

# Friedel–Crafts alkylation of a cage enone: synthesis of aralkyl substituted tetracyclo[5.3.1.0<sup>[2,6]</sup>.0<sup>[4,8]</sup>]undeca-9,11-diones and the formation of fascinating novel cage compounds with pyrrole and thiophene using Montmorillonite K-10

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**Abstract**—The intrinsic catalytic properties of Montmorillonite K-10 clay have been utilized for Friedel–Crafts alkylation of the polycyclic caged enone **1** using different carbo and heterocyclic aromatic systems leading to novel compounds. Carbon–carbon bond formation between the aromatic compounds and the cage system has led to three different types of products.

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## 1. Introduction

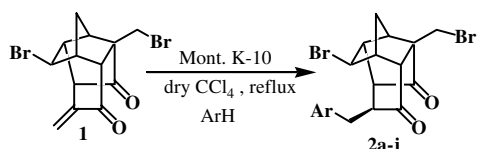
The synthesis and study of the chemical properties of novel strained polycyclic cage molecules is of high contemporary interest.<sup>1</sup> Cage molecules possess rigid, highly compact structures, and therefore such molecules frequently display unusual properties and chemical reactivities.<sup>2</sup> They have been employed as intermediates in organic synthesis, especially for natural products<sup>3</sup> and as templates for nanoarchitectural construction of rigid molecular systems that possess increasing levels of complexity.<sup>4,5</sup> Recently, there has been renewed interest in this area due to the novel pharmacological effects of these compounds.<sup>6–8</sup> Incorporation of carbo and heterocyclic aromatic systems into polycyclic cage frameworks provides novel compounds that may possess useful synthetic, medicinal and pharmacological properties. Careful placement of different aromatic systems into the cage framework can provide novel classes of compounds, which have the inherent chemical properties of both systems. As part of a study on the synthesis of biologically active polycyclic cage compounds, we required a method for introducing aromatic and heteroaromatic side chains on to the cage systems at various ring junctions. Thus,

the synthesis of such compounds via carbon–carbon bond formation between electron rich aromatic compounds and an enone bearing polycyclic system through Friedel–Crafts alkylation appeared to be a suitable method.

Friedel–Crafts reactions which are usually carried out using Lewis acids such as anhydrous AlCl<sub>3</sub>, ZnCl<sub>2</sub>, BF<sub>3</sub>·OEt<sub>2</sub>, SnCl<sub>4</sub>, etc. are among the most important reactions in organic chemistry as they lead to C–C bond formation.<sup>9</sup>

However, Lewis acid catalysts in industrially significant Friedel–Crafts (F–C) reactions are associated with pollution of the environment. It is now well accepted that different types of clays such as Montmorillonite K-10, bentonite, zeolite, etc. can catalyze Friedel–Crafts alkylation and acylation reactions in an eco-friendly way.<sup>10,11</sup> The F–C alkylation of aromatic and heteroaromatic compounds to  $\alpha,\beta$ -unsaturated systems has been known for many years, but has not been exploited to any great extent. Recently, there has been a revival of interest in this area and several reports on the catalytic asymmetric F–C alkylation of activated olefins have appeared in the literature.<sup>12</sup> Friedel–Crafts alkylations of electron rich aromatics to  $\alpha,\beta$ -unsaturated systems have not been explored using clay catalysts even though the Lewis acid properties of Montmorillonite K-10 (Mont. K-10) have

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Scheme 1.

been successfully utilized for many other synthetic transformations.<sup>10,13</sup> In this Letter, we describe the reactivity of the enone moiety of cage compound **1** in the Friedel–Crafts alkylation with various aromatic systems using Mont. K-10 as an acidic catalyst and report the structural features of the novel aralkyl substituted cage compounds thus obtained (Scheme 1).

The synthesis of cage compound **1**, that is, 3-bromo-7-(bromomethyl)tetracyclo[5.3.1.0<sup>[2,6]</sup>.0<sup>[4,8]</sup>]undeca-10(12)-ene-9,11-dione was accomplished in 63% yield through an unusual rearrangement using sunlight as reported earlier.<sup>14</sup>

Friedel–Crafts alkylation reactions of tetracyclic system **1** with various carbo and heteroaromatic systems furnished the corresponding addition products **2a–j** in fairly good yields as summarized in Table 1. The product formation can be explained by initial activation of enone moiety of compound **1** by Mont. K-10 clay followed by the nucleophilic attack of the electron rich aromatic system on the electron deficient double bond of the enone, and subsequent re-aromatization.

