

# Synthesis, Spectroscopic and Crystal Structure Studies on Ethyl 5,7-Dimethyl Coumarin-4-Acetate

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## ABSTRACT

Ethyl ester of 5,7-dimethyl coumarin-4-acetic acid has been synthesized from 3,5-Xylenol in a two step sequence of reaction involving Pechmann cyclisation and acid catalyzed esterification. The title compound **2** crystallizes in Monoclinic form, space group P 1 21/c 1, with  $a = 8.6248(4) \text{ \AA}$ ,  $b = 18.9103(8) \text{ \AA}$ ,  $c = 8.4204(4) \text{ \AA}$ ,  $\beta = 101.241(2)$ ,  $V = 1347.00(11) \text{ \AA}^3$ ,  $D_{\text{cal}} = 1.283 \text{ Mg/cm}^3$ ,  $Z = 4$ . The molecule is stabilized by intermolecular C-H ... O bonds.

**Keywords:** Coumarin-4-Acetic acid Ethyl Ester; X-Ray Diffraction

## 1. Introduction

Coumarins are a group of naturally occurring lactones with wide ranging biological activities [1]. Varieties of 4-substituted coumarins possessing hydroxyl [2], aminoalkyl [3] arylaminomethyl [4] sulphonamido [5] and aryloxymethyl [6] groups have exhibited anti coagulant, anti microbial and anti inflammatory activities. Coumarin 4-acetic acids have been found to exhibit good inflammation inhibiting activity in animal models [7]. They have been employed as key intermediates in the design and synthesis of polycyclic coumarins related to Protoberberine alkaloids [8]. The reactivity of C<sub>4</sub>-methylene group has been employed for the construction of many 4-substituted bi-heterocyclic coumarins. Solid state conformational studies on coumarin 4-acetic acid [9], ester [10,11] and dithionate [12] have been reported recently. It needs to be emphasized that the crystallographic study on esters is of considerable biological interest [13] since it determines the preferred orientation of the rotamer (Figure 1), in turn the direction of the electron pair on

alkyl oxygen. In view of the biological significance of 4-substituted coumarins and interest associated with the geometry of esters the title compound has been synthesized, characterized and studied for its solid state conformation by X-ray studies.

## 2. Experimental

### 2.1. Synthesis of the Title Compound

Compound **1** has been prepared by the reaction of 3,5-xylenol and citric acid by using sulphuric acid as condensing agent according to general procedure reported for coumarin 4-acetic acids [14]. Compound **1** was further converted into its ester (compound **2**) by refluxing in dry ethanol with catalytic quantity of sulphuric acid by Fischer esterification. The resulting solution was poured into crushed ice, the precipitate was filtered off, washed with 5% NaHCO<sub>3</sub>, and with water and recrystallized from ethanol. (Figure 2) M.P. 123-125.C, yield 95%. The authenticity of the compound has been established by UV, IR, <sup>1</sup>H, <sup>13</sup>C NMR, and Mass spectra. Crystals suitable for diffraction study were grown by a slow evaporation technique using 1:1 mixture of ethanol and dioxan at room temperature.

### 2.2. Characterization and Physical Measurements

The melting point was determined in open capillaries and is uncorrected. The IR absorption spectrum was obtained

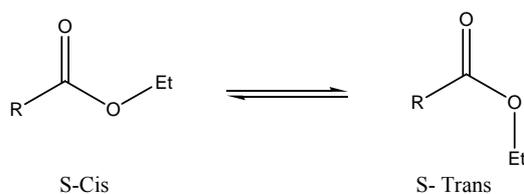


Figure 1. General structure for Rotamers of Esters.

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by KBr pellet using a FT IR spectrometer. UV-vis spectrum was recorded in the range of 200 nm to 800 nm using a Lambda 35 Perkin-Elmer spectrophotometer. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were determined on a Bruker Avance 400 model at 400 and 200 MHz respectively. Solvents were dried by refluxing with the appropriate drying agents and distilled before use.

