



## Synthesis of optically active 1,2,3-trisubstituted azetidines employing an organocatalytic approach with L-proline

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### ABSTRACT

A concise organocatalytic approach towards optically active 1,2,3-trisubstituted azetidines, including a study of the scope and limitations of the synthetic sequence, is reported. The synthesis comprises the one-pot L-proline promoted three-component reaction between substituted benzaldehydes, anilines and enolizable aldehydes, followed by the in situ reduction of the resulting  $\beta$ -aminoaldehydes to the corresponding  $\gamma$ -aminoalcohols and final intramolecular cyclization of the latter by way of the intermediate tosylates, formed in situ.

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Azetidines are four-membered nitrogen heterocycles. They are of great interest for fundamental research and useful for practical applications; for example, 2-azetidinone is the key feature of the  $\beta$ -lactam antibiotics.<sup>1</sup> Several natural products carry the azetidine motif; among them, are the  $\alpha$ -aminoacid azetidine-2-carboxylic acid, a powerful proline antagonist in plant tissue cultures,<sup>2</sup> and some of its functionalized derivatives, such as the phytosiderophores nicotianamine<sup>3a–c</sup> and mugineic acid,<sup>3d–g</sup> and the structurally related 2"-hydroxynicotianamine, an ACE-inhibitor (Fig. 1).<sup>3h,i</sup>

Other naturally-occurring azetidines include the vioprolides, antifungal and cytotoxic peptolides, exemplified by vioprolide A,<sup>4a</sup> and the polyoxins A, F, H and K, peptide nucleosides with antifungal and antiparasitic activity, possibly involved in cell wall chitin biosynthesis.<sup>4b–e</sup> Additional representatives of natural azetidines are the cytotoxic and antibacterial penaresidines<sup>5</sup> and the related penazetidine A, an inhibitor of protein kinase C.<sup>6</sup> Interestingly, natural products such as gelsemoxonine,<sup>7a–c</sup> the insecticidal alkaloid okaramine B<sup>7d,e</sup> and calydaphninone<sup>7f</sup> also carry fused polysubstituted azetidine moieties.

Azetidines are also of interest because of their presence in synthetic intermediates and bioactive compounds,<sup>8</sup> including the non-opioid analgesic ABT-594, the thrombin inhibitors exenta and melagatran,<sup>9a,b</sup> and aggrecanase and  $\beta$ -amyloid cleaving enzyme-1 inhibitors.<sup>9c,d</sup> They are also found in certain NMDA receptor<sup>10a</sup> and cholinergic channel modulators,<sup>10b</sup> antivirals<sup>10c</sup> and inducers of cytokine production.<sup>10d</sup> Their suitability as natural

aminoacid surrogates,<sup>11a</sup> and tools in peptidomimetics<sup>11b</sup> and nucleic acid chemistry,<sup>11c–e</sup> is also remarkable.

