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Highly efficient one-pot, three-component Mannich reaction catalysed by boric acid and glycerol in water with major '*syn*' diastereoselectivity

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ABSTRACT

Boric acid and glycerol efficiently catalysed the one-pot, three-component Mannich reaction of aldehydes, aromatic amines and cyclic ketones in water at ambient temperature to afford the corresponding β-amino carbonyl compounds in good yields. All but one reaction proceeded with moderate '*syn*' diastereoselectivity. This observation is just the reverse of the major *anti* diastereoselectivity obtained in most of the earlier reported procedures. The methodology is mild and efficient using minute quantities of catalyst with no side products and a very simple work-up procedure.

1. Introduction

In recent years, water-mediated organic synthesis[1] without using organic solvents has become one of the most important aspects in Organic Chemistry in order to meet the environmental demands.[2] Carrying out organic synthesis in aqueous phase is highly challenging both from the synthetic view point and also from the impact of the environmental pollution. Apart from being environmentally friendly, water possesses some unique properties (such as being non-toxic, available in large quantities, cheap, non-flammable and non-hazardous) that are different from other solvents thus making it a very good reaction medium for organic synthesis.

It is very well known that the Mannich products, that is, β-amino carbonyl compounds are extensively used for the synthesis of the nitrogen-containing drugs and natural products.[3,4] Classical Mannich reactions have some disadvantages and limited applications.[5] It was initially a two-component system using electrophiles such as imines and nucleophiles like enolates, enol-ethers, enamines and enol silyl ethers.[6] However, there was a serious drawback in that the nucleophiles had to be prepared from the corresponding carbonyl compounds and in most cases, an organic solvent was necessary. Use of surfactants such as SDS and DBSA produces colloidal dispersion by emulsion formation[7] as a result of which, phase separation was difficult. Very recently, use of heteropoly acid as catalyst[8] and a complex catalyst such as (sodium tetrakis 3.5-trifluoro-methyl-phenyl) borate in water[9] proved to be quite efficient. Other three-component Mannich reactions particularly of cyclohexanone are cited in Refs. 10–13. All these procedures produced major *anti* diastereoisomers and also suffered from poor diastereoselectivity. Therefore, modification of the existing procedures by improved techniques is important to overcome the previous drawbacks and particularly to reverse the diastereoselectivity. The development of new catalysts that increase the *syn* diastereoselectivity under mild reaction conditions would be highly useful.

2. Results and discussion

Herein we report an efficient method for the preparation of Mannich products in water from aldehydes, aromatic amines and cycloalkanones under very mild conditions by using boric acid and glycerol (Scheme 1).

It is well known[14] that boric acid and glycerol form a boron chelate complex (BCC) in water (Scheme 2). Although boric acid is a weak acid, its complex with polyhydroxy compounds such as glycerol is stronger due to chelate formation and release of H^+ ions in the aqueous medium.

The in situ-generated chelate complex of boron in the reaction mixture with corresponding increased acidity of the solvent increases both the yield and diastereoselectivity of the Mannich

