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An unexpected pentacarbonyl chromium complexation of a cyano group of the ABC core of cephalotaxine

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ABSTRACT

A new penta-carbonyl chromium(0) complex of the type $[Cr(CO)_5(L)]$ (L = tetracyclic pyrrolobenzazepine unit **3**) was surprisingly obtained by reacting $[Cr(CO)_3$(naphthalene)] or $[Cr(CO)_3$(tmtach)] with the tetracyclic pyrrolobenzazepine unit **3** in octane-ether/THF-solvent mixtures or acetone under ambient temperature or reflux. The new complex **13** has been characterized by spectral analysis including IR, ^1H and ^{13}C NMR data. For comparison purposes, the safrole-tricarbonyl chromium(0) complex **12** was prepared and characterized. X-ray diffraction analyses of both complexes were determined. Based on the above data, an octahedral structure has been assigned to the new complