

# Neighboring group effect: DBU-promoted ring transformation of substituted isoxazoles to substituted pyrroles<sup>1</sup>

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**Abstract:** A novel DBU-promoted ring transformation of substituted isoxazoles to substituted pyrroles is described.

**Key words:** Isoxazole, Pyrrole, Baylis-Hillman, DBU, ring transformation, neighboring group effect.

Recently, we have described the synthesis of 5,8-dihydro-isoxazolo[4,5-c]azepin-4-ones (**A**) from the acetates of Baylis-Hillman adducts of 5-formyl-3-aryl-isoxazole-4-carboxylate (Fig.1).<sup>2</sup> During this study, a few attempts to carry out direct intramolecular cyclization of the secondary amines, obtained from Baylis-Hillman adducts, involving the NH group and the ester group present on the isoxazole ring, were unsuccessful. However, it was envisioned that a strong base may trigger the desired cyclization to yield the isoxazole annulated system (**B**) and this consideration prompted us to study the possibility of desired intramolecular ring closure by DBU. Interestingly, this reaction, instead of yielding the desired bicyclic derivatives, led to the formation of a substituted pyrrole. The details of this observation are described herein.

The required amino derivatives (**4-8a-c**) were obtained by the Michael addition of several primary amines on the Baylis-Hillman adducts (**2-3a-c**) prepared from 5-formyl-3-aryl-isoxazole-4-carboxylate (**1a-c**) as described earlier.<sup>2</sup> All amines were obtained as diastereoisomeric mixtures and no attempts were made to separate them. These sec-amines were subsequently refluxed in the presence of DBU in THF (Scheme 1). The starting material disappeared in 5 h as evident by TLC. Column chromatography of the reaction products led to isolation of the pure products (**9-13a-c**), which exhibited mass of 44 amu less than the expected azepinones. The one and two-dimensional NMR experiments of a model product **13a** indicated the product to be a pyrrole derivative. In order to confirm the structure of the product unambiguously, the X-ray crystal structure of a representative compound **13b** was examined. The ORTEP diagram, Fig. 2 shows the crystal structure of compound **13b** and its conformation with atomic numbering scheme.<sup>3</sup>

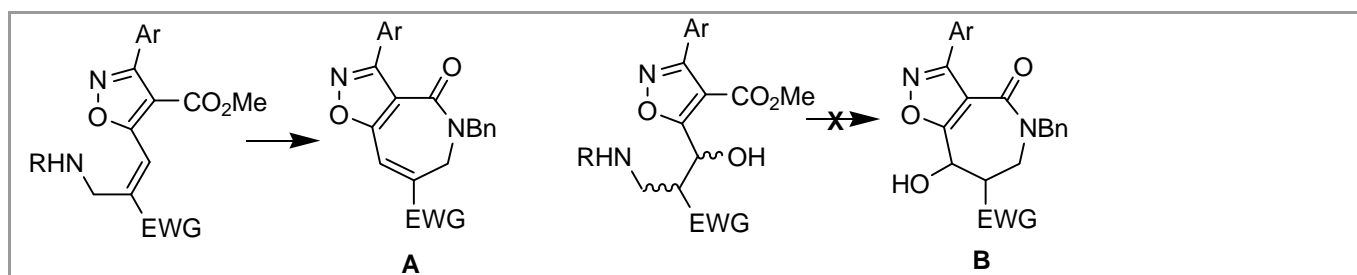
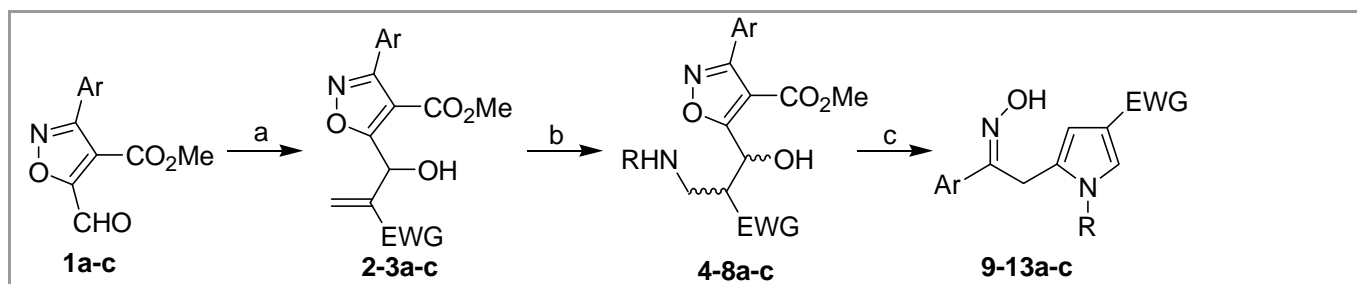


Figure 1.

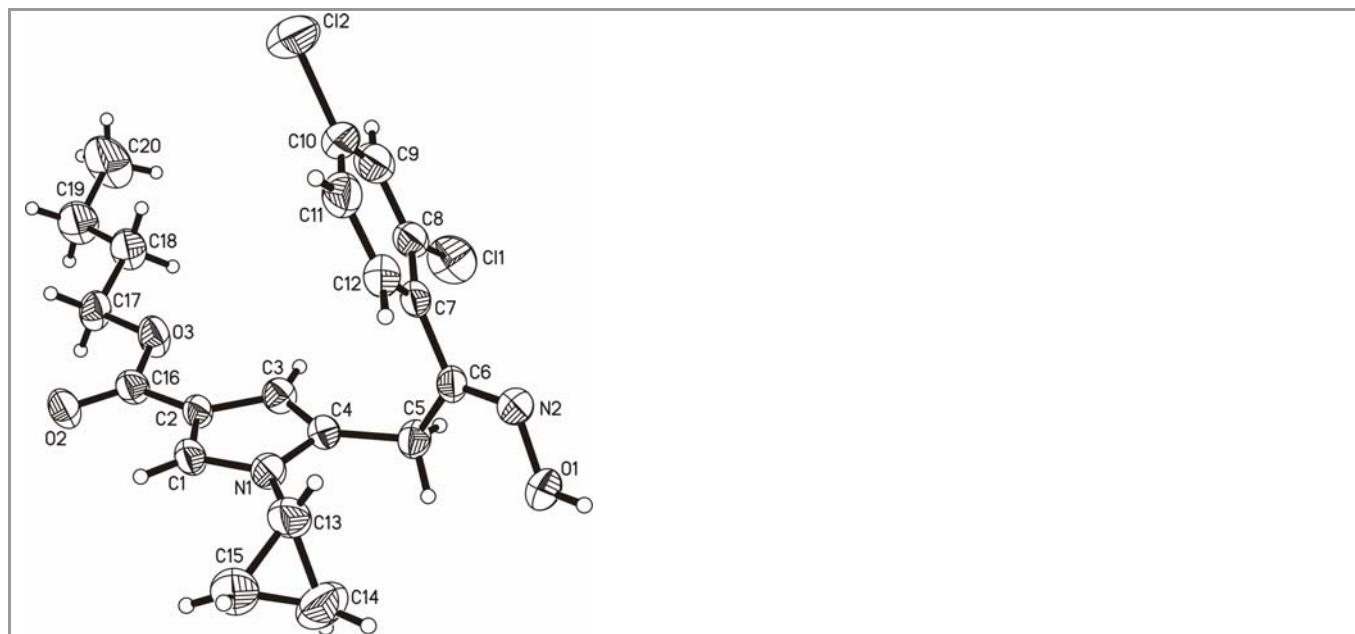
During the optimization studies the reaction was carried out in different solvent systems. It was observed that though dioxane and dimethylformamide gave similar pyrrole derivatives, the best yields were achieved when the reaction was performed in THF. The reaction failed to occur in methanol. In order to evaluate the generality of this reaction several analogs of substituted pyrroles (**9-13a-c**) were synthesized (Table 1).