Structural details of the products were confirmed through spectroscopic analysis. Notably, the IR spectrum of the products showed two strong carbonyl absorptions suggestive of both strained as well as less strained ring carbonyl groups. The proton NMR spectra showed the total absence of olefinic protons, indicating that the double bond in each case was involved in the Friedel–Crafts reaction. The presence of aromatic systems was also confirmed from the proton NMR spectra. The <sup>13</sup>C NMR spectra showed the presence of two carbonyl groups and the signals corresponding to the aromatic carbons; the signals of the olefinic carbons of the enone moiety were absent in the <sup>13</sup>C NMR spectra thus providing further evidence of the structures of the products.

The Montmorillonite K-10 catalyzed F–C alkylation reaction of the enone moiety of **1** was initially studied with anhydrous benzene (Scheme 1). The reaction gave a single product, which was characterized as **2a** from spectroscopic analysis. Single-crystal X-ray analysis unambiguously confirmed the structure and conformation of **2a**<sup>15</sup> (Fig. 1) as 3-bromo-7-(bromomethyl)-10-benzyl-tetracyclo[5.3.1.0<sup>[2,6]</sup>.0<sup>[4,8]</sup>]undeca-9,11-dione.

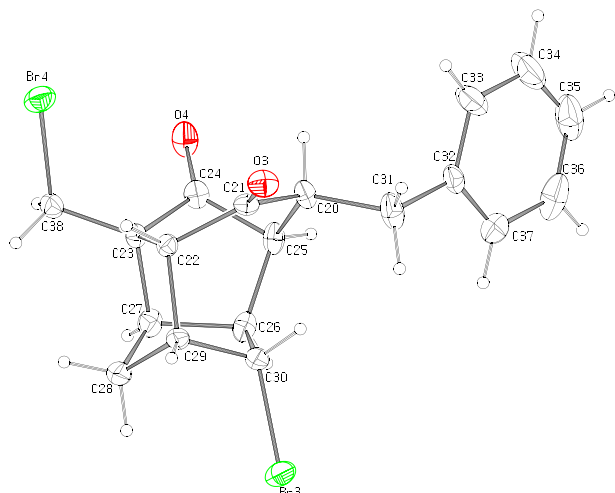
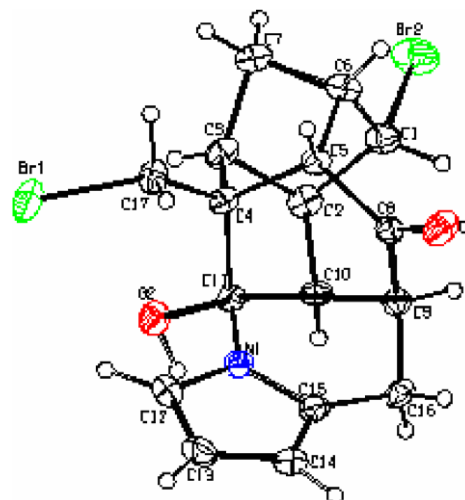
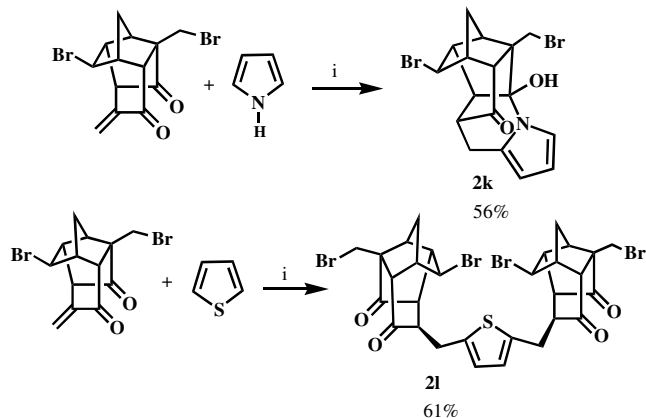
As expected, reaction with furan, 2-methylfuran and 2-methylthiophene occurred at C-2 and C-5, respectively, whereas with indoles, the addition occurred at C-3. It was clear from the proton NMR spectrum of **2i** that the addition occurred at C-2 since the two aromatic pro-

Table 1.