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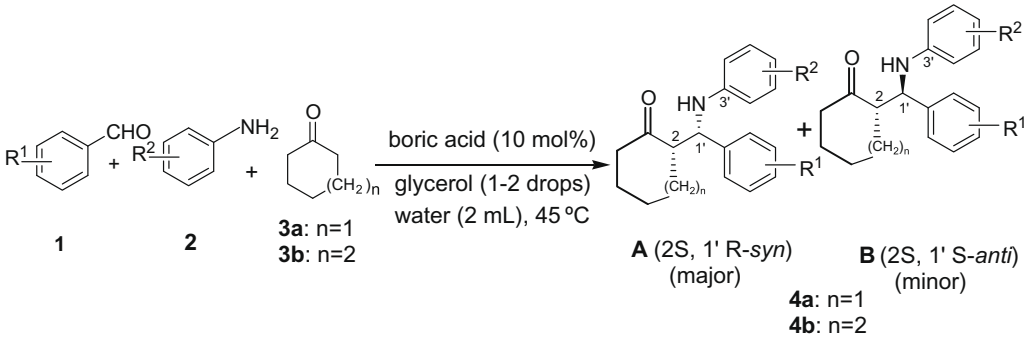
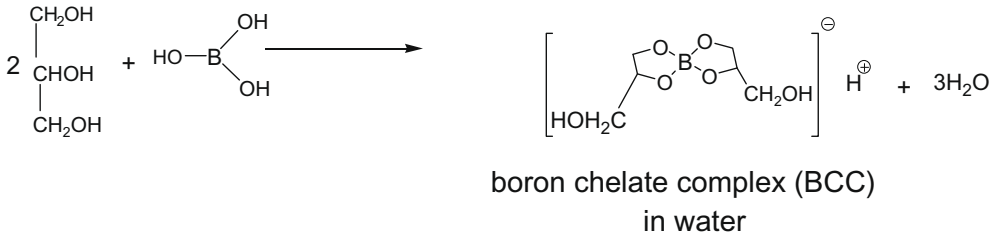


Scheme 1. Mannich reaction of aromatic aldehydes, aromatic amines and cycloalkanones catalysed by boric acid and glycerol in water.



Scheme 2. Formation of boron chelate complex (BCC) in water.

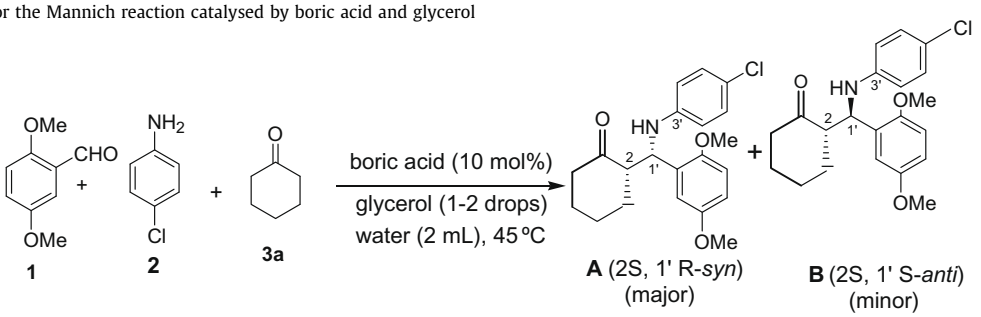
products in water when carried out following the present methodology. Rather, the formation of this boron chelate reverses the diastereoselectivity of the Mannich products: the *syn* diastereoisomer being obtained in major amount.

Different polar and non-polar solvents have been used for optimisation of the solvent, though water is the only solvent where the yield is maximum (Table 1). Use of either boric acid or glycerol in water could not increase the yield much but on simultaneous use of boric acid and glycerol, the product yield became exceedingly high (Table 1, entry 10).

Various organic solvents such as THF, CH_2Cl_2 and MeCN when used, suppress the yield of the Mannich products (although the *syn*:*anti* ratio remains almost the same) rather than when carried out in water. This indicates that the *syn*:*anti* ratio corresponds to the thermodynamic mixture rather than to the kinetic distribution of products. Therefore, use of a chiral catalyst for implementation of enantioselectivity in the product would seem rather unlikely under these reaction conditions as kinetic control of the reaction is mandatory for enantioselectivity. Use of surfactants such as SDS or CTAB did not improve the yield. It is therefore obvious from Table 1, that boric acid and glycerol work best in aqueous medium rather than in organic solvents.