The formation of such pyrroles can be explained on the basis of mechanism shown in Fig. 3. Initially in

the presence of base, due to the neighboring group participation of the secondary hydroxyl group hydrolysis of the ester present on the ring occurs followed by concomitant fission of the isoxazole ring to yield the acetylene intermediate **III**. The acetylene bond undergoes an intramolecular attack of the NH group leading to the dihydro pyrrole system **IV** which rearranges by a 1,5-shift to furnish the substituted pyrroles (**9-13**). It was observed that the oxime with *E*-stereochemistry was obtained.



**Scheme 1** Reagents and conditions: a)  $\text{CH}_2=\text{CHEWG}$ , DABCO, THF, rt, 5 min. b)  $\text{RNH}_2$ , MeOH, rt, 8-12h. c) DBU, THF, reflux, 5h.



**Figure 2** ORTEP diagram for compound **13b**.

**Table 1** Yield and physical characterization data for new pyrroles

Reactant	Ar	EWG	R	Product	Yield	Physical appearance, mp ( $^{\circ}\text{C}$ )	HPLC <sup>a</sup> (Retention time in min)
<b>4a</b>	$\text{C}_6\text{H}_5$	$\text{CO}_2\text{Me}$	$\text{CH}_2\text{C}_6\text{H}_5$	<b>9a</b>	50	white solid, 170-172	18.7
<b>4b</b>	(2-Cl)- $\text{C}_6\text{H}_4$	$\text{CO}_2\text{Me}$	$\text{CH}_2\text{C}_6\text{H}_5$	<b>9b</b>	58	white solid, 134-135	19.2
<b>4c</b>	(2-Cl) <sub>2</sub> - $\text{C}_6\text{H}_3$	$\text{CO}_2\text{Me}$	$\text{CH}_2\text{C}_6\text{H}_5$	<b>9c</b>	52	white solid, 153-154	20.7
<b>5a</b>	$\text{C}_6\text{H}_5$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{C}_6\text{H}_5$	<b>10a</b>	55	white solid, 168-169	21.7
<b>5b</b>	(2-Cl)- $\text{C}_6\text{H}_4$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{C}_6\text{H}_5$	<b>10b</b>	36	light brown solid, 93-95	22.3
<b>5c</b>	(2-Cl) <sub>2</sub> - $\text{C}_6\text{H}_3$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{C}_6\text{H}_5$	<b>10c</b>	49	pale yellow solid, 114-115	23.7
<b>6a</b>	$\text{C}_6\text{H}_5$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{C}_6\text{H}_4(4\text{-F})$	<b>11a</b>	57	white solid, 166-168	21.2
<b>6b</b>	(2-Cl)- $\text{C}_6\text{H}_4$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{C}_6\text{H}_4(4\text{-F})$	<b>11b</b>	42	light brown solid, 97-99	22.3
<b>6c</b>	(2-Cl) <sub>2</sub> - $\text{C}_6\text{H}_3$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{C}_6\text{H}_4(4\text{-F})$	<b>11c</b>	53	white solid, 151-152	22.3
<b>7a</b>	$\text{C}_6\text{H}_5$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{-furan-2-yl}$	<b>12a</b>	51	white solid, 142-144	19.8
<b>7b</b>	(2-Cl)- $\text{C}_6\text{H}_4$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{-furan-2-yl}$	<b>12b</b>	45	Brown oil	21.1
<b>7c</b>	(2-Cl) <sub>2</sub> - $\text{C}_6\text{H}_3$	$\text{CO}_2\text{Bu-n}$	$\text{CH}_2\text{-furan-2-yl}$	<b>12c</b>	53	pale yellow solid, 107-109	22.5
<b>8a</b>	$\text{C}_6\text{H}_5$	$\text{CO}_2\text{Bu-n}$	cyclopropyl	<b>13a</b>	55	white solid, 97-98	19.9
<b>8b</b>	(2-Cl)- $\text{C}_6\text{H}_4$	$\text{CO}_2\text{Bu-n}$	cyclopropyl	<b>13b</b>	56	white solid, 80-81	21.2
<b>8c</b>	(2-Cl) <sub>2</sub> - $\text{C}_6\text{H}_3$	$\text{CO}_2\text{Bu-n}$	cyclopropyl	<b>13c</b>	50	white solid, 148-149	22.7

<sup>a</sup>The HPLC was carried out using a 0-100% gradient of Acetonitrile: water containing 0.1 TFA at the rate of 1mL/min in a RP-18E column (250x4.5mm, 5 $\mu$ ) over a period of 30 min

In order to establish that the secondary hydroxyl group facilitates the deesterification of the ester present on the isoxazole ring through neighboring group participation, in a model reaction the methoxy analog **14b** of compound **4b** was prepared (scheme 2).<sup>4</sup> This was then subjected to Michael addition in the presence of benzyl amine to yield the amino derivative (**15b**). The product

**15b**, upon refluxing in the presence of DBU was recovered unreacted even after 24 h, thereby proving the role of the hydroxyl group in cyclization.

Thus we have described a novel DBU-promoted ring transformation of substituted isoxazoles to pyrrole derivatives. We have also provided the experimental evi-

dence for the neighboring group effect that is responsible for this rearrangement.

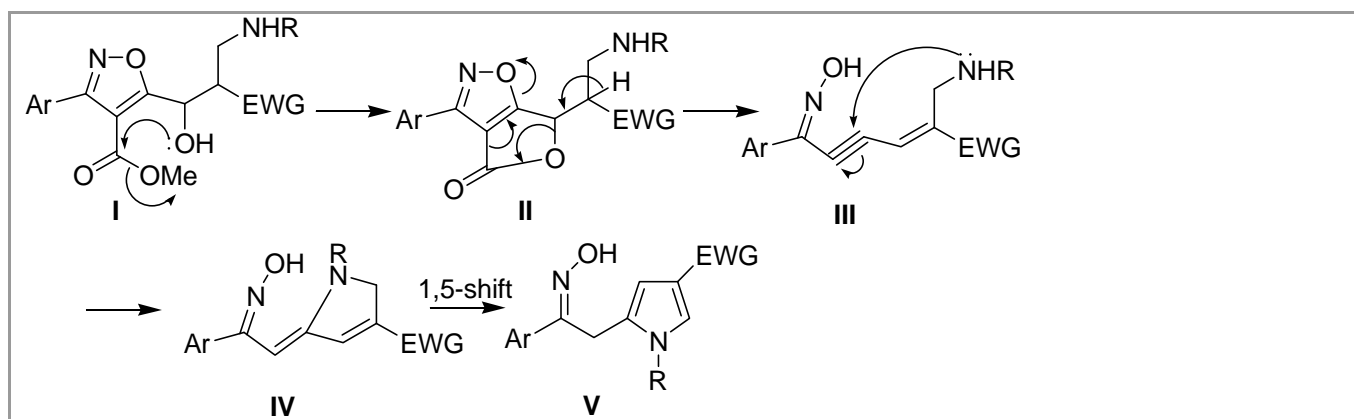
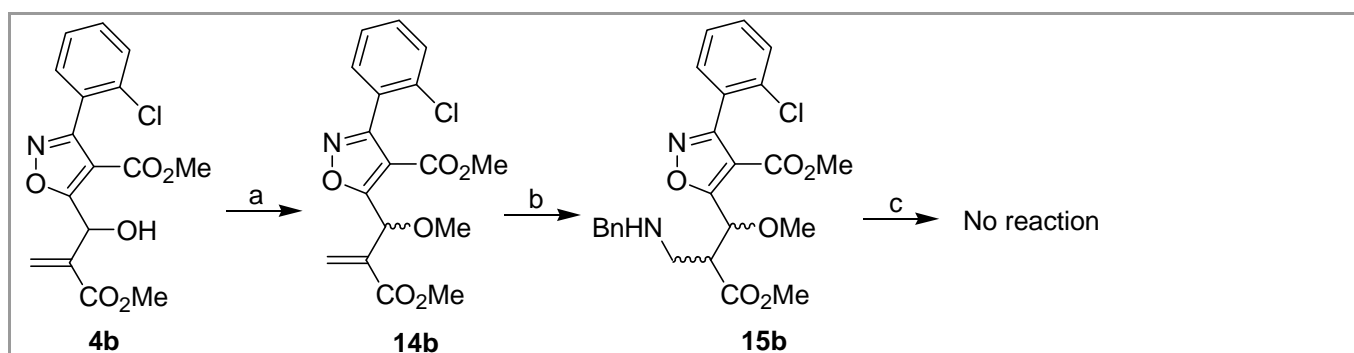


Figure 3. Mechanism for the formation of pyrroles.