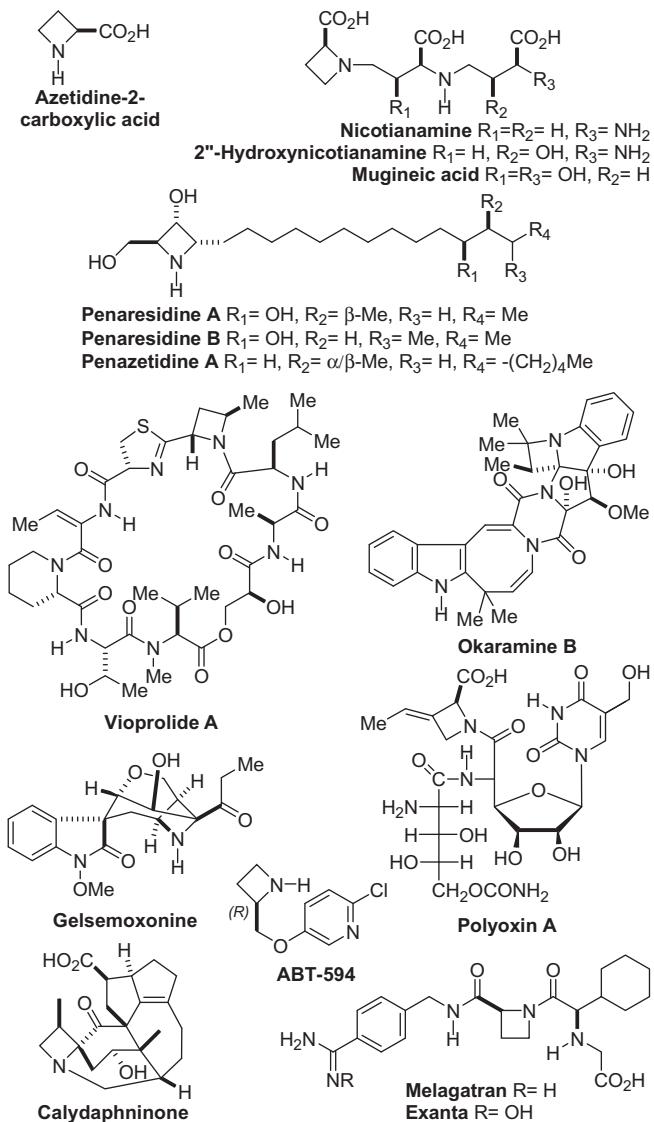
Ligands featuring the azetidine moiety have been employed in various catalytic processes, including reductions,<sup>12a,b</sup> asymmetric Et<sub>2</sub>Zn,<sup>12c–g</sup> and Henry additions to aldehydes,<sup>12g</sup> cycloadditions,<sup>13a</sup> cyclopropanations<sup>13b</sup> and other C–C bond forming reactions (Suzuki, Sonogashira, Michael)<sup>13b–e</sup> with promising results. In addition, C<sub>2</sub>-symmetric bis(aziridines) have been used as bidentate ligands in transition metal catalysed reactions.<sup>14</sup>

Synthetic approaches towards optically active polysubstituted azetidines have been recently reviewed.<sup>15</sup> These have been comparatively less studied than the aziridines, pyrrolidines and piperidines, their lower and higher homologous small-ring saturated single-nitrogen heterocycles, and several authors have pointed out the paucity of short, general and efficient methods for the synthesis of enantiopure azetidines.<sup>16</sup>

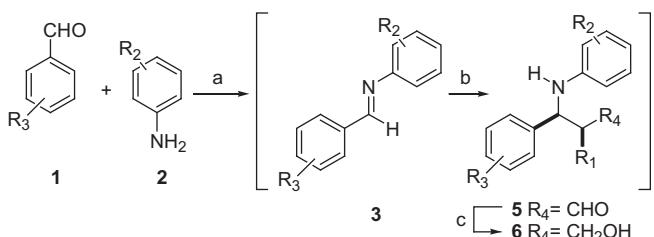
Furthermore, the low number of publications on optically active polysubstituted azetidines also reflects the need of new enantioselective approaches towards these heterocycles.<sup>16b</sup> Marinetti et al.<sup>16c</sup> conjectured that the reason for the lack of progress in the development of the chemistry of optically active azetidines could be related to synthetic difficulties associated to the formation of the four-membered ring from acyclic derivatives; this is a disfavored process compared to the analogous construction of slightly larger and even smaller rings.

Therefore, herein we report the development of the first enantioselective organocatalysed approach to 1,2,3-trisubstituted azetidines employing a one-pot synthesis of  $\gamma$ -aminoalcohols followed by their microwave-assisted cyclization with TsCl–Et<sub>3</sub>N. No

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**Figure 1.** Some relevant azetidine-type natural and pharmaceutical products.