Entry	Reaction conditions	Product 2	Yield (%)
a	Excess dry benzene, reflux, 5 h		47
b	Mesitylene, dry CCl <sub>4</sub> , reflux, 6 h		68
c	Furan, rt, 3 h		40
d	2-Methylfuran, dry CCl <sub>4</sub> , reflux, 8 h		49
e	Anisole, dry CCl <sub>4</sub> , reflux, 6 h		35
f	Indole, dry CCl <sub>4</sub> , reflux, 7 h		60
g	1-Methylindole, dry CCl <sub>4</sub> , reflux, 5 h		48
h	2-Methylthiophene, dry CCl <sub>4</sub> , reflux, 7 h		61
i	3-Methylthiophene, dry CCl <sub>4</sub> , reflux 7 h		44
j	1-Methylpyrrole, dry CCl <sub>4</sub> , reflux, 3 h		45

tons in the adduct resonated as separate doublets at  $\delta$  7.09 and  $\delta$  6.81 with *J* values of 5.1 Hz.

The alkylation of dione **1** with pyrrole using Montmorillonite K-10 catalyst yielded a novel product whose <sup>1</sup>H NMR spectrum showed the presence of three aromatic protons indicating that F–C alkylation had taken place (Scheme 2). However, the presence of absorptions at 3407 cm<sup>-1</sup> and 1712 cm<sup>-1</sup> in the IR spectrum indicated

Figure 1. ORTEP plot of **2a**.Figure 2. ORTEP plot for **2k**.Scheme 2. Reagents and conditions: (i) montmorillonite K-10, dry  $\text{CCl}_4$ , reflux, 8 h.

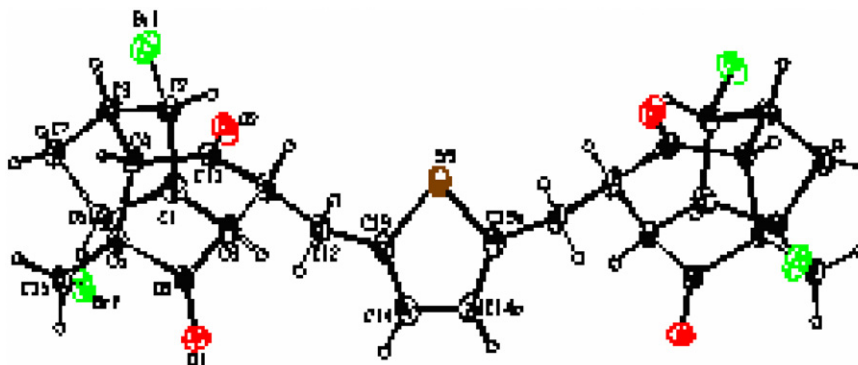
that one carbonyl group had undergone reduction while the other was intact. This was further corroborated by the  $^{13}\text{C}$  NMR spectrum, which showed signals at  $\delta$  210.1, 127.0, 116.2, 110.9 and 105.3 due to the carbonyl carbon and the four aromatic carbons of the pyrrole in addition to a characteristic resonance at  $\delta$  90.7 (quaternary carbon bearing the hydroxyl group). This salient

feature as well as the absence of an NH proton suggested that a further caging process had occurred leading to product **2k**.

The structure and stereochemistry of **2k** were confirmed through single-crystal X-ray analysis (Fig. 2).<sup>16</sup>

F–C alkylation of **1** with thiophene occurred smoothly to yield a bis-alkylated product in 61% yield (Scheme 2).  $^1\text{H}$  NMR (presence of two aromatic protons only) and  $^{13}\text{C}$  NMR spectroscopy clearly indicated the formation of **2l**. The structure was further confirmed by single-crystal X-ray diffraction (Fig. 3).<sup>17</sup>

In conclusion, we have synthesized several novel aralkyl substituted tetracyclo[5.3.1.0<sup>[2,6]</sup>.0<sup>[4,8]</sup>]undeca-9,11-diones through C–C bond formation between aromatic systems and a cage compound using Montmorillonite K-10 via Friedel–Crafts reactions. Thus the intrinsic catalytic properties of commercially available Montmorillonite K-10 have been exploited for the synthesis of polycyclic cage systems for the first time. The addition of nitrogen-, oxygen- and sulfur-containing heteroaromatic systems was noteworthy because the use of  $\text{AlCl}_3$  for the same reaction led to undesired side products. The biological activity of these novel compounds are currently under study.