Scheme 2 Reagents and conditions: a) MeI, Ag<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12h (Ref. 4). b) BnNH<sub>2</sub>, MeOH, rt, 12h. c) DBU, THF, reflux, 24h.

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. The HPLC were carried out on Agilent 1100 system having DA detector ( $\lambda_{\max}$  = 220nm, 254nm) using a gradient run of 10-100% acetonitrile in water containing 0.1% TFA in 30 min on a RP-18e column (250 X 4.6 mm) having particle size of 5 $\mu$ m. IR spectra were recorded using a Perkin Elmer RX TIR spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in  $\delta$  values, *J* in Hz). The FABMS were recorded on JEOL/ SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. The HRMS were recorded on JEOL-JMS-600H at 70eV. Elemental analyses were performed on a Elementar's Vario EL III microanalyzer. All amines were prepared as described in reference 4.

**5-(3-Benzylamino-1-hydroxy-2-methoxycarbonyl-propyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (4a)**

Yield 81%, colourless oil

$\nu_{\max}$  (Neat) 3321 (OH and NH), 1731 (C=O) cm<sup>-1</sup>, mass (ES+) *m/z* 424.83 (M<sup>+</sup>+1), 446.80 (M<sup>+</sup>+Na)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ = 0.5-3.08 (m, 2H, 2 x 1H of CH<sub>2</sub>), 3.38-3.42 (m, 4H, 2 x CH and 2 x 1H of CH<sub>2</sub>), 3.72 (s, 6H, 2 x OCH<sub>3</sub>), 3.76 (s, 6H, 2 x OCH<sub>3</sub>), 3.92-4.09 (dd, 4H, *J*= 13.0 Hz, 2 x CH<sub>2</sub>), 5.71 (d, 1H, *J*= 5.0 Hz, CHO), 5.93 (d, 1H, *J*= 5.0 Hz, CHO), 7.32-7.51 (m, 16H, 2 x 8ArH), 7.57-7.62 (m, 4H, 2 x CH<sub>2</sub>), 8.33 (bs, 1H, NH)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz)  $\delta$ = 47.7, 48.1, 52.4, 52.9, 54.5, 70.7, 108.2, 127.8, 128.6, 128.7, 129.0, 129.7, 130.4, 139.1, 162.5, 162.8, 172.3, 178.5.

**5-(3-Benzylamino-1-hydroxy-2-methoxycarbonyl-propyl)-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4b)**

Yield 71%, pale yellow oil

$\nu_{\max}$  (Neat) 3326 (OH and NH), 1732 (C=O) cm<sup>-1</sup>; mass (ES+) *m/z* 459.00 (M<sup>+</sup>+1), 481.00 (M<sup>+</sup>+Na)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ = 2.97-3.01 (m, 2H, 2 x 1H of CH<sub>2</sub>), 3.30 (brs, 2H, 2 x CH), 3.39-3.43 (m, 2H, 2 x 1H of CH<sub>2</sub>), 3.65-3.68 (m, 6H, 2 x OCH<sub>3</sub>), 3.74 (s, 6H, 2 x OCH<sub>3</sub>), 3.92- 4.09 (dd, 4H, *J*= 9.0 Hz, 2 x CH<sub>2</sub>), 5.75 (bs, 1H, CHO), 5.97 (bs, 1H, CHO), 7.35-7.50 (m, 18H, 2 x 9ArH).

**5-(3-Benzylamino-1-hydroxy-2-methoxycarbonyl-propyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4c)**

Yield 73%, colorless oil

$\nu_{\max}$  (Neat) 3449 (OH and NH), 1732 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  492.93 ( $M^+$ +1), 514.60 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 2.95-2.99 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.22-3.30 (m, 2H, CH), 3.43-3.52 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.66-3.70 (m, 6H, 2 x  $\text{OCH}_3$ ), 3.90-4.03 (dd, 4H,  $J$ = 12.6 Hz, 2 x  $\text{CH}_2$ ), 5.84 (bs, 1H, CHOH), 5.97 (d, 1H,  $J$ = 4.5 Hz, CHOH), 7.37 (s, 14H, 2 x 7ArH), 7.51 (s, 2H, 2 x 1ArH).

**5-(3-Benzylamino-2-butoxycarbonyl-1-hydroxy-propyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (5a)**

Yield 75%, colorless oil

$\nu_{\max}$  (Neat) 3445 (OH and NH), 1729 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  467.20 ( $M^+$ +1), 488.80 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200MHz)  $\delta$ = 0.82-0.96 (m, 6H, 2 x  $\text{CH}_3$ ), 1.26-1.43 (m, 4H, 2 x  $\text{CH}_2$ ), 1.57-1.66 (m, 4H, 2 x  $\text{CH}_2$ ), 2.80-2.91 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.08-3.22 (m, 2H, 2 x CH), 3.32-3.45 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.73-3.81 (m, 8H, 2 x  $\text{OCH}_3$  and 2 x 1H of  $\text{CH}_2$ ), 3.92-3.98 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 4.14-4.20 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.75 (brs, 1H, CHOH), 5.96 (d, 1H,  $J$ = 4.4 Hz, CHOH), 7.29-7.33 (m, 10H, 2 x 5ArH), 7.47 (s, 6H, 2 x 3ArH), 7.56-7.64 (m, 4H, 2 x 2ArH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ = 14.1, 19.5, 30.7, 30.9, 47.8, 48.3, 49.1, 52.4, 54.5, 65.7, 70.6, 108.3, 127.8, 128.4, 128.7, 129.0, 129.7, 130.4, 139.1, 162.4, 162.8, 171.8, 178.4.

**5-(3-Benzylamino-2-butoxycarbonyl-1-hydroxy-propyl)-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (5b)**

Yield 76%, light brown oil

$\nu_{\max}$  (Neat) 3445 (OH and NH), 1729 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  500.73 ( $M^+$ +1), 522.87 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.84-0.97 (m, 6H, 2 x  $\text{CH}_3$ ), 1.22-1.45 (m, 4H, 2 x  $\text{CH}_2$ ), 1.58-1.65 (m, 4H, 2 x  $\text{CH}_2$ ), 2.78-2.87 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.14-3.16 (m, 2H, 2 x CH), 3.36-3.45 (m, 2H, CH, 2 x 1H of  $\text{CH}_2$ ), 3.64-3.70 (m, 6H, 2 x  $\text{OCH}_3$ ), 3.81-3.91 (m, 4H, 2 x  $2\text{CH}_2$ ), 4.08-4.21 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.75 (d, 1H,  $J$ = 4.4 Hz, CHOH), 6.01 (d, 1H,  $J$ = 4.4 Hz, CHOH), 7.32-7.51 (m, 18H, 2 x 9ArH).