Thus, the three-component Mannich reactions of various aromatic amines (with both electron-withdrawing and

Table 1
Optimisation of solvent for the Mannich reaction catalysed by boric acid and glycerol



Entry	Solvent	Boric acid (isolated) (+) (present) (−) (absent)	Yield % (*syn*:*anti*)
1	CH_2Cl_2	(−)	–
2	CH_2Cl_2	(+)	–
3	THF	(+)	–
4	MeCN	(+)	15 (54:46)
5	MeOH	(−)	10 (55:45)
6	MeOH	(+)	20 (54:46)
7	H_2O	(−)	20 (55:45)
8	H_2O	(+)	45 (57:43)
9	H_2O + glycerol	(−)	35 (55:45)
10	H_2O + glycerol	(+)	85 (57:43)

Reagents: 2,5-dimethoxybenzaldehyde (1 mmol), 4-chloroaniline (1 mmol) and cyclohexanone (2 mmol).

Table 2
Mannich reaction of various aldehydes, aromatic amines and cycloalkanones catalysed by boric acid and glycerol in water

Entry	R^1	R^2	**3**	Time (h)	Yield[a] (%)	(*syn*:*anti* ratio[b])[references]
1	H	H	**a**	44	80	(64:36)[8]
2	H	6′-Cl	**a**	36	84	(61:39)[8]
3	H	6′-OMe	**a**	35	76	(62:38)[7]
4	R^1-C_6H_4 = 2-furyl	H	**a**	32	73	(64:36)[7]
5	4-Cl	6′-Cl	**a**	36	78	(60:40)[8]
6	4-OMe	6′-Cl	**a**	37	82	(50:50)[8]
7	2-OMe	H	**a**	32	62	(62:38)[8]
8	4-NO_2	6′-Cl	**a**	36	85	(56:44)[8]
9	3-NO_2	H	**a**	38	80	(56:44)[8]
10	R^1-C_6H_4 = 2-thienyl	6′-Cl	**a**	35	85	(61:39)[8]
11	H	5′-NO_2	**a**	42	75	(56:44)
12	2,5-$(OMe)_2$	6′-Cl	**a**	35	85	(57:43)
13	4-Br	6′-Cl	**a**	37	80	(73:27)
14	2-NO_2	6′-Cl	**a**	40	75	(86:14)
15	2-Cl	6′-Cl	**a**	33	83	(63:37)
16	4-OH-3-OMe	6′-Cl	**a**	30	95	(100:0)
17	3,4-$(OMe)_2$	6′-Cl	**a**	36	81	(61:39)
18	3,4-$(OMe)_2$	5′-NO_2	**a**	44	73	(54:46)
19	4-OH-3-OMe	5′-NO_2	**a**	42	78	(60:40)
20	4-OMe	5′-NO_2	**a**	40	80	(65:35)
21	2,5-$(OMe)_2$	5′-NO_2	**a**	43	74	(50:50)
22	2-Cl	5′-NO_2	**a**	45	76	(58:42)
23	4-Cl	H	**a**	35	80	(65:35)[8]
24	3-NO_2	4-Cl	**a**	40	77	(60:40)[8]
25	H	6′-OMe	**b**	32	75	(62:38)[7]
26	2-Cl	6′-Cl	**b**	38	79	(65:35)
27	4-OH-3-OMe	6′-Cl	**b**	36	80	(61:39)

[a] Isolated yields.
[b] The *syn*:*anti* ratios were determined by the ^{1}H NMR integration ratios of the adjacent (C_2–$C_{1'}$) hydrogens of the crude reaction products.

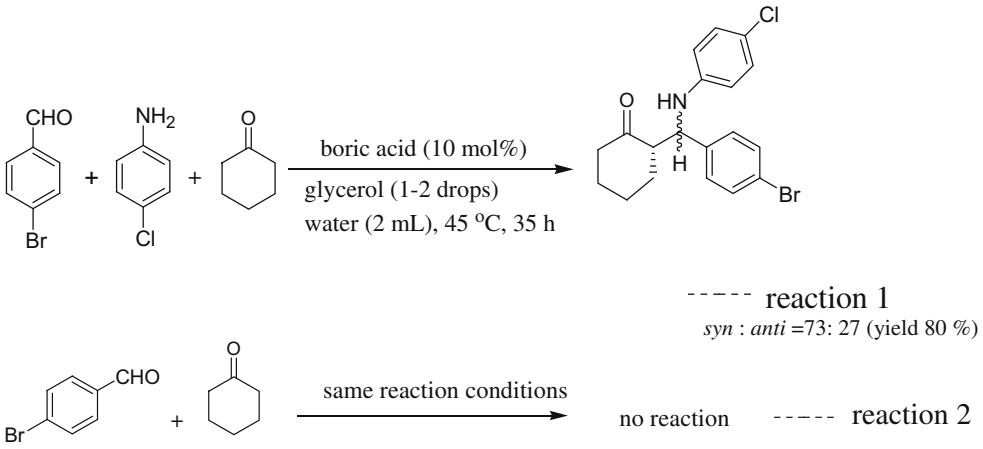
electron-donating substituents), aldehydes (heterocyclic, aromatic with various substituents), cyclohexanone and cycloheptanone were examined and the results are depicted in Table 2.