Figure 3. ORTEP plot of **2l**.

## 2. General procedure for the Friedel–Crafts alkylation

A mixture of compound **1** (0.1 g, 0.28 mmol) and Montmorillonite K-10 clay (100% w/w) (previously activated at 80 °C) in 20 ml of dry  $\text{CCl}_4$  was stirred at reflux temperature for half an hour. The aromatic compound was added and the mixture refluxed for different times (3–8 h). After the reaction was complete, the catalyst was filtered off and the crude compound purified by column chromatography using silica gel to afford products **2a–1**.

## 3. Spectroscopic data for selected compounds

### 3.1. 3-Bromo-7-(bromomethyl)-10-benzyl-tetracyclo[5.3.1.0<sup>2,6</sup>.0<sup>4,8</sup>]undeca-9,11-dione (**2a**)

Crystallized from dichloromethane–petroleum ether (1:2). Melting point: 162–164 °C; yield: 47%; FT-IR (KBr,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2980, 1759, 1707, 1460, 1135, 878, 703;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.16 (m, 5H), 4.52 (s, 1H), 3.54–3.49 (q,  $J = 10.5$  Hz, 2H), 3.22–3.16 (m, 3H), 3.02 (s, 1H), 2.79–2.69 (m, 3H), 2.61–2.55 (m, 2H), 1.94 (d,  $J = 11.8$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  208.9, 208.7, 137.6, 129.6, 129.1, 128.9, 127.1, 64.6, 59.1, 58.7, 50.7, 50.5, 46.7, 45.4, 44.6, 36.5, 35.9, 30.2; HRMS ( $\text{M}^+$ ): 435.9677,  $\text{C}_{19}\text{H}_{18}\text{O}_2\text{Br}_2$  requires 435.9673.

### 3.2. 3-Bromo-7-(bromomethyl)-10-(indolylmethylene)-tetracyclo[5.3.1.0<sup>2,6</sup>.0<sup>4,8</sup>]undeca-9,11-dione (**2f**)

Crystallized from dichloromethane–petroleum ether (1:2). Melting point: 225–227 °C; yield: 60%; FT-IR (KBr,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3412, 1754, 1718, 1460, 1130, 744;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.05 (s, 1H, aromatic), 7.70 (d,  $J = 7.5$  Hz, 1H), 7.36 (d,  $J = 8.1$  Hz, 1H), 7.21–7.12 (m, 3H), 4.46 (s, 1H), 3.58 (d,  $J = 10.4$  Hz, 1H), 3.43 (m, 1H), 3.22 (d,  $J = 10.4$  Hz, 1H), 3.09 (d,  $J = 4.8$  Hz, 1H), 2.91 (m, 3H), 2.76 (d,  $J = 11.6$  Hz, 1H norbornyl), 2.67–2.56 (m, 3H), 1.92 (d,  $J = 11.4$  Hz, 1H norbornyl);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  208.6, 206.3, 136.3, 126.7, 123.9, 122.3, 119.7, 118.7, 111.5, 111.2, 65.2, 57.2, 54.3, 50.4, 48.4, 46.4, 44.6, 44.1, 35.9, 30.6, 24.9; HRMS ( $\text{M}^+$ ): 474.9780,  $\text{C}_{21}\text{H}_{19}\text{NO}_2\text{Br}_2$  requires 474.9783.

### 3.3. 3-Bromo-7-(bromomethyl)-10-(2<sup>1</sup>methylthienylmethylene)-tetracyclo[5.3.1.0<sup>2,6</sup>.0<sup>4,8</sup>]undeca-9,11-dione (**2h**)

Crystallized from dichloromethane–petroleum ether (1:2). Melting point: 133–135 °C; yield: 61%; FT-IR (KBr,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1753, 1707, 1588, 1454, 1119, 790;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.72 (s, 1H, aromatic), 6.56 (s, 1H, aromatic), 4.49 (s, 1H), 3.56 (d,  $J = 10.4$  Hz, 1H), 3.32–3.27 (m, 1H), 3.21–3.07 (m, 3H), 2.89 (s, 1H), 2.80 (m, 2H), 2.68–2.59 (m, 3H), 2.44 (s, 3H), 1.93 (d,  $J = 11.7$  Hz, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  207.9, 205.2, 138.8, 137.2, 127.2, 125.0, 65.2, 57.3, 55.8, 50.2, 48.4, 46.4, 44.7, 43.7, 35.9, 30.4,

29.4, 15.3; HRMS ( $\text{M}^+$ ): 455.9386,  $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Br}_2\text{S}$  requires 455.9394.

### 3.4. 3-Bromo-7-(bromomethyl)-10-(*N*-methylpyrrolyl methylene)-tetracyclo[5.3.1.0<sup>2,6</sup>.0<sup>4,8</sup>]undeca-9,11-dione (**2j**)

Crystallized from dichloromethane–petroleum ether (1:2). Melting point: 226–228 °C; yield: 45%; FT-IR (KBr,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1757, 1712, 1494, 1460, 1143, 732, 646;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.58 (s, 1H, aromatic), 6.05 (d,  $J = 2.9$  Hz, 1H), 5.96 (s, 1H, aromatic), 5.43 (s, 1H), 3.55 (s, 3H, *N*-methyl), 3.52 (s, 1H), 3.41–3.36 (m, 1H), 3.23–3.15 (m, 3H), 3.01 (s, 1H), 2.83–2.62 (m, 5H), 1.94 (d,  $J = 11.8$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  209.4, 209.2, 127.9, 122.6, 107.8, 107.2, 77.2, 64.7, 58.9, 56.9, 50.6, 46.7, 45.4, 44.9, 36.0, 33.7, 30.4, 26.9; HRMS ( $\text{M}^+$ ): 438.9780,  $\text{C}_{18}\text{H}_{19}\text{O}_2\text{Br}_2\text{N}$  requires 438.9783.

### 3.5. Data for **2k**

Crystallized from dichloromethane–petroleum ether (1:3). Melting point: 250–252 °C; yield: 56%; FT-IR (KBr,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3407, 1712, 1475, 1269, 1187, 883, 734;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.03 (s, 1H), 6.21–6.19 (t,  $J = 3.2$  Hz, 1H) 5.83 (s, 1H), 4.51 (s, 1H), 4.01 (s, 1H), 3.72 (d,  $J = 11.7$  Hz, 1H), 3.37 (d,  $J = 11.8$  Hz, 1H), 3.30–3.23 (m, 3H), 2.85–2.74 (m, 2H), 2.69–2.59 (m, 3H), 2.29 (d,  $J = 5.0$  Hz, 1H), 1.83 (d,  $J = 11.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  210.1, 127.0, 116.2, 110.9, 105.3, 90.7, 60.6, 59.7, 51.9, 47.9, 47.8, 47.1, 46.9, 46.1, 33.6, 31.7, 26.6; HRMS ( $\text{M}^+$ ): 424.9632,  $\text{C}_{17}\text{H}_{17}\text{O}_2\text{Br}_2\text{N}$  requires 424.9626.

### 3.6. Bis-alkylated compound (**2l**)

Crystallized from dichloromethane–petroleum ether (1:3). Melting point: 259–261 °C; yield: 61%; FT-IR (KBr,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2979, 1753, 1717, 1460, 1135, 878, 703;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.79 (s, 2H), 4.52 (s, 2H), 3.58 (d,  $J = 10.3$  Hz, 2H), 3.32 (d,  $J = 11.9$  Hz, 2H), 3.23–3.09 (m, 6H), 2.93 (s, 2H), 2.81 (m, 4H), 2.73–2.64 (m, 6H), 1.94 (d,  $J = 11.8$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  208.5, 205.7, 138.9, 127.7, 65.4, 57.5, 55.6, 50.3, 48.5, 46.5, 44.8, 43.9, 36.1, 30.8, 29.6; Mass analysis (FAB,  $\text{M}^+\text{H}$ , 800.84) for  $(\text{C}_{15}\text{H}_{14}\text{O}_2\text{Br}_2)_2\text{S}$ .

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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.2007.06.028](https://doi.org/10.1016/j.tetlet.2007.06.028).