**5-(3-Benzylamino-2-butoxycarbonyl-1-hydroxy-propyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (5c)**

Yield 77%, colorless oil

$\nu_{\max}$  (Neat) 3321(OH and NH), 1728 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  534.87 ( $M^+$ +1), 556.93 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.84-0.97 (m, 6H, 2 x  $\text{CH}_3$ ), 1.26-1.45 (m, 4H, 2 x  $\text{CH}_2$ ), 1.58-1.68 (m, 4H, 2 x  $\text{CH}_2$ ), 2.78-2.87 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.15-3.18 (m, 2H, 2 x CH), 3.36-3.44 (m, 2H, CH, 2 x 1H of  $\text{CH}_2$ ), 3.64-3.70 (m, 6H, 2 x  $\text{OCH}_3$ ), 3.81-3.91 (m, 4H, 2 x  $2\text{CH}_2$ ), 4.07-4.18 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.76 (brs, 1H, CHOH), 6.01 (brs, 1H, CHOH), 7.33 (brs, 14H, 2 x 7ArH), 7.51 (s, 2H, 2 x ArH).

**5-[2-Butoxycarbonyl-3-(4-fluoro-benzylamino)-1-hydroxy-propyl]-3-phenyl-isoxazole-4-carboxylic acid methyl ester (6a)**

Yield 80%, yellow oil

$\nu_{\max}$  (Neat) 3319 (OH and NH), 1730 (C=O)  $\text{cm}^{-1}$ , Mass (ES+)  $m/z$  485.40 ( $M^+$ +1), 506.93 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.86-0.96 (m, 6H, 2 x  $\text{CH}_3$ ), 1.26-1.39 (m, 4H, 2 x  $\text{CH}_2$ ), 1.49-1.63 (m, 4H, 2 x  $\text{CH}_2$ ), 2.80-2.98 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.10-3.21 (m, 2H, 2 x CH), 3.31-3.49 (m, 2H, CH, 2 x 1H of  $\text{CH}_2$ ), 3.73-3.81 (m, 8H, 2 x  $\text{OCH}_3$  and 2 x 1H of  $\text{CH}_2$ ), 3.86-3.98 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 4.06-4.20 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.74 (d, 1H,  $J$ = 3.8 Hz, CHOH), 5.97 (d, 1H,  $J$ = 4.4 Hz, CHOH), 6.99-7.07 (m, 4H, 2 x 2ArH), 7.22-7.36 (m, 4H, 2 x 2ArH), 7.48- 7.64 (m, 10H, 2 x 6ArH).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ = 14.1, 19.5, 31.0, 47.8, 48.1, 52.4, 53.4, 65.6, 70.6, 108.0, 115.6, 116.0, 128.6, 129.7, 130.1, 130.2, 130.4, 134.9, 162.4, 162.9, 171.9, 178.4.

**5-[2-Butoxycarbonyl-3-(4-fluoro-benzylamino)-1-hydroxy-propyl]-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (6b)**

Yield 73%, colorless oil

$\nu_{\max}$  (Neat) 3323 (OH and NH), 1729 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  518.87 ( $M^+$ +1), 541.00 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.85-0.97 (m, 6H, 2 x  $\text{CH}_3$ ), 1.25-1.41 (m, 4H, 2 x  $\text{CH}_2$ ), 1.58-1.69 (m, 4H, 2 x  $\text{CH}_2$ ), 2.70-2.84 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.13-3.15 (m, 2H, 2 x CH), 3.30-3.4 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.64-3.70 (m, 8H, 2 x  $\text{OCH}_3$  and 2 x 1CH of  $\text{CH}_2$ ), 3.78-3.84 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 4.08-4.18 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.72 (d, 1H,  $J$ = 3.8 Hz, CHOH), 5.99 (d, 1H,  $J$ = 3.8 Hz, CHOH), 6.98-7.07 (m, 4H, 2 x 2ArH), 7.31-7.47 (m, 12H, 2 x 6ArH).

**5-[2-Butoxycarbonyl-3-(4-fluoro-benzylamino)-1-hydroxy-propyl]-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (6c)**

Yield 73%; pale yellow oil

$\nu_{\max}$  (Neat) 3320 (OH and NH), 1730 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  552.87 ( $M^+$ +1), 575.00 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.81-0.90 (m, 6H, 2 x  $\text{CH}_3$ ), 1.18-1.37 (m, 4H, 2 x  $\text{CH}_2$ ), 1.54-1.61 (m, 4H, 2 x  $\text{CH}_2$ ), 2.63-2.77 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.00-3.10 (m, 2H, 2 x CH), 3.25-3.35 (m, 24H, 2 x 1H of  $\text{CH}_2$ ), 3.59-3.64 (m, 8H, 2 x  $\text{OCH}_3$  and 2 x 1H of  $\text{CH}_2$ ), 3.71-3.82 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.97-4.14 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.62 (d, 1H,  $J$ = 4.0 Hz, CHOH), 5.92 (d, 1H,  $J$ = 4.1 Hz, CHOH), 6.91-6.99 (m, 4H, 2 x 2ArH), 7.19-7.30 (m, 8H, 2 x 4ArH), 7.44 (m, 2H, 2 x ArH).

**5-[2-Butoxycarbonyl-3-[(furan-2-ylmethyl)-amino]-1-hydroxy-propyl]-3-phenyl-isoxazole-4-carboxylic acid methyl ester(7a)**

Yield 81%, pale yellow oil

IR (Neat) 3323, 1729  $\text{cm}^{-1}$ ; Mass (ES+)  $m/z$  457.00 ( $M^+$ +1), 479.00 ( $M^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 0.86-0.93 (m, 6H, 2 x  $\text{CH}_3$ ), 1.25-1.37 (m, 4H, 2 x  $\text{CH}_2$ ), 1.54-1.61 (m, 4H, 2 x  $\text{CH}_2$ ), 2.99-3.04 (m, 2H, CH, 2 x 1H of  $\text{CH}_2$ ), 3.25-3.27 (m, 2H, 2 x CH), 3.33-3.39 (m, 2H, CH, 2 x 1H of  $\text{CH}_2$ ), 3.77 (s, 6H, 2 x  $\text{OCH}_3$ ), 3.90-4.05 (m, 4H, 2 x  $\text{CH}_2$ ), 4.13 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.75 (brs, 1H, CHOH), 5.91 (d, 1H,  $J$ = 3.0 Hz, CHOH), 6.32-6.33 (m, 4H, 2 x 2H of Furan), 7.40-7.47 (m, 8H, 2 x 4ArH), 7.56-7.62 (m, 4H, 2 x ArH and 2 x 1H of Furan), 8.31 (bs, 2H, 2 x NH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ = 14.1, 19.4, 30.8, 45.9, 47.2, 47.5, 52.5, 65.9, 69.3, 108.6, 109.2, 110.8, 128.3, 128.6, 129.7, 130.4, 143.1, 151.1, 162.5, 171.5, 177.8.

**5-(2-Butoxycarbonyl-3-[(furan-2-ylmethyl)-amino]-1-hydroxy-propyl)-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (7b)**

Yield 79%, brown oil

$\nu_{\text{max}}$  (Neat) 3326 (OH and NH), 1729 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  490.93 ( $\text{M}^+$ +1), 513.00 ( $\text{M}^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.85-0.97 (m, 6H, 2 x  $\text{CH}_3$ ), 1.28-1.41 (m, 4H, 2 x  $\text{CH}_2$ ), 1.55-1.68 (m, 4H, 2 x  $\text{CH}_2$ ), 2.70-2.81 (m, 2H, CH, 2 x 1H of  $\text{CH}_2$ ), 3.13-3.15 (m, 2H, 2 x CH), 3.31-3.37 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.65-3.70 (m, 8H, 2 x  $\text{OCH}_3$  and 2 x 1CH of  $\text{CH}_2$ ), 3.84-3.90 (m, 2H, 2 x 1CH of  $\text{CH}_2$ ), 4.05-4.21 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.72 (d, 1H,  $J$ = 4.4 Hz, CHOH), 5.97 (d, 1H,  $J$ = 4.8 Hz, CHOH), 6.23 (m, 2H, 2 x 1CH of Furan), 6.31 (m, 2H, 2 x 1H of Furan), 7.38-7.46 (m, 10H, 2 x 4ArH and 2 x 1H of Furan).