**Scheme 1.** Reagents and conditions: (a) L-Proline (20 mol %), NMP, MW (70 °C, 1 h); (b)  $R_1CH_2CHO$  (4), NMP,  $-20^{\circ}C$ , 24 h; (c)  $NaBH_4$ ,  $MeOH$ ,  $Et_2O$ ,  $0^{\circ}C$ , 1 h.  $1:2:4 = 1.0:1.1:3.0$ . For the identity of  $R_1-R_3$ , see Table 2.

protecting groups are employed. The  $\gamma$ -aminoalcohols result from a tri-component cross-Mannich synthesis of  $\beta$ -amino aldehydes,<sup>17</sup> followed by their *in situ* reduction.

To that end, 4-nitrobenzaldehyde (**1**), propanal (**4**) and 3,4-dimethoxyaniline (**2**) were reacted with 20 mol % L-proline as chiral organocatalyst (Scheme 1).<sup>18</sup> Under these conditions, the use of NMP at rt met with failure, while adding 4 Å MS to a mixture of the benzaldehyde and the amine in order to promote pre-formation of the Schiff base (**3**), and reacting the latter at  $-20^{\circ}C$  with propanal

(**4**) provided only minor amounts of the expected intermediate **5**, which proved to be highly unstable to silica gel column chromatography.

Therefore, the protocol was modified to include pre-formation of the Schiff base and to avoid isolation of the  $\beta$ -aminoaldehyde. Schiff base pre-formation in the absence of molecular sieves proved to be more efficient under microwave irradiation ( $70^{\circ}C$ , 1 h) than under conventional heating. Dropwise addition of **4** (3 equiv) furnished the expected  $\beta$ -aminoaldehyde **5**, which was reduced *in situ* with  $NaBH_4$  in  $MeOH$ , to the corresponding  $\gamma$ -aminoalcohol **6**, which was uneventfully purified (62% overall yield).<sup>19</sup>

It was also observed that the reaction solvent played a key role in the yield and outcome of the transformation. Anhydrous DMSO, gave 45%  $\gamma$ -aminoalcohol, while a 1:1 DMSO/ $CH_2Cl_2$  mixture yielded no useful products and a 2:1 DMSO/ $CH_2Cl_2$  solvent furnished mainly aldol condensation derivatives. Analogously, 50% yield of  $\gamma$ -aminoalcohol was realized in DMF, while a 1:1 mixture of DMF and  $CH_2Cl_2$  gave mainly the imine. Therefore, the syntheses of  $\gamma$ -aminoalcohols **6** to explore the scope and limitations of the reaction were carried out in NMP.

The amination of alcohols has been performed employing various strategies, which involve converting the carbinol into a suitable leaving group (Mitsunobu, Appel-type halogenation, formation of sulfonates, carbonates and other esters), followed by base-assisted displacement of the latter with the cyclizing nitrogen moiety, as the final step.<sup>20</sup>

Thus, suitable cyclization conditions were screened (Table 1). Initially, formation of the benzoate ( $PhCOCl-Et_3N$ ) followed by intramolecular displacement of the latter was attempted;<sup>21</sup> however, this resulted in an incomplete sequence, yielding a mixture of products which included the intermediate benzoate (runs 3 and 11). On the other hand, activation of the primary alcohol as the carbonate ( $ClCO_2Et-Et_3N$ ) prior to intramolecular displacement gave several inseparable products and low yields of the expected products (runs 1 and 4). The Letter by Couty and co-workers, that chloroformates can cleave the azetidine ring, may explain the observed low yields.<sup>22</sup>

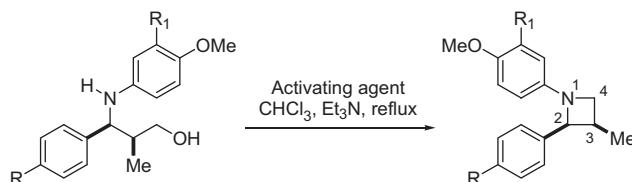
Finally, reaction with  $TsCl$  and  $Et_3N$  under microwave irradiation resulted in smooth and clean cyclizations (entries 2, 5, 9 and 10), which successfully competed with the corresponding thermal conditions (entry 7) and with the related  $MsCl-Et_3N$  process (entry 12),<sup>23</sup> perhaps because in the latter case, the sulfene intermediates generated under the reaction conditions may undergo side reactions lowering product yields or demanding a great excess of the reagent.<sup>24</sup>