### 2.3. X-Ray Crystallography

For the crystal structure determination, the single-crystal of the compound  $\text{C}_{15}\text{H}_{16}\text{O}_4$  was used for data collection. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with  $Z = 4$  for the formula unit  $\text{C}_{15}\text{H}_{16}\text{O}_4$ . The final anisotropic full-matrix least-squares refinement on F2 with 176 variables converged at  $R1 = 4.03\%$ , for the observed data and  $wR2 = 12.44\%$  for all data. The goodness-of-fit was 1.008. The largest peak in the final difference electron density synthesis was  $0.148 \text{ e}^-/\text{\AA}$  and the largest hole was  $-0.136 \text{ e}^-/\text{\AA}$  with an RMS deviation of  $0.029 \text{ e}^-/\text{\AA}$ . On the basis of the final model, the calculated density was  $1.283 \text{ g/cm}^3$  and  $F(000)$ ,  $552 \text{ e}^-/\text{\AA}$ . Molecular structure of the compound showing the atomic numbering scheme is shown in **Figure 3**. The crystallographic parameters of the compound were presented in **Table 1**. Selected bond distances and bond angles are listed in **Table 2** and selected Hydrogen-bonding parameters listed in **Table 3**.

### 3. Results and Discussion

Title compound crystallizes in the monoclinic centrosymmetric space group P 1 21/c 1 with  $Z = 4$ . The struc-

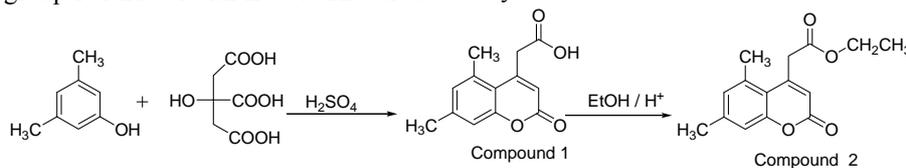
ture of the compound consists of ethyl ester group. Selected bond lengths and bond distances for the title compound are listed in **Table 3**.

#### 3.1 Molecular Skeleton

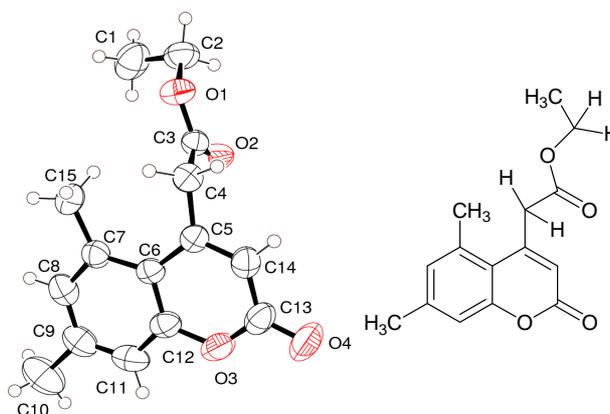
Coumarin ring is planar and carboxy group attached to the  $\text{C}_4\text{-CH}_2$  is out of plane by an angle of  $11.26^\circ$ . The methyl group oriented at an angle of  $90^\circ$  to the mean plane of the bicyclic system. The ester carbonyl is oriented perpendicular to the  $\text{C}_3\text{-C}_4$  double bond. The molecule adopts the S-cis arrangement across the alkyl-oxygen bond as revealed in the ORTEP diagram (**Figure 3**). The exocyclic Oxygen is involved in intermolecular hydrogen bonding ( $\text{O}_4 \cdots \text{H-C}_1$ ) with the  $\text{CH}_3$  group of ester. A weak hydrogen bonding ( $\text{O}_2 \cdots \text{H-C}_4$ ) is also observed between the  $\text{C}_4\text{-CH}_2$  and the carbonyl oxygen of ester. The molecular packing diagram (**Figure 4**) shows hydrogen bonding and the crystalline state is stabilized by vander waals forces of attraction. The S-cis arrangement is also supported by the dihedral angle of  $1.8$  between  $\text{C}_2\text{-O}_1\text{-C}_3\text{-O}_2$  indicating an eclipsed arrangement (**Table 3**).