**5-(2-Butoxycarbonyl-3-[(furan-2-ylmethyl)-amino]-1-hydroxy-propyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (7c)**

Yield 72%, light brown oil

$\nu_{\text{max}}$  (Neat) 3324 (OH and NH), 1729 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  525.00 ( $\text{M}^+$ +1), 546.80 ( $\text{M}^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.78-0.90 (m, 6H, 2 x  $\text{CH}_3$ ), 1.14-1.35 (m, 4H, 2 x  $\text{CH}_2$ ), 1.53-1.57 (m, 4H, 2 x  $\text{CH}_2$ ), 2.60-2.70 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.01-3.10 (m, 2H, 2 x CH), 3.15-3.30 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.57-3.64 (m, 8H, 2 x  $\text{OCH}_3$  and 2 x 1CH of  $\text{CH}_2$ ), 3.67-3.79 (m, 2H, 2 x 1CH of  $\text{CH}_2$ ), 4.00-4.10 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.62 (d, 1H,  $J$ = 4.0 Hz, CHOH), 5.88 (d, 1H,  $J$ = 5.0 Hz, CHOH), 6.11-6.14 (m, 2H, 2 x 1H of Furan), 6.22-6.23 (m, 2H, 2 x 1H of Furan), 7.19-7.29 (m, 6H, 2 x 3ArH), 7.40-7.43 (m, 2H, 2 x 1H of Furan).

**5-(2-Butoxycarbonyl-3-cyclopropylamino-1-hydroxy-propyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (8a)**

Yield 77%, pale yellow oil

$\nu_{\text{max}}$  (Neat) 3319 (OH and NH), 1730 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  417.13 ( $\text{M}^+$ +1), 438.73 ( $\text{M}^+$ +Na)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.48-0.52 (m, 8H, 2 x 2 $\text{CH}_2$  of cyclopropane), 0.88-0.98 (m, 6H, 2 x  $\text{CH}_3$ ), 1.31-1.46 (m, 4H, 2 x  $\text{CH}_2$ ), 1.59-1.69 (m, 4H, 2 x  $\text{CH}_2$ ), 2.13-2.15 (m, 2H, 2 x CH of cyclopropane), 2.85-2.99 (m, 2H, 2 x CH of  $\text{CH}_2$ ), 3.10-3.13 (m, 2H, 2 x CH), 3.45-3.57 (m, 2H, 2 x CH of  $\text{CH}_2$ ), 3.78 (s, 6H, 2 x  $\text{OCH}_3$ ), 5.65 (brs,

1H, CHOH), 5.93 (d, 1H,  $J$ = 4.0 Hz, CHOH), 7.47-7.65 (m, 10H, 2 x 5ArH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ = 6.3, 6.6, 14.0, 19.4, 30.9, 31.1, 47.7, 48.5, 52.3, 65.6, 70.6, 108.1, 128.5, 129.7, 130.3, 162.4, 162.8, 171.9, 178.4.

**5-(2-Butoxycarbonyl-3-cyclopropylamino-1-hydroxy-propyl)-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (8b)**

Yield 68%, pale yellow oil

$\nu_{\text{max}}$  (Neat) 3318 (OH and NH), 1729 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  452.27 ( $\text{M}^+$ +1), 474.87 ( $\text{M}^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.58-0.73 (m, 8H, 2 x 2 $\text{CH}_2$  of cyclopropane), 0.89-0.97 (m, 6H, 2 x  $\text{CH}_3$ ), 1.29-1.39 (m, 4H, 2 x  $\text{CH}_2$ ), 1.56-1.63 (m, 4H, 2 x  $\text{CH}_2$ ), 2.15-2.28 (m, 1H, CH of cyclopropane), 2.32-2.41 (m, 1H, CH of cyclopropane), 3.0-3.15 (m, 2H, 2 x CH of  $\text{CH}_2$ ), 3.20-3.30 (m, 2H, 2 x CH), 3.37-3.50 (m, 2H, 2 x CH of  $\text{CH}_2$ ), 3.69, 3.70 (2s, 6H, 2 x  $\text{OCH}_3$ ), 4.10-4.19 (m, 4H, 2 x  $\text{OCH}_2$ ), 5.79 (d, 1H,  $J$ = 3.58 Hz, CHOH), 5.91 (d, 1H,  $J$ = 5.18 Hz, CHOH), 7.35-7.47 (m, 8H, 2 x 4ArH).

**5-(2-Butoxycarbonyl-3-cyclopropylamino-1-hydroxy-propyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (8c)**

Yield 65%; pale yellow oil

$\nu_{\text{max}}$  (Neat) 3407 (OH and NH), 1729 (C=O)  $\text{cm}^{-1}$ ; mass (ES+)  $m/z$  484.67 ( $\text{M}^+$ +1), 506.93 ( $\text{M}^+$ +Na)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.49-0.52 (m, 8H, 2 x 2 $\text{CH}_2$  of cyclopropane), 0.88-0.98 (m, 6H, 2 x  $\text{CH}_3$ ), 1.25-1.42 (m, 4H, 2 x  $\text{CH}_2$ ), 1.62-1.69 (m, 4H, 2 x  $\text{CH}_2$ ), 2.14-2.18 (m, 2H, 2 x CH of cyclopropane), 2.90-2.98 (m, 2H, 2 x 1H of  $\text{CH}_2$ ), 3.13-3.15 (m, 2H, 2 x CH), 3.39-3.47 (m, 2H, 2 x CH of  $\text{CH}_2$ ), 3.69, 3.73 (2s, 6H, 2 x  $\text{OCH}_3$ ), 4.04-4.22 (m, 4H,  $\text{OCH}_2$ ), 5.71 (d, 1H,  $J$ = 4.2 Hz, CHOH), 5.95 (d, 1H,  $J$ = 4.2 Hz, CHOH), 7.37 (s, 4H, 2 x 2ArH), 7.51 (m, 2H, 2 x ArH).

**General method for the preparation of pyrroles (9-13a-c)**- To the stirred solution of compound from **4-8a-c** (2.0 mmol) in THF (10mL) was added DBU (0.32 mL, 2.0 mmol) at rt and the reaction was allowed to reflux for 5h. On completion the reaction mixture was extracted with EtOAc (3X20mL) and water (25mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to yield an oily residue which was purified through chromatography over silica gel. Elution with hexane: EtOAc (8:2, v/v) afforded the pure product.

**1-Benzyl-5-(2-hydroxyimino-2-phenyl-ethyl)-1H-pyrrole-3-carboxylic acid methyl ester (9a)**

$\nu_{\text{max}}$  (KBr) 3361 (OH), 1683 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+)  $m/z$  349 ( $\text{M}^+$ +1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 3.73 (s, 3H,  $\text{OCH}_3$ ), 3.94 (s, 2H,  $\text{CH}_2$ ), 5.12 (s, 2H,  $\text{CH}_2$ ), 6.33 (s, 1H, =CH), 7.02-7.05 (m, 2H, ArH), 7.28-7.30 (m, 7H, ArH), 7.40-7.44 (m, 2H, ArH and =CH), 8.14 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3+\text{DMSO-d}_6$ , 75 MHz)  $\delta$ = 21.9, 49.8, 49.9, 108.2, 113.5, 125.1, 125.8, 126.8, 127.3, 127.7, 127.8, 128.1, 134.7, 136.0, 152.3, 168.0; HRMS for  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3$  Calcd, 348.1474, Found, 348.1468.

**1-Benzyl-5-[2-(2-chloro-phenyl)-2-hydroxyimino-ethyl]-1H-pyrrole-3-carboxylic acid methyl ester (9b)**

$\nu_{\text{max}}$  (KBr) 3368 (OH), 1677 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+) 383 ( $\text{M}^++1$ )

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 3.74 (s, 3H,  $\text{OCH}_3$ ), 4.03 (s, 2H,  $\text{CH}_2$ ), 4.96 (s, 2H,  $\text{CH}_2$ ), 6.32 (s, 1H, =CH), 6.97-7.05 (m, 2H, ArH), 7.19-7.41 (m, 7H, ArH and =CH), 9.38 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ = 25.4, 50.9, 51.0, 110.4, 114.8, 126.7, 127.0, 127.8, 128.8, 129.8, 130.2, 130.9, 131.1, 132.6, 134.4, 136.6, 156.2, 165.3

HRMS for  $\text{C}_{21}\text{H}_{19}\text{ClN}_2\text{O}_3$  Calcd, 382.1084, Found, 382.1119.

**1-Benzyl-5-[2-(2,4-dichloro-phenyl)-2-hydroxyimino-ethyl]-1H-pyrrole-3-carboxylic acid methyl ester (9c)**

$\nu_{\text{max}}$  (KBr) 3285 (OH), 1665 (C=O)  $\text{cm}^{-1}$ , mass (FAB+) 417 ( $\text{M}^++1$ )

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 3.76 (s, 3H,  $\text{OCH}_3$ ), 3.99 (s, 2H,  $\text{CH}_2$ ), 4.98 (s, 2H,  $\text{CH}_2$ ), 6.33 (s, 1H, =CH), 6.94 (m, 3H, ArH), 7.09-7.12 (m, 1H, ArH), 7.22-7.31 (m, 5H, ArH and =CH), 9.43 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ = 25.3, 50.9, 51.1, 110.5, 114.9, 126.6, 127.1, 127.2, 127.9, 128.9, 129.7, 131.7, 132.9, 133.4, 135.5, 136.5, 155.4, 165.4.

HRMS for  $\text{C}_{21}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_3$  Calcd, 416.0695, Found, 416.0671.

**1-Benzyl-5-(2-hydroxyimino-2-phenyl-ethyl)-1H-pyrrole-3-carboxylic acid butyl ester (10a)**

$\nu_{\text{max}}$  (KBr) 3244 (OH), 1665 (C=O)  $\text{cm}^{-1}$ , mass (FAB+)  $m/z$  391 ( $\text{M}^++1$ )

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 0.92 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.35-1.42 (m, 2H,  $\text{CH}_2$ ), 1.64 (brs, 2H,  $\text{CH}_2$ ), 3.94 (s, 2H,  $\text{CH}_2$ ,  $\text{CH}_2$ ), 4.15 (t, 2H,  $J$ = 6.5 Hz,  $\text{OCH}_2$ ), 5.12 (s, 2H,  $\text{CH}_2$ ), 6.33 (s, 1H, =CH), 7.01-7.05 (m, 2H, ArH), 7.22-7.43 (m, 9H, ArH, and =CH), 8.38 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  14.2, 19.6, 23.9, 31.3, 51.5, 63.9, 110.2, 115.8, 126.9, 126.9, 127.4, 128.3, 128.6, 128.9, 129.3, 129.8, 135.3, 137.2, 156.0, 165.4

HRMS for  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3$  Calcd 390.1944, Found, 390.1943

**1-Benzyl-5-[2-(2-chloro-phenyl)-2-hydroxyimino-ethyl]-1H-pyrrole-3-carboxylic acid butyl ester (10b)**

$\nu_{\text{max}}$  (KBr) 3371 (OH), 1691 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+) 425  $m/z$  ( $\text{M}^++1$ ), 426 ( $\text{M}^++2$ )

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 0.93 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.31-1.48 (m, 2H,  $\text{CH}_2$ ), 1.55-1.69 (m, 2H,  $\text{CH}_2$ ), 4.01 (s, 2H,  $\text{CH}_2$ ), 4.15 (t, 2H,  $J$ = 6.3 Hz,  $\text{OCH}_2$ ), 4.96 (s, 2H,  $\text{CH}_2$ ), 6.32 (s, 1H, =CH), 6.96-7.04 (m, 3H,

ArH), 7.12-7.44 (m, 7H, ArH and =CH), 9.55 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ = 14.2, 19.7, 25.8, 31.3, 51.3, 64.0, 110.9, 115.7, 127.1, 127.8, 128.2, 129.3, 130.2, 130.6, 131.3, 133.0, 134.9, 137.1, 156.7, 165.4

HRMS for  $\text{C}_{24}\text{H}_{25}\text{ClN}_2\text{O}_3$  Calcd, 424.1554, Found, 424.1551.

**1-Benzyl-5-[2-(2,4-dichloro-phenyl)-2-hydroxyimino-ethyl]-1H-pyrrole-3-carboxylic acid butyl ester (10c)**

$\nu_{\text{max}}$  (KBr) 3316 (OH), 1683 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+) 458 ( $\text{M}^++1$ )

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 0.94 (t, 3H,  $J$ = 7.5 Hz,  $\text{CH}_3$ ), 1.34-1.49 (m, 2H,  $\text{CH}_2$ ), 1.56-1.70 (m, 2H,  $\text{CH}_2$ ), 3.99 (s, 2H,  $\text{CH}_2$ ), 4.17 (t, 2H,  $J$ = 6.6 Hz,  $\text{OCH}_2$ ), 4.99 (s, 2H,  $\text{NCH}_2$ ), 6.32 (s, 1H, =CH), 6.92-6.97 (m, 2H, ArH), 7.12-7.36 (m, 7H, ArH and =CH), 8.31 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ = 14.2; 19.7, 25.7, 31.3, 51.3, 64.1, 110.9, 115.8, 126.9, 127.5, 127.9, 128.2, 129.3, 130.1, 132.2, 133.4, 133.9, 135.9, 137.0, 155.9, 165.4

HRMS for  $\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_3$  Calcd, 458.1164, Found, 458.1140.

**1-(4-Fluoro-benzyl)-5-(2-hydroxyimino-2-phenyl-ethyl)-1H-pyrrole-3-carboxylic acid butyl ester (11a)**

$\nu_{\text{max}}$  (KBr) 3291 (OH), 1674 (C=O)  $\text{cm}^{-1}$ , mass (FAB+)  $m/z$  409 ( $\text{M}^++1$ )

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.92 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.25-1.48 (m, 2H,  $\text{CH}_2$ ), 1.60-1.71 (m, 2H,  $\text{CH}_2$ ), 3.93 (s, 2H,  $\text{CH}_2$ ), 4.15 (t, 2H,  $J$ = 6.6 Hz,  $\text{OCH}_2$ ), 5.08 (s, 2H,  $\text{CH}_2$ ), 6.34 (s, 1H, =CH), 6.93-7.01 (m, 3H, 2ArH and =CH), 7.28-7.45 (m, 7H, ArH), 8.10 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta$ = 14.2, 19.6, 23.9, 31.3, 50.8, 64.1, 110.4, 116.0, 116.4, 126.8, 127.3, 128.6, 128.7, 128.9, 129.9, 132.9, 135.3, 155.8, 160.3, 165.2, 165.4

HRMS for  $\text{C}_{24}\text{H}_{25}\text{FN}_2\text{O}_3$  Calcd, 408.1849, Found, 408.1866.