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- Crystal data for 2a*: C<sub>19</sub>H<sub>18</sub>Br<sub>2</sub>O<sub>2</sub>, formula weight: 438.15, monoclinic, space group P2<sub>1</sub>/c, a = 23.459(6), b = 12.973(4), c = 11.788(3) Å, β = 103.590(5)°, V = 3486.9(16) Å<sup>3</sup>, D<sub>c</sub> = 1.669 g/cm<sup>3</sup> for Z = 8. A total of 20,431 reflections were measured up to 2θ = 28.33°, of which 7912 [R(int) = 0.0477] were unique [I > 2σ(I)]. The data were reduced using SAINTPLUS<sup>18</sup> and a multiscan absorption correction using SADABS<sup>19</sup> was performed. The structure was solved using SHELXS-97 and refined using SHELXL-97.<sup>20</sup> All hydrogens were assigned on the basis of geometrical considerations and were allowed to ride upon the respective carbon atoms. Final R indices: R (F<sub>o</sub><sup>2</sup>) = 0.0487, R<sub>w</sub> (F<sub>o</sub><sup>2</sup>) = 0.1023, GOF on F<sup>2</sup> = 0.995. Largest difference in peak and hole 0.862 and -0.832 e Å<sup>-3</sup>, respectively. CCDC 298645 contains the Supplementary data for this Letter. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). The crystal structure revealed two independent molecules present in the asymmetric unit having almost similar conformations.
- Crystal data for 2k*: Empirical formula: C<sub>17</sub>H<sub>17</sub>Br<sub>2</sub>NO<sub>2</sub>; formula weight: 427.14; temperature: 273(2) K; wavelength: 0.71073 Å; crystal system: monoclinic; space group: P2<sub>1</sub>/c; unit cell dimensions: a = 7.184(2) Å, α = 90°, b = 11.999(4) Å, β = 98.485(5)°, c = 17.950(5) Å, γ = 90°; volume: 1530.3(8) Å<sup>3</sup>; Z = 4; density (calculated): 1.854 Mg/m<sup>3</sup>; absorption coefficient: 5.304 mm<sup>-1</sup>; F(000): 848; crystal size: 0.40 × 0.33 × 0.28 mm; theta range for data collection: 2.05–28.33°. Index ranges: -9 ≤ h ≤ 9, -15 ≤ k ≤ 15, -22 ≤ l ≤ 11; reflections collected: 8720; independent reflections: 3512 [R(int) = 0.0270]; absorption correction: SADABS; refinement method: full-matrix least-squares on F<sup>2</sup>; data/restraints/parameters: 3512/0/267; goodness-of-fit on F<sup>2</sup>: 1.065; final R indices: [I > 2σ(I)] R<sub>1</sub> = 0.0443, wR<sub>2</sub> = 0.1192; R indices (all data): R<sub>1</sub> = 0.0702, wR<sub>2</sub> = 0.1312; largest diff. peak and hole: 1.350 and -0.944 e Å<sup>-3</sup>. CCDC 616644.
- Crystal data for 2l*: Empirical formula: C<sub>15</sub>H<sub>14</sub>Br<sub>2</sub>O<sub>2</sub>; formula weight: 402.11; temperature: 296(2) K; wavelength: 0.71073 Å; crystal system: orthorhombic; space group: P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>; unit cell dimensions: a = 9.069(2) Å, α = 90°, b = 22.763(6) Å, β = 90°, c = 6.9120(17) Å, γ = 90°; volume: 1427.0(6) Å<sup>3</sup>; Z = 4; density (calculated): 1.872 Mg/m<sup>3</sup>; absorption coefficient: 5.750 mm<sup>-1</sup>; F(000): 792; crystal size: 0.20 × 0.13 × 0.06 mm; theta range for data collection: 1.79–25.00°; index ranges: -7 ≤ h ≤ 10, -26 ≤ k ≤ 27, -7 ≤ l ≤ 8; reflections collected: 6823; independent reflections: 2500 [R(int) = 0.0390]; absorption correction: SADABS; refinement method: full-matrix least-squares on F<sup>2</sup>; data/restraints/parameters: 2500/0/177; goodness-of-fit on F<sup>2</sup>: 1.024; final R indices [I > 2σ(I)] R<sub>1</sub> = 0.0549, wR<sub>2</sub> = 0.1429; R indices (all data) R<sub>1</sub> = 0.0682, wR<sub>2</sub> = 0.1533; absolute structure parameter: 0.46 (3); largest diff. peak and hole: 1.246 and -0.571 e Å<sup>-3</sup>. CCDC 616643.
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