Substituted aldehydes with electron-donating groups, 4-chloroaniline and cyclohexanone gave excellent yields. Thus, 2,5-DMB, 4-chloroaniline and cyclohexanone (Table 2, entry 12) produced the product in 85% yield with *syn*:*anti* ratio 57:43. On the other hand, 3-nitroaniline, under the same reaction conditions, did not yield to that extent (Table 2, entry 21) due to deactivation by the nitro group. All the reactions were completed within 30–45 h which is either less or comparable to previously reported procedures. The reactivity of the aromatic amines follows the order: 4-chloroaniline > aniline > 4-anisidine > 3-nitroaniline. Not only aromatic aldehydes, but also heteroaromatic aldehydes such as furfural and thiophene-2-aldehyde worked well.

The results proved to be very exciting with vanillin as the aromatic aldehyde. Use of vanillin resulted in a single diastereoisomer in 95% isolated yield with cyclohexanone (**3a**, $n = 1$) and 4-chloroaniline (Table 2, entry 16). Thus the reaction was highly diastereoselective in this case. With cycloheptanone (**3b**, $n = 2$) and 4-chloroaniline, vanillin resulted in 80% yield with 61:39 diastereoisomeric ratio (Table 2, entry 27). With regard to the cyclic ketones, the reactivity order with respect to both yield and diastereoselectivity was: cyclohexanone > cycloheptanone. β-Amino carbonyl compounds were not obtained with cyclopentanone and acetophenone. Cyclopentanone being most reactive, produced the aldol product in major amount rather than the desired Mannich product. Acetophenone having very low reactivity being conjugated, produced the Mannich product in only 10–15% yield (by TLC) and hence could not be isolated from the reaction mixture in pure form.

The high chemoselectivity of cyclohexanone towards aldimines (generated by the reaction of aldehydes and amines) in preference to aldehydes is shown in Scheme 3, using 4-bromobenzaldehyde and 4-chloroaniline. Strong evidence for the above-mentioned chemoselectivity was that the aldimine obtained from 4-bromobenzaldehyde and 4-chloroaniline was isolated (δ 8.36 for the imine proton in ^{1}H NMR) from the reaction mixture of reaction 1 (Scheme 3).

The separation of the diastereoisomers were performed in two cases as shown in Table 3 by means of a long column (20 in. in height and 0.5 in. in diameter) with 100–200 mesh silica gel and 7-8% EtOAc/petroleum ether as eluant. From Table 3, entry 1, it can be noticed that both the major and the minor isomers could be separated and characterised (though being liquids). For entry 2, it was possible to isolate only the minor isomer because of its lower solubility. In almost all the previous reports, it has been mentioned that the *anti* isomer is the major one with a comparatively low δ value and a high J value compared to the *syn* isomer with a high δ value and a low J value. From the rigorous analysis of the ^{1}H NMR data of the crude Mannich reaction products, we find that in all our major isomers, the δ value is high and the J value is low. Thus, by analogy, all our major diastereoisomers have been assigned as '*syn*' in contrast to *anti* as reported earlier. When the reaction was carried out with an aliphatic aldehyde (*n*-butanal), 4-chloroaniline and cyclohexanone, the '*syn*' diastereoisomer was major.[15] [ν_{max} (liquid film: 2943, 1685, 1607, 1496, 1313 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, major:minor = 71:29) δ: 0.85–1.10 (m,



Scheme 3. Chemoselectivity of cyclohexanone towards aldimine.