**5-[2-(2-Chloro-phenyl)-2-hydroxyimino-ethyl]-1-(4-fluoro-benzyl)-1H-pyrrole-3-carboxylic acid butyl ester (11b)**

$\nu_{\text{max}}$  (KBr) 3342 (OH), 1682 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+)  $m/z$  443 ( $\text{M}^++1$ )

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 0.93 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.33-1.48 (m, 2H,  $\text{CH}_2$ ), 1.57-1.69 (m, 2H,  $\text{CH}_2$ ), 3.99 (s, 2H,  $\text{CH}_2$ ), 4.15 (t, 2H,  $J$ = 6.6 Hz,  $\text{OCH}_2$ ), 4.93 (s, 2H,  $\text{CH}_2$ ), 6.31 (s, 1H, =CH), 6.91-6.94 (m, 4H, ArH), 7.02-7.04 (m, 1H, ArH), 7.13-7.23 (m, 2H, ArH and =CH), 7.28-7.36 (m, 2H, ArH), 9.50 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ = 13.8, 19.0, 25.4, 30.8, 50.2, 63.7, 110.6, 115.6, 115.9, 126.7, 127.3, 128.3, 128.4, 129.8, 130.2, 130.9, 132.4, 132.6, 134.3, 156.1, 160.6, 163.9, 165.0

HRMS for  $\text{C}_{24}\text{H}_{25}\text{ClFN}_2\text{O}_3$  Calcd, 442.1460, Found, 442.1467.

**5-[2-(2,4-Dichloro-phenyl)-2-hydroxyimino-ethyl]-1-(4-fluoro-benzyl)-1H-pyrrole-3-carboxylic acid butyl ester (11c)**

$\nu_{\max}$  (KBr) 3281 (OH), 1680 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+)  $m/z$  477 ( $M^+$ +1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz.)  $\delta$ = 0.94 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.37-1.44 (m, 2H,  $\text{CH}_2$ ), 1.61-1.71 (m, 2H,  $\text{CH}_2$ ), 3.98 (s, 2H,  $\text{CH}_2$ ), 4.17 (t, 2H,  $J$ = 6.0 Hz,  $\text{OCH}_2$ ), 4.97 (s, 2H,  $\text{CH}_2$ ), 6.31 (s, 1H, =CH), 6.31-7.01 (m, 4H, ArH), 7.14-7.19 (m, 3H, ArH and =CH), 7.36 (d, 1H,  $J$ = 3.0 Hz, ArH), 7.75 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz.)  $\delta$ = 13.8, 19.2, 25.2, 30.8, 50.2, 63.7, 110.6, 115.5, 115.6, 115.9, 126.8, 126.9, 127.1, 128.1, 128.3, 129.7, 132.3, 132.8, 133.4, 135.5, 155.4, 160.6, 163.9, 164.9

HRMS for  $\text{C}_{24}\text{H}_{23}\text{Cl}_2\text{FN}_2\text{O}_3$  Calcd, 476.1070, Found, 476.1037.

**1-Furan-2-ylmethyl-5-(2-hydroxyimino-2-phenyl-ethyl)-1H-pyrrole-3-carboxylic acid butyl ester (12a)**

$\nu_{\max}$  (KBr) 3309 (OH), 1672 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+)  $m/z$  381 ( $M^+$ +1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.91 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.26-1.47 (m, 2H,  $\text{CH}_2$ ), 1.56-1.69 (m, 2H,  $\text{CH}_2$ ), 4.10-4.17 (t merged with s, 4H,  $\text{OCH}_2$  and  $\text{CH}_2$ ), 5.05 (s, 2H,  $\text{CH}_2$ ), 6.21-6.22 (d, 1H,  $J$ = 3.2 Hz, 1H of Furan), 6.28-6.33 (m, 3H, 2H of Furan and =CH), 7.31-7.38 (m, 5H, ArH), 7.52-7.56 (m, 2H, ArH and =CH), 8.44 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ = 13.8, 19.2, 23.5, 30.9, 44.0, 63.6, 108.5, 109.6, 110.5, 115.4, 126.5, 127.9, 128.5, 129.4, 134.9, 142.9, 149.6, 155.5, 165.0; HRMS for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$  Calcd, 380.1736, Found, 380.1741.

**5-[2-(2-Chloro-phenyl)-2-hydroxyimino-ethyl]-1-furan-2-ylmethyl-1H-pyrrole-3-carboxylic acid butyl ester (12b)**

$\nu_{\max}$  (neat) 3348 (OH)  $\text{cm}^{-1}$ , 1682 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+)  $m/z$  415 ( $M^+$ +1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz.)  $\delta$  0.93 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.35-1.47 (m, 2H,  $\text{CH}_2$ ), 1.59-1.68 (m, 2H,  $\text{CH}_2$ ), 4.12-4.16 (t merged with s, 4H,  $\text{OCH}_2$  and  $\text{CH}_2$ ), 4.94 (s, 2H,  $\text{CH}_2$ ), 6.20-6.23 (m, 2H, 1H of Furan and =CH), 6.29-6.31 (m, 1H, 1H of Furan), 7.05 (d of d, 1H,  $J$ = 7.5 Hz,  $J$ = 1.2 Hz, ArH), 7.14-7.19 (m, 2H, ArH), 7.24-7.29 (m, 1H, FuranH), 7.34-7.37 (m, 2H, ArH and =CH), 8.48 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ = 13.7, 19.2, 25.3, 30.8, 43.7, 63.5, 108.6, 110.2, 110.4, 115.2, 126.4, 126.7, 127.1, 129.7, 130.1, 130.8, 132.5, 134.3, 142.9, 149.4, 156.1, 165.0; HRMS for  $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_4$  Calcd., 414.1346, Found, 414.1329.

**5-[2-(2,4-Dichloro-phenyl)-2-hydroxyimino-ethyl]-1-furan-2-ylmethyl-1H-pyrrole-3-carboxylic acid butyl ester (12c)**

$\nu_{\max}$  (KBr) 3278 (OH), 1680 (C=O)  $\text{cm}^{-1}$ , mass (FAB+) 449 ( $M^+$ +1)

$^1\text{H}$ NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$ = 0.94 (t, 3H,  $J$ = 7.2 Hz,  $\text{CH}_3$ ), 1.33-1.45 (m, 2H,  $\text{CH}_2$ ), 1.59-1.69 (m, 2H,  $\text{CH}_2$ ), 4.12-4.17 (s merged with t, 4H,  $\text{OCH}_2$  and  $\text{CH}_2$ ), 4.96 (s, 2H,  $\text{CH}_2$ ), 6.21-6.22 (d merged with s, 2H, 1H of Furan and =CH), 6.31-6.32 (m, 1H, FuranH), 6.95 (d, 1H,  $J$ = 8.1Hz, ArH), 7.15 (d of d, 1H,  $J$ = 9.0 Hz,  $J$ = 2.1 Hz, ArH), 7.20 (d, 1H,  $J$ = 1.8 Hz, FuranH), 7.35 (d, 1H,  $J$ = 1.2 Hz, =CH), 7.38 (d, 1H,  $J$ = 2.1 Hz, ArH), 7.95 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz.)  $\delta$ = 13.8, 15.8, 19.2, 25.2, 30.8, 43.8, 63.6, 108.6, 110.3, 110.5, 115.5, 126.6, 127.1, 129.7, 131.6, 132.8, 133.4, 135.5, 143.0, 149.4, 155.6, 164.9

HRMS for  $\text{C}_{22}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_4$  Calcd, 448.0957, Found, 448.0941.