With suitable cyclizing conditions, the scope and limitations of the protocol were studied with different benzaldehydes and anilines.<sup>25</sup> It was observed that steric hindrance exerted a major effect on the outcome. On the benzaldehyde side, the reaction accepted compounds carrying electron withdrawing and electron releasing substituents, but the presence of substituents *ortho* to the formyl moiety resulted in intermediate imines (**3**), which failed to undergo the Mannich reaction (entries 9, 11 and 12), except with the more activated aldehydes (entries 5 and 8), albeit at the expense of reduced yield (entry 8); *meta*-substituted aldehydes reacted uneventfully (entries 6 and 10).

On the other hand, the results of steric effects were more evident on the aniline side. The bulky 2-phenylaniline failed to react (entries 14 and 17), while the reaction with  $\alpha$ -naphthylamine and 2-methoxyaniline (entries 15 and 16) furnished the corresponding Schiff bases, which failed to further undergo the Mannich reaction with propanal. Finally, it was observed that the synthetic sequence accepts enolizable aldehydes other than propanal, such as 3-phenylpropanal (entry 20).

The configuration of the azetidines was inferred from that of the precursor  $\gamma$ -aminoalcohols<sup>18</sup> and NOE experiments confirmed

**Table 1**  
Selection of the cyclizing agent



Run No	Starting $\gamma$ -aminoalcohol	Activating agent	Azetidine % yield	Azetidine <sup>a</sup> ee (%)
1	R = NO <sub>2</sub> , R <sub>1</sub> = H	CICO <sub>2</sub> Et	33	92
2		TsCl	94	92
3		BzCl	— <sup>b</sup>	
4	R = NO <sub>2</sub> , R <sub>1</sub> = OMe	CICO <sub>2</sub> Et	27	97
5		TsCl	95	97
6		CICO <sub>2</sub> Et	6 <sup>c</sup>	97
7		TsCl	51 <sup>d</sup>	
8	R = H, R <sub>1</sub> = OMe	CICO <sub>2</sub> Et	16	91
9		TsCl	69	91
10	R = Cl, R <sub>1</sub> = OMe	TsCl	90	96
11		BzCl	— <sup>b</sup>	
12		MsCl	55	96

<sup>a</sup> Determined by chiral HPLC with a Chiralcel OD column, eluting with hexanes:IPA (10:1) at 1 mL/min.

<sup>b</sup> Formation of the benzoate was observed.

<sup>c</sup> Formation of the carbamate was observed (27%).

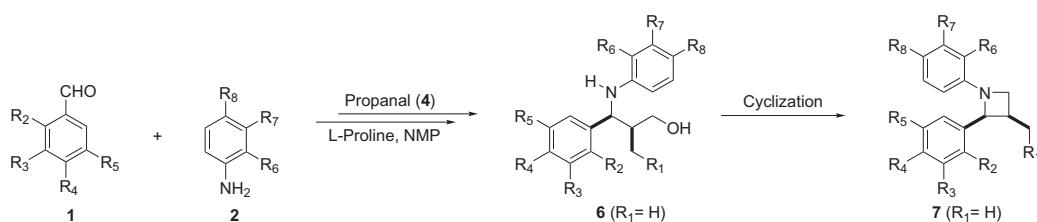
<sup>d</sup> Under conventional heating.

their relative configuration. The C<sub>2</sub>–C<sub>3</sub> coupling constants of the heterocycles were in the range of 7.2–8.5 Hz in their <sup>1</sup>H NMR spectra and only one diastereomer was always obtained.

Chemical yields ranged from moderate to good for both main stages (total = five steps), the synthesis of the  $\gamma$ -aminoalcohol and its cyclization, while enantiomeric excesses (ees) of

the resulting products were mostly above 90%. A tendency to lower enantiomeric excess values was observed when electron releasing substituents were present in the benzaldehyde derived moiety (entries 8 and 10) of the  $\gamma$ -aminoalcohol and/or the starting aniline carried electron withdrawing substituents (entry 18).

**Table 2**  
Synthesis of 1,2,3-trisubstituted azetidines



No	Aldehyde (1)	Aniline (2)	6, % yield	7, % yield <sup>a</sup> (ee, %)	7, [α] <sub>D</sub> (CHCl <sub>3</sub> )
1	R <sub>2</sub> = R <sub>3</sub> = R <sub>4</sub> = R <sub>5</sub> = H	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	41	69 (91)	-191.5 (c = 0.5)
2	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = Br	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	66	15 (93)	-156.3 (c = 0.2)
3	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = Me	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	52	67 (95)	-161.9 (c = 0.5)
4	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = NO <sub>2</sub>	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	62	57 (97)	-207.4 (c = 1.0)
5	R <sub>2</sub> = R <sub>3</sub> = OMe, R <sub>4</sub> = R <sub>5</sub> = H	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	67	70 (99)	-219.8 (c = 0.5)
6	R <sub>2</sub> = R <sub>4</sub> = R <sub>5</sub> = H, R <sub>3</sub> = OBN	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	50	45 (81)	-192.9 (c = 0.32)
7	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = Cl	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	67	90 (96)	-218.9 (c = 1.1)
8	R <sub>2</sub> = Br, R <sub>3</sub> = H, R <sub>4</sub> = R <sub>5</sub> = OMe	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	7	36 (86)	-129.5 (c = 0.12)
9	R <sub>2</sub> = Cl, R <sub>3</sub> = R <sub>4</sub> = R <sub>5</sub> = H	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	Imine	—	
10	R <sub>2</sub> = H, R <sub>3</sub> = R <sub>4</sub> = R <sub>5</sub> = OMe	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	33	62 (88)	-143.7 (c = 0.2)
11	R <sub>2</sub> = CF <sub>3</sub> , R <sub>3</sub> = R <sub>4</sub> = R <sub>5</sub> = H	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	Imine	—	
12	R <sub>2</sub> = CF <sub>3</sub> , R <sub>3</sub> = R <sub>4</sub> = R <sub>5</sub> = H	R <sub>6</sub> = H, R <sub>7</sub> = R <sub>8</sub> = OMe	Imine	—	
13	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = Cl	R <sub>6</sub> = R <sub>7</sub> = H, R <sub>8</sub> = OMe	35	69 (92)	-168.7 (c = 1.2)
14	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = NO <sub>2</sub>	R <sub>6</sub> = Ph, R <sub>7</sub> = R <sub>8</sub> = H	No reaction	—	
15	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = NO <sub>2</sub>	$\alpha$ -Naphthylamine	Imine	—	
16	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = OMe	R <sub>7</sub> = R <sub>8</sub> = H, R <sub>6</sub> = OMe	Imine	—	
17	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = OMe	R <sub>6</sub> = Ph, R <sub>7</sub> = R <sub>8</sub> = H	No reaction	—	
18	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = OMe	R <sub>6</sub> = R <sub>7</sub> = H, R <sub>8</sub> = CO <sub>2</sub> Et	21	34 (83)	-174.3 (c = 0.3)
19	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = NO <sub>2</sub>	R <sub>6</sub> = R <sub>7</sub> = H, R <sub>8</sub> = OMe	62	94 (93)	-223.4 (c = 1.1)
20	R <sub>2</sub> = R <sub>3</sub> = R <sub>5</sub> = H, R <sub>4</sub> = NO <sub>2</sub>	R <sub>6</sub> = R <sub>7</sub> = H, R <sub>8</sub> = OMe	56 <sup>b</sup>	36 (97)	-196.7 (c = 0.4)

<sup>a</sup> By chiral HPLC with a Chiralcel OD column, eluting with hexanes:IPA (10:1) at 1 mL/min.