Table 3
Separation of diastereoisomers resulting in diastereopure forms

Entry	R^1	R^2	Reactant **3**	*syn*:*anti* ratio	*syn* (yield) (isolated)	*anti* (yield) (isolated)	NMR (pure *syn*) ^{1}H, ^{13}C δ	NMR (pure *anti*) ^{1}H, ^{13}C δ
1	2-Cl	6′-Cl	$n = 1$	63:37	40	25	5.28 (J = 3.6 Hz) 53.90	4.83 (J = 4.5 Hz) 55.68
2	2,5-$(OMe)_2$	6′-Cl	$n = 1$	57:43	—	35	—	4.89 (J = 7.2 Hz) 55.56

8H), 1.12–1.86 (m, 7H), 3.24–3.37 (m, 1H, COCH), 3.88 (br s, 1H, NH), 4.30 (major d, J = 2.4 Hz, 0.71H, C*H*NH), 4.66–4.67 (minor d, J = 4.6 Hz, 0.29H, C*H*NH), 6.57 (major td, J = 8.7 Hz and 1.8 Hz, 1.42 H, $C_{4'}$-H and $C_{8'}$-H), 6.63 (minor td, J = 7.5 Hz and 2.4 Hz, 0.58 H, $C_{4'}$-H and $C_{8'}$-H), 7.11-7.17 (m, 2H, $C_{5'}$-H and $C_{7'}$-H); ^{13}C NMR (75 MHz, $CDCl_3$, major:minor = 71:29) δ: 14.1 (CH_3), 21.7 (CH_2), 23.3 (CH_2), 23.6 (CH_2), 26.6 (CH_2), 29.8 (CH_2), 40.1 ($CO\underline{C}H_2$), (49.6, 49.7) (CO<u>C</u>H), 53.0 (CHNH), (114.4, 114.6) ($C_{4'}$ and $C_{8'}$), (129.2, 129.32) ($C_{5'}$ and $C_{7'}$), 143.0 ($C_{3'}$/$C_{6'}$), 144.9 ($C_{6'}$/$C_{3'}$), 201.2(C=O)].[7]

Further and final confirmation comes from X-ray crystallographic data. Using vanillin, 4-chloroaniline and cyclohexanone (Table 2, entry 16) with our present methodology, only one diastereoisomer (crude ^{1}H NMR) was isolated (**4aA**). The coupling constant value (J = 4.5 Hz) indicates the diastereopure isomer to be *syn* (2*S*,1′*R*). Finally, the single crystal analysis of **4aA** obtained from Table 2, entry 16 was done and is shown (**CCDC 709686**) in Figure 1. The reaction was therefore 100% stereoselective in this case.

From the ortep plot, we clearly see that the adjacent C_1- and C-(ortep numbering) hydrogens have the '*syn*' configuration (2*S*,1′*R*) which is in total agreement with our previously assigned stereochemistry. With 2,5-dimethoxybenzaldehyde, 4-chloroaniline and cyclohexanone, two diastereoisomers were obtained in 57:43 ratio. The major diastereoisomer has been again assigned as '*syn*' in analogy with previous reports as it reveals a higher δ value and a low J value [δ 5.13 (major d, J = 4.8 Hz, 0.57H)] compared to the minor '*anti*' isomer (2*S*,1′*S*) possessing a lower δ value and high J value. [4.88 (minor d, J = 7.2 Hz, 0.43H)]. The 'minor' isomer in this case with a lower solubility could be separated and isolated in pure form (**4aB**, Table 2, entry 12). Finally, X-ray crystal of its single crystal was done (**CCDC 709650**) and is shown in Figure 2.