#### 3.2. Bond Lengths

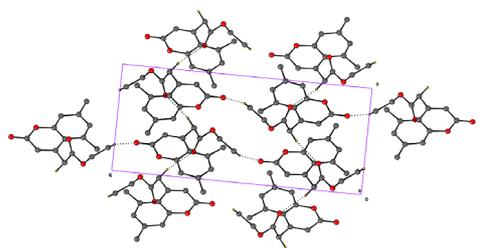
Bond lengths have been discussed in **Table 2**. The aromatic C-C bond lengths are in the range of  $1.30 - 1.40 \text{ \AA}$ . The ester  $\text{C}_{13}\text{-O}_4$  bond shows a bond length of  $1.20 \text{ \AA}$  which is similar to the lactone distance of  $1.19 \text{ \AA}$  between  $\text{O}_2\text{-C}_3$ . The alkyl oxygen  $\text{O}_1\text{-C}_3$  bond is  $1.32 \text{ \AA}$  whereas the corresponding bond of  $\text{O}_3\text{-C}_{13}$  bond is slightly longer by  $1.35 \text{ \AA}$ .



**Figure 2.** Chemical structure and synthetic pathway of the title compound.



**Figure 3.** ORTEP plot of molecule with displacement ellipsoids drawn at 50% probability Covalent structure of compound 2.



**Figure 4.** Packing diagram dotted lines indicate C-H...O hydrogen bonds of the molecule viewed down a-axis.

**Table 1.** Crystallographic data and structure refinement parameters.

Empirical formula	C <sub>15</sub> H <sub>16</sub> O <sub>4</sub>
Formula weight	260.28 g/mol
Crystal colour	Colourless
Temperature	296 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2 <sub>1</sub> /c
Unit cell dimensions	8.6248 (4), 18.9103 (8), 8.4204 (4)
a, b, c (Å) α, β, (°)	90, 101.241 (2), 90
Volume	1347.00 (11) (Å <sup>3</sup> )
Z, Calculated density	4 Mg m <sup>-3</sup>
Absorption coefficient	0.09 mm <sup>-1</sup>
F(000)	552
Crystal size	0.3 × 0.25 × 0.2 mm
Theta range for data collection	2.41 to 26.07°
Limiting indices	-10 ≤ h ≤ 10, -23 ≤ k ≤ 22, 10 ≤ l ≤ 10
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Absorption correction	Multi-scan
No. of measured, independent [I > 2(I)] reflections R <sub>int</sub>	12192, 2675, 2113 and observed 0.021
(sin θ/λ) <sub>max</sub> (Å <sup>-1</sup> ) <sub>max</sub> (Å <sup>-1</sup> )	0.618
Data/restraints/parameters	2675/0/176
Goodness-of-fit on F <sup>2</sup>	1.008
H-atom treatment	H atoms constrained
Δρ <sub>max</sub> , Δρ <sub>min</sub> (e Å <sup>-3</sup> )	0.15, -0.14
Final R indices	R1 = 0.0403, wR2 = 0.1138
R indices(all data)	R1 = 0.0533, wR2 = 0.1244
Large diff. peak and hole	0.148 and -0.136e Å <sup>-3</sup>

### 3.3. Bond Angles

Bond angles have been discussed in **Table 2**. All the aromatic C-C bond angles are in the expected range

**Table 2.** Selected bond lengths and bond angles (Å, °).

O <sub>1</sub> -C <sub>2</sub>	1.458 (2)	C <sub>5</sub> -C <sub>14</sub>	1.346 (2)
O <sub>1</sub> -C <sub>3</sub>	1.3240 (17)	C <sub>6</sub> -C <sub>7</sub>	1.421 (2)
O <sub>2</sub> -C <sub>3</sub>	1.1949 (18)	C <sub>6</sub> -C <sub>12</sub>	1.402 (2)
O <sub>3</sub> -C <sub>12</sub>	1.3777 (19)	C <sub>7</sub> -C <sub>8</sub>	1.384 (2)
O <sub>3</sub> -C <sub>13</sub>	1.359 (2)	C <sub>7</sub> -C <sub>15</sub>	1.507 (2)
O <sub>4</sub> -C <sub>13</sub>	1.207 (2)	C <sub>8</sub> -C <sub>9</sub>	1.385 (2)
C <sub>1</sub> -C <sub>2</sub>	1.482 (3)	C <sub>9</sub> -C <sub>10</sub>	1.511 (3)
C <sub>3</sub> -C <sub>4</sub>	1.504 (2)	C <sub>9</sub> -C <sub>11</sub>	1.363 (3)
C <sub>4</sub> -C <sub>5</sub>	1.504 (2)	C <sub>11</sub> -C <sub>12</sub>	1.380 (2)
C <sub>5</sub> -C <sub>6</sub>	1.4586 (19)	C <sub>13</sub> -C <sub>14</sub>	1.437 (2)
C <sub>2</sub> -O <sub>1</sub> -C <sub>3</sub>	117.29 (11)	C <sub>6</sub> -C <sub>7</sub> -C <sub>15</sub>	124.66 (14)
C <sub>12</sub> -O <sub>3</sub> -C <sub>13</sub>	122.35 (13)	C <sub>8</sub> -C <sub>7</sub> -C <sub>15</sub>	116.36 (15)
O <sub>1</sub> -C <sub>2</sub> -C <sub>1</sub>	110.46 (16)	C <sub>7</sub> -C <sub>8</sub> -C <sub>9</sub>	123.46 (16)
O <sub>1</sub> -C <sub>3</sub> -O <sub>2</sub>	123.71 (13)	C <sub>8</sub> -C <sub>9</sub> -C <sub>10</sub>	120.61 (19)
O <sub>1</sub> -C <sub>3</sub> -C <sub>4</sub>	110.87 (11)	C <sub>8</sub> -C <sub>9</sub> -C <sub>11</sub>	117.94 (15)
O <sub>2</sub> -C <sub>3</sub> -C <sub>4</sub>	125.41 (13)	C <sub>10</sub> -C <sub>9</sub> -C <sub>11</sub>	121.45 (18)
C <sub>3</sub> -C <sub>4</sub> -C <sub>5</sub>	112.83 (11)	C <sub>9</sub> -C <sub>11</sub> -C <sub>12</sub>	120.23 (16)
C <sub>4</sub> -C <sub>5</sub> -C <sub>6</sub>	124.09 (12)	O <sub>3</sub> -C <sub>12</sub> -C <sub>6</sub>	122.36 (13)
C <sub>4</sub> -C <sub>5</sub> -C <sub>14</sub>	116.56 (13)	O <sub>3</sub> -C <sub>12</sub> -C <sub>11</sub>	114.29 (14)
C <sub>6</sub> -C <sub>5</sub> -C <sub>14</sub>	119.33 (13)	C <sub>6</sub> -C <sub>12</sub> -C <sub>11</sub>	123.34 (14)
C <sub>5</sub> -C <sub>6</sub> -C <sub>7</sub>	127.90 (12)	O <sub>3</sub> -C <sub>13</sub> -O <sub>4</sub>	117.41 (16)
C <sub>5</sub> -C <sub>6</sub> -C <sub>12</sub>	116.07 (12)	O <sub>3</sub> -C <sub>13</sub> -C <sub>14</sub>	116.33 (14)
C <sub>7</sub> -C <sub>6</sub> -C <sub>12</sub>	116.02 (12)	O <sub>4</sub> -C <sub>13</sub> -C <sub>14</sub>	126.25 (17)
C <sub>6</sub> -C <sub>7</sub> -C <sub>8</sub>	118.97 (14)	C <sub>5</sub> -C <sub>14</sub> -C <sub>13</sub>	123.52 (14)
