J* = 6.8, OCH); 2.86 (*d*, *J* = 5.2, CH_2); 2.22 (*s*, Me). ESI-MS: 232.20 ($[M+Na]^+$).

4-Hydroxy-4-(2-nitrophenyl)butan-2-one (**15**; *Table 3*, *Entry 14*). ^{1}H-NMR ($CDCl_3$): 8.19 (*dd*, *J* = 7.2, 8.2, 1 arom. H); 7.89 (*d*, *J* = 7.5, 1 arom. H); 7.64–7.69 (*m*, 1 arom. H); 7.41–7.47 (*m*, 1 arom. H); 5.68 (*dd*, *J* = 7.6, 9.4, OCH); 3.14 (*dd*, *J* = 15.8, 17.8, CH); 2.77 (*q*, *J* = 9.4, CH); 2.25 (*s*, Me). ESI-MS: 232.25: ($[M+Na]^+$).

4-Hydroxy-4-phenylbutan-2-one (**16**; *Table 3*, *Entry 15*). ^{1}H-NMR ($CDCl_3$): 7.28–7.40 (*m*, 5 arom. H); 5.28 (*t*, *J* = 5.6, OCH); 3.10 (*d*, *J* = 5.3, CH_2); 2.31 (*s*, Me). ESI-MS: 187.30 ($[M+Na]^+$).

1-Hydroxy-1-(4-nitrophenyl)pentan-3-one (**17a**; *Table 3*, *Entry 16*). ^{1}H-NMR ($CDCl_3$): 8.21 (*d*, *J* = 8.7, 2 arom. H); 7.54 (*d*, *J* = 8.6, 2 arom. H); 5.29 (*q*, *J* = 4.6, OCH); 2.84 (*t*, *J* = 4.0, CH_2); 2.52 (*q*, *J* = 7.2, CH_2); 1.11 (*t*, *J* = 7.3, Me). ESI-MS: 246.27 ($[M+Na]^+$).

4-Hydroxy-3-methyl-4-(4-nitrophenyl)butan-2-one (**17b**; *Table 3*, *Entry 16*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 8.18 (*dd*, *J* = 6.5, 8.8, 2 arom. H); 7.45–7.53 (*m*, 2 arom. H); 5.27 (*d*, *J* = 2.3, OCH); 2.81–2.86 (*m*, CH); 2.25 (*s*, Me); 1.06 (*d*, *J* = 7.4, Me). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 8.18 (*dd*, *J* = 6.5, 8.8, 2 arom. H); 7.45–7.53 (*m*, 2 arom. H); 4.87 (*d*, *J* = 7.8, OCH); 2.95 (*q*, *J* = 7.4, CH); 2.24 (*s*, Me); 1.03 (*d*, *J* = 7.4, Me). ESI-MS: 246.30 ($[M+Na]^+$).

1-Hydroxy-1-(2-nitrophenyl)pentan-3-one (**18a**; *Table 3*, *Entry 17*). ^{1}H-NMR ($CDCl_3$): 7.41–8.04 (*m*, 4 arom. H); 5.68 (*dd*, *J* = 8.3, 9.1, OCH); 3.16 (*d*, *J* = 1.7, CH_2); 3.08–3.13 (*m*, CH_2); 1.12 (*t*, *J* = 7.3, Me). ESI-MS: 246.28 ($[M+Na]^+$).

4-Hydroxy-3-methyl-4-(2-nitrophenyl)butan-2-one (**18b**; *Table 3*, *Entry 17*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 7.41–8.04 (*m*, 4 arom. H); 5.78 (*d*, *J* = 1.1, OCH); 3.16 (*d*, *J* = 1.8, CH); 2.43–2.55 (*m*, CH); 2.31 (*s*, Me); 1.13 (*d*, *J* = 7.3, Me). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 7.41–8.04 (*m*, 4 arom. H); 5.39 (*d*, *J* = 6.0, OCH); 3.10 (*d*, *J* = 5.4, CH); 2.72 (*q*, *J* = 9.3, CH); 2.14 (*s*, Me); 1.06 (*d*, *J* = 7.4, Me). ESI-MS: 246.35 ($[M+Na]^+$).

2-[Hydroxy(3-nitrophenyl)methyl]cyclopentan-1-one (**19**; *Table 3*, *Entry 18*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 8.22 (*s*, 1 arom. H); 8.10–8.17 (*m*, 1 arom. H); 7.69 (*t*, *J* = 7.7, 1 arom. H); 7.50–7.55 (*m*, 1 arom. H); 5.42 (*d*, *J* = 2.3, OCH); 1.53–2.53 (br. *m*, 7 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 8.22 (*s*, 1 arom. H); 8.10–8.17 (*m*, 1 arom. H); 7.69 (*t*, *J* = 7.7, 1 arom. H); 7.50–7.55 (*m*, 1 arom. H); 4.83 (*d*, *J* = 9.3, OCH); 1.53–2.53 (br. *m*, 7 H). ESI-MS: 258.32 ($[M+Na]^+$).

2-[Hydroxy(3-nitrophenyl)methyl]cyclohexan-1-one (**20**; *Table 3*, *Entry 19*). ^{1}H-NMR ($CDCl_3$; *syn* isomers): 8.19 (*s*, 1 arom. H); 8.13 (*dd*, *J* = 7.1, 8.1, 1 arom. H); 7.66 (*d*, *J* = 7.8, 1 arom. H); 7.50 (*t*,

$J=7.8$, 1 arom. H); 5.46 (*d*, $J=0.9$, OCH); 1.36–2.64 (br. *m*, 9 H). ^{1}H-NMR ($CDCl_3$; *anti* isomers): 8.19 (*s*, 1 arom. H); 8.13 (*dd*, $J=7.1$, 8.1, 1 arom. H); 7.66 (*d*, $J=7.8$, 1 arom. H); 7.50 (*t*, $J=7.8$, 1 arom. H); 4.90 (*d*, $J=8.4$, OCH); 1.36–2.64 (br. *m*, 9 H). ESI-MS: 272.35 ($[M+Na]^+$).

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