**1-Cyclopropyl-5-(2-hydroxyimino-2-phenyl-ethyl)-1H-pyrrole-3-carboxylic acid butyl ester (13a)**

$\nu_{\max}$  (KBr) 3337 (OH), 1680 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+)  $m/z$  341 ( $M^+$ +1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz.)  $\delta$ = 0.86-1.03 (m, 7H, 2 x  $\text{CH}_2$  of cyclopropane and  $\text{CH}_3$ ), 1.26-1.41 (m, 2H,  $\text{CH}_2$ ), 1.58-1.67 (m, 2H,  $\text{CH}_2$ ), 3.13-3.20 (m, 1H, CH of cyclopropyl), 4.14 (t, 2H,  $J$ = 6.6 Hz,  $\text{OCH}_2$ ), 4.19 (s, 2H,  $\text{CH}_2$ ), 6.25 (s, 1H, =CH), 7.21 (d, 1H,  $J$ = 1.5 Hz, =CH), 7.32-7.34 (m, 3H, ArH), 7.57-7.61 (m, 2H, ArH), 9.64 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ = 6.7, 13.7, 19.1, 24.0, 28.5, 30.8, 63.5, 108.8, 114.3, 126.1, 126.4, 128.4, 129.2, 130.0, 135.3, 155.5, 165.0

HRMS for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$  Calcd, 340.1787, Found, 340.1807.

**5-[2-(2-Chloro-phenyl)-2-hydroxyimino-ethyl]-1-cyclopropyl-1H-pyrrole-3-carboxylic acid butyl ester (13b)**

$\nu_{\max}$  (KBr) 3272 (OH), 1669 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+)  $m/z$  375 ( $M^+$ +1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ = 0.85-0.97 (m, 7H, 2 x  $\text{CH}_2$  of cyclopropane and  $\text{CH}_3$ ), 1.31-1.49 (m, 2H,  $\text{CH}_2$ ), 1.64-1.69 (m, 2H,  $\text{CH}_2$ ), 2.94-3.01 (m, 1H, CH of cyclopropyl), 4.15 (t, 2H,  $J$ = 6.46 Hz,  $\text{OCH}_2$ ), 4.26 (s, 2H,  $\text{CH}_2$ ), 6.29 (s, 1H, =CH), 7.12-7.21 (m, 3H, ArH), 7.35-7.39 (m, 2H, ArH and =CH), 8.24 (bs, 1H, OH)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$ = 6.7, 13.8, 19.2, 25.5, 28.4, 30.9, 63.5, 109.6, 114.4, 125.9, 126.8, 129.1, 129.4, 129.8, 130.1, 131.0, 132.7, 134.9, 156.4, 165.1

HRMS for  $\text{C}_{20}\text{H}_{23}\text{ClN}_2\text{O}_4$  Calcd, 374.1397, Found, 374.1417.

**1-Cyclopropyl-5-[2-(2,4-dichloro-phenyl)-2-hydroxyimino-ethyl]-1H-pyrrole-3-carboxylic acid butyl ester (13c)**

$\nu_{\max}$  (KBr) 3245 (OH), 1667 (C=O)  $\text{cm}^{-1}$ ; mass (FAB+) 409 ( $M^+$ +1)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz.)  $\delta$ = 0.85-0.99 (m, 7H, 2 $\text{CH}_2$  of cyclopropyl and  $\text{CH}_3$ ), 1.25-1.49 (m, 2H,  $\text{CH}_2$ ), 1.58-1.72 (m, 2H,  $\text{CH}_2$ ), 2.96-3.03 (m, 1H, CH of cyclopropyl)

pyl), 4.16 (t, 2H,  $J = 6.5$  Hz, OCH<sub>2</sub>), 4.24 (s, 2H, CH<sub>2</sub>), 6.26 (s, 1H, =CH), 7.09-7.22 (m, 3H, ArH and =CH), 7.39-7.40 (m, 1H, ArH)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta = 6.7, 13.8, 19.2, 25.5, 28.4, 30.9, 63.6, 109.6, 114.4, 126.1, 127.2, 128.9, 129.7, 131.8, 133.4, 155.4, 165.1$

HRMS for C<sub>20</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub> Calcd, 408.1008, Found, 408.1007.

**3-(2-Chloro-phenyl)-5-(1-methoxy-2-methoxycarbonyl-allyl)-isoxazole-4-carboxylic acid methyl ester (14b)**

Yield 78%, colorless oil

$\nu_{\max}$  (Neat) 1713 (CO<sub>2</sub>Me) cm<sup>-1</sup>; mass (ES+) 388.07 (M<sup>+</sup>+Na)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta = 3.51$  (s, 3H, CH<sub>3</sub>), 3.73 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.74 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 5.98 (s, 1H, =CHH), 6.26 (s, 1H, CHOCH<sub>3</sub>), 6.61 (s, 1H, =CHH), 7.34-7.49 (m, 4H, ArH)

Anal. Calcd. for C<sub>17</sub>H<sub>16</sub>ClNO<sub>6</sub> C, 55.82; H, 4.41; N, 3.83. Found: C, 56.02; H, 4.44; N, 3.85.

**5-(3-Benzylamino-1-methoxy-2-methoxycarbonyl-propyl)-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (15b)**

Yield 82%, colorless oil

$\nu_{\max}$  (Neat) 3347 (NH), 1734 (CO<sub>2</sub>Me) cm<sup>-1</sup>; mass (ES+) 472.87 (M<sup>+</sup>), 495.07 (M<sup>+</sup>+Na)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) diastereoisomeric  $\delta = 3.02$ -3.08 (m, 2H, 2 x 1H of CH<sub>2</sub>), 3.15-3.21 (m, 2H, 2 x 1H of CH<sub>2</sub>), 3.33-3.38 (m, 8H, 2 x 3H of OCH<sub>3</sub> and 2 x 1H of CH), 3.63 (s, 6H, 2 x 3H of CO<sub>2</sub>CH<sub>3</sub>), 3.68-3.72 (s merged with d, 10H, 2 x 3H of CO<sub>2</sub>CH<sub>3</sub> and 2 x 1H of CH<sub>2</sub>), 3.77-3.80 (m, 2H, 2 x 1H of CH<sub>2</sub>), 5.44 (d, 2H,  $J = 7.5$  Hz, 2 x 1H of CHOCH<sub>3</sub>), 7.22-7.31 (m, 18H, 2 x 9H, ArH)

Anal. Calcd. for C<sub>24</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>6</sub> C, 60.95; H, 5.33; N, 5.92. Found: C, 61.11; H, 5.64; N, 3.79

**Acknowledgment**

Three of the authors (AKR, RP and GPY) gratefully acknowledge the financial support from CSIR, N. Delhi in the form of fellowships. We also acknowledge the assistance of Mr. A. D. Roy and Dr. R. Roy in elucidation of structure through NMR. This work was supported by the financial grant under DST Project no. SR/SI/OC-04/2003.

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- (3) The crystal data of compound 13b: C<sub>20</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>,  $M = 409.30$ , monoclinic,  $P2_1/c$ ,  $a = 10.891(1)$  Å,  $b = 17.066(1)$  Å,  $c = 11.343(1)$  Å,  $\beta = 95.31(1)^\circ$ ,  $V = 2099.2(3)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.2951(2)$  g cm<sup>-3</sup>,  $\mu$  (Mo-K $\alpha$ ) = 0.331 mm<sup>-1</sup>,  $F(000) = 857.51$ , rectangular colourless crystal, size = 0.2 x 0.2 x 0.275 mm, 4628 reflections measured ( $R_{int} = 0.05$ ), 3688 unique,  $wR2 = 0.111$  for all data, conventional  $R = 0.062$  [ $(\Delta/\sigma)_{\max} = 000$ ] on F-values of 1274 reflections with

$I > 2\sigma(I)$ ,  $S = 0.907$  for all data and 247 parameters. Unit cell determination and intensity data collection ( $2\theta = 50^\circ$ ) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on  $F^2$ . Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997]. CCDC (deposit No: 284175) contains the supplementary crystallographic data. These data can be obtained free of charge from [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U. K; Fax: (internet) + 44-1223/336-033; E-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk).

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