C <sub>3</sub> -O <sub>1</sub> -C <sub>2</sub> -C <sub>1</sub>	-86.04 (18)	C <sub>5</sub> -C <sub>6</sub> -C <sub>7</sub> -C <sub>15</sub>	4.1 (2)
C <sub>2</sub> -O <sub>1</sub> -C <sub>3</sub> -O <sub>2</sub>	-1.8 (2)	C <sub>12</sub> -C <sub>6</sub> -C <sub>7</sub> -C <sub>8</sub>	1.8 (2)
C <sub>2</sub> -O <sub>1</sub> -C <sub>3</sub> -C <sub>4</sub>	179.39 (12)	C <sub>12</sub> -C <sub>6</sub> -C <sub>7</sub> -C <sub>15</sub>	-176.54 (15)
C <sub>13</sub> -O <sub>3</sub> -C <sub>12</sub> -C <sub>6</sub>	-1.2 (2)	C <sub>5</sub> -C <sub>6</sub> -C <sub>12</sub> -O <sub>3</sub>	0.02 (19)
C <sub>13</sub> -O <sub>3</sub> -C <sub>12</sub> -C <sub>11</sub>	-180.00 (14)	C <sub>5</sub> -C <sub>6</sub> -C <sub>12</sub> -C <sub>11</sub>	178.72 (14)
C <sub>12</sub> -O <sub>3</sub> -C <sub>13</sub> -O <sub>4</sub>	178.99 (15)	C <sub>7</sub> -C <sub>6</sub> -C <sub>12</sub> -O <sub>3</sub>	-179.43 (13)
C <sub>12</sub> -O <sub>3</sub> -C <sub>13</sub> -C <sub>14</sub>	0.5 (2)	C <sub>7</sub> -C <sub>6</sub> -C <sub>12</sub> -C <sub>11</sub>	-0.7 (2)
O <sub>1</sub> -C <sub>3</sub> -C <sub>4</sub> -C <sub>5</sub>	-166.99 (12)	C <sub>6</sub> -C <sub>7</sub> -C <sub>8</sub> -C <sub>9</sub>	-1.8 (2)
O <sub>2</sub> -C <sub>3</sub> -C <sub>4</sub> -C <sub>5</sub>	14.3 (2)	C <sub>15</sub> -C <sub>7</sub> -C <sub>8</sub> -C <sub>9</sub>	176.68 (16)
C <sub>3</sub> -C <sub>4</sub> -C <sub>5</sub> -C <sub>6</sub>	76.53 (17)	C <sub>7</sub> -C <sub>8</sub> -C <sub>9</sub> -C <sub>10</sub>	-179.68 (17)
C <sub>3</sub> -C <sub>4</sub> -C <sub>5</sub> -C <sub>14</sub>	-101.80 (15)	C <sub>7</sub> -C <sub>8</sub> -C <sub>9</sub> -C <sub>11</sub>	0.6 (2)
C <sub>4</sub> -C <sub>5</sub> -C <sub>6</sub> -C <sub>7</sub>	2.9 (2)	C <sub>8</sub> -C <sub>9</sub> -C <sub>11</sub> -C <sub>12</sub>	0.6 (2)
C <sub>4</sub> -C <sub>5</sub> -C <sub>6</sub> -C <sub>12</sub>	-176.50 (13)	C <sub>10</sub> -C <sub>9</sub> -C <sub>11</sub> -C <sub>12</sub>	-179.14 (17)
C <sub>14</sub> -C <sub>5</sub> -C <sub>6</sub> -C <sub>7</sub>	-178.84 (14)	C <sub>9</sub> -C <sub>11</sub> -C <sub>12</sub> -O <sub>3</sub>	178.28 (14)
C <sub>14</sub> -C <sub>5</sub> -C <sub>6</sub> -C <sub>12</sub>	1.79 (19)	C <sub>9</sub> -C <sub>11</sub> -C <sub>12</sub> -C <sub>6</sub>	-0.5 (2)
C <sub>4</sub> -C <sub>5</sub> -C <sub>14</sub> -C <sub>13</sub>	175.85 (14)	O <sub>3</sub> -C <sub>13</sub> -C <sub>14</sub> -C <sub>5</sub>	1.4 (2)
C <sub>6</sub> -C <sub>5</sub> -C <sub>14</sub> -C <sub>13</sub>	-2.6 (2)	O <sub>4</sub> -C <sub>13</sub> -C <sub>14</sub> -C <sub>5</sub>	-176.91 (18)
C <sub>5</sub> -C <sub>6</sub> -C <sub>7</sub> -C <sub>8</sub>	-177.55 (14)		