From the ortep plot, we clearly see that the adjacent **C_1–C** (ortep numbering) hydrogens have the '*anti*' configuration (2*S*,1′*S*) which is in complete agreement with our earlier assigned stereochemistry.

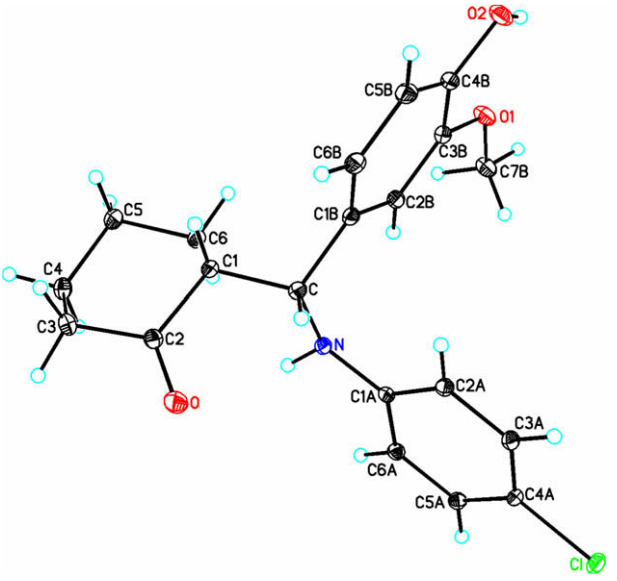


Figure 1. Ortep diagram of single crystal of **4aA** (single isomer) obtained from Table 2, entry 16 showing the crystallographic numbering.

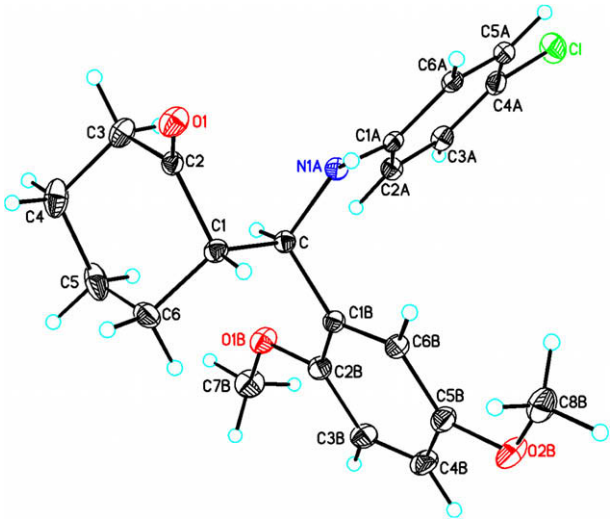


Figure 2. Ortep diagram of single crystal of **4aB** (minor isomer) obtained from Table 2, entry 12 showing the crystallographic numbering.

3. Conclusion

We have developed a rather novel protocol for the three-component Mannich reaction for aldehydes, aromatic amines and cycloalkanones catalysed by boric acid and glycerol in water with major '*syn*' diastereoselectivity in contrast to major '*anti*' diastereoselectivity in all the earlier reported methods. These reactions, which proceed very slowly in organic solvents, take place quite fast in water that is attributed to its unique property as a reaction medium. The formation of the boron chelate complex in water increases its acidity, thus accelerating the reaction. This catalyst system probably increases and at the same time reverses the diastereoselectivity compared to earlier reported procedures. This procedure offers several advantages such as high diastereoselectivity, high yields, mild reaction conditions and very simple work-up procedures. The separation of the diastereoisomers could be efficiently achieved in two cases. These β-amino carbonyl compounds are important synthetic intermediates for various pharmaceuticals and natural products.