<sup>b</sup> Reaction with 3-phenylpropanal (R<sub>1</sub> = Ph in 6 and 7).

In conclusion, a two-stage organocatalytic enantioselective approach to the synthesis of 1,2,3-trisubstituted azetidines, which does not require protective groups, was developed; its scope and limitations were studied. Overall chemical and optical yields were highly satisfactory; however, the one-pot synthesis of the intermediate  $\gamma$ -aminoalcohols was influenced by steric and electronic factors, sometimes resulting in unsuccessful transformations. Due to its simplicity and effectiveness, the sequence may find use in synthetic organic chemistry.

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- Typical experimental procedure for the synthesis of the azetidines (7):* DMAP (cat.), Et<sub>3</sub>N (4 equiv) and TsCl (2.5 equiv) were successively added to a solution of the  $\gamma$ -aminoalcohol (1 equiv) in CHCl<sub>3</sub> (2 mL) and the mixture was subjected to microwave irradiation at 70 °C for 1 h. Then, brine (10 mL) was added and the organic materials were extracted with EtOAc (4 × 20 mL). The organic phases were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuum and the residue was submitted to chromatography. *Data of selected azetidines:* (2S,3R)-1-(3,4-dimethoxyphenyl)-3-methyl-2-(4-nitrophenyl)azetidine: IR (film, v): 2957, 2850, 1598, 1465, 1452, 1343, 1239, 1221, 1140, 1027, 849, 823 and 745 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.89 (d, *J* = 7.3, 3H), 2.95 (ddd, *J* = 3.0, 7.3 and 8.3, 1H), 3.61 (dd, *J* = 3.0 and 6.4, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.92 (dd, *J* = 6.4 and 7.3, 1H), 5.07 (d, *J* = 8.3, 1H), 5.86 (dd, *J* = 2.6 and 8.6, 1H), 6.03 (d, *J* = 2.6, 1H), 6.71 (d, *J* = 8.6, 1H), 7.52 (d, *J* = 8.7, 2H) and 8.23 (d, *J* = 8.7, 2H); <sup>13</sup>C NMR  $\delta$ : 16.2, 29.9, 55.8, 56.7, 57.0, 68.6, 97.7, 103.5, 112.9, 123.6 (2C), 127.5 (2C), 142.2, 146.2, 147.2, 147.5 and 149.9. HRMS obsd.: *m/z* 329.1490; C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub> requires *m/z* 329.1496. (25R)-2-(3,4,5-Trimethoxyphenyl)-1-(3,4-dimethoxyphenyl)-3-methylazetidine: IR (film, v): 2955, 2849, 1680, 1588, 1501, 1140, 1349, 1209, 1033 and 795 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.95 (d, *J* = 7.0, 3H), 2.81 (dd, *J* = 2.9, 7.0 and 8.2, 1H), 3.54 (dd, *J* = 2.9 and 6.6, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.85 (dd, *J* = 6.6 and 7.0), 3.87 (s, 3H), 4.89 (d, *J* = 8.2, 1H), 5.96 (dd, *J* = 2.6 and 8.7, 1H), 6.08 (d, *J* = 2.6, 1H), 6.57 (s, 2H), 6.72 (d, *J* = 8.7, 1H); <sup>13</sup>C NMR  $\delta$ : 15.9, 30.1, 55.8, 56.2 (2C), 56.7, 56.9, 60.9, 70.0, 98.0, 103.5 (2C), 103.8, 112.9, 135.5, 136.7, 141.9, 147.3, 149.7 and 153.2 (2C). HRMS obsd.: *m/z* 396.1781; C<sub>21</sub>H<sub>27</sub>NaO<sub>5</sub> requires *m/z* 396.1781.