**Table 3. Selected hydrogen-bond parameters.**

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
$C_1-H_1B\cdots O_4^i$	0.9600	2.5100	3.448 (3)	164.00
$C_4-H_4B\cdots O_2^{ii}$	0.9700	2.4500	3.3963 (19)	166.00

Symmetry code(s): (i)  $-x + 1, y - 1/2, -z + 1/2$ ; (ii)  $x, -y + 1/2, z - 1/2$

carbon. The angles  $O_2-C_3-O_1$  and  $O_2-C_3-C_4$  are  $123.7^\circ$  and  $125.4^\circ$  whereas the  $O_1-C_3-C_4$  angle is significantly reduced to  $110.8^\circ$ . The values supporting the fractional (sp) hybridized orbitals are involved in bonding.

### 3.4. Spectral Studies

**UV—Visible spectrum**—The UV spectrum of the title compound 2 in DMSO shows a strong band at 297 nm whereas fluorescence band appears at 387 nm which shows emission over a long range.

**FT IR spectrum**—The FT IR spectrum of the title compound 2 shows the strong characteristic absorption band at  $1725\text{ cm}^{-1}$  region due to lactone carbonyl stretching frequency and band at  $1615\text{ cm}^{-1}$  observed due to C = C stretching.

**$^1\text{H}$  NMR spectrum**—The structure of the title compound 2 was further characterized by NMR absorption. Important structural information can be obtained from its NMR Spectra.  $^1\text{H}$  NMR(400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.34 (s, 3H,  $C_5\text{-CH}_3$ ), 2.54 (s, 3H,  $C_7\text{-CH}_3$ ), 1.15 (t, 3H,  $\text{CH}_3$ -of ester,  $J = 7.2\text{Hz}$ ), 4.15 (q, 4H,  $C_4\text{-CH}_2$  and  $\text{CH}_2$  of ester  $J = 7.2\text{Hz}$ ) 6.39 (s, 1H,  $C_3\text{-H}$ ), 7.0 (s, 1H,  $C_6\text{-H}$ ), 7.1 (s, 1H,  $C_8\text{-H}$ )

**$^{13}\text{C}$  NMR spectrum:**  $^{13}\text{C}$  NMR spectrum (100 MHz DMSO- $d_6$ ) ( $\delta$  ppm) 14- $\text{CH}_3$ , 20  $C_7\text{-CH}_3$ , 22  $C_5\text{-CH}_3$ , 40  $C_4\text{-CH}_2$ , 61 O- $\text{CH}_2$ , 115, 118, 130, 136, 142, 150, 155 these shifts correspond to aromatic carbons. Low intensity signals at 159, 170 are for carbonyl carbons of coumarin and ester respectively.

### 3.5. Crystal Structure

A specimen of  $C_{15}H_{16}O_4$  was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 2.50 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 12192 reflections to a maximum  $\theta$  angle of  $26.07^\circ$  (0.81 Å resolution), of which 2675 were independent (average redundancy 4.558, completeness = 99.9%,  $R_{\text{int}} = 2.13\%$ ,  $R_{\text{sig}} = 1.71\%$ ) and 2113 (78.99%) were greater than  $2\sigma(F^2)$ . The final cell constants of  $a = 8.6248$  (4) Å,  $b = 18.9103$  (8) Å,  $c = 8.4204$  (4) Å,  $\beta = 101.241$  (2)°, volume =  $1347.00$  (11) Å<sup>3</sup>, are based upon the refinement of the XYZ-centroids of 3786 reflections above  $20\sigma(I)$  with

$5.382^\circ < 2\theta < 51.85^\circ$ . Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.920. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with  $Z = 4$  for the formula unit,  $C_{15}H_{16}O_4$ . The final anisotropic full-matrix least-squares refinement on  $F^2$  with 176 variables converged at  $R1 = 4.03\%$ , for the observed data and  $wR2 = 12.44\%$  for all data. The goodness-of-fit was 1.008. The largest peak in the final difference electron density synthesis was  $0.148\text{ e}^-/\text{Å}^3$  and the largest hole was  $-0.136\text{ e}^-/\text{Å}^3$  with an RMS deviation of  $0.029\text{ e}^-/\text{Å}^3$ . On the basis of the final model, the calculated density was  $1.283\text{ g/cm}^3$  and  $F(000)$ , 552  $e^-$ .

### 4. Conclusion

It can be concluded that the newly synthesized 5, 7-dimethyl coumarin-4-acetic ethyl ester exists mainly in the S-cis arrangement in the solid state. The packing diagram revealed the existence of only S-cis isomer which is stabilized by C-H $\cdots$ O bonds.

### 5. Acknowledgements

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