4. Experimental

4.1. General procedure for the Mannich reaction catalysed by boric acid and glycerol in water

Aromatic aldehyde (1 mmol), aromatic amine (1 mmol) and [cyclohexanone or cycloheptanone (2 mmol)] were successively added to a solution of boric acid (10 mol %) and glycerol (1–2 drops) in water (2 mL) placed in a 25 mL round-bottomed flask. The reaction mixture was vigorously stirred at 45 °C on a water bath for 35–50 h. It was then diluted with ethyl acetate (10 mL), extracted further from the aqueous layer with ethyl acetate

(5 mL) and the combined organic layers were washed with water (2 × 5 mL) to remove glycerol and boric acid. The organic layer was dried with anhydrous Na_2SO_4. The solvent was distilled out on a hot water bath to give desired products. The crude products were purified either by crystallisation from ethanol or by column chromatography (10% ethyl acetate/90% petroleum ether). The first aqueous extract could be utilised for further Mannich reaction at least twice. The *syn*:*anti* ratio of the diastereoisomeric mixture was determined by ^{1}H NMR of the crude reaction mixture. The physical and spectral data of one unknown compound are given below. The data for all the other unknown compounds are given in Supplementary data.

4.2. 2-[1′–(*N*-*p*-chlorophenylamino)-1′-2,5-dimethoxyphenyl]methylcyclohexanone (Table 2, entry 12)

The title compound was obtained as yellowish brown oil (317.8 mg, 85%) in 57:43 (*syn*:*anti*) ratio of the diastereoisomers; [Calcd for $C_{21}H_{24}NO_3Cl$: C, 67.46; H, 6.47; N, 3.75%. Found: C, 67.68; H, 6.64; N, 3.97%.]; R_f (25% EtOAc/petroleum ether) [0.48 (*syn*) and 0.38 (*anti*)]; ν_{max} (neat): 3336, 2932, 1704, 1601. 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, major:minor = 57:43) δ: 1.53–1.68 (m, 4H, –CH_2–CH_2), 1.72–1.92 (m, 2H, –CH_2), 2.28–2.44 (m, 2H, $COCH_2$), 2.84–2.88 (m, 1H, –COCH), 3.68 (s, 3H, –OMe), [3.81 (major, s, 1.71H), 3.85 (minor, s, 1.29H)] (OMe), 4.49 (br s, 1H, NH), [4.89 (minor d, J = 7.2 Hz, 0.43H), 5.13 (major d, J = 4.8 Hz, 0.57H)] (C*H*–NH), 6.43–6.47 (m, 2H, $C_{4'}$–H and $C_{8'}$–H), 6.66–6.70 (m, 1H, aromatic C_4–H/C_3–H), 6.76–6.79 (m, 1H, aromatic C_3–H/C_4–H), 6.87–6.92 (d, J = 3 Hz, 1H, C_6–H), 6.95–6.99 (m, 2H, $C_{5'}$–H and $C_{7'}$–H); ^{13}C NMR (75 MHz, $CDCl_3$, major:minor = 57:43) δ: (23.7, 24.7) (CH_2), (27.2, 28.3) (CH_2), 31.7 (CH_2), (41.9, 42.3) (CO$\underline{C}H_2$), (51.4, 52.7) (CO$\underline{C}$H), (54.5, 55.5) (*C*H–NH), (55.5, 55.8, 55.9) (2 × OMe), (111.0, 111.3) (aromatic C_3/C_6), (111.9, 112.3) (aromatic C_6/C_3), (114.3, 114.6) ($C_{4'}$ + $C_{8'}$), (115.0, 115.2) (aromatic C_4), (121.8, 122.0) (aromatic C_1),(128.7, 128.8) ($C_{5'}$ + $C_{7'}$), 130.2 ($C_{6'}$), (145.9, 146.3) ($C_{3'}$), (150.9, 151.4) ($\underline{C}$–OMe), (153.6, 153.7) ($\underline{C}$–OMe), (211.4, 213.5) (C=O); MS (EI) *m*/*z*: 373 (M^+,100), 375 (32), 374 (23).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.135.

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15. The assignment of the major diastereoisomer as '*syn*' with *n*-butanal as the aliphatic aldehyde was done by analogy with earlier reports (Ref. 7), where of course, the major isomer obtained was '*anti*' in contrast to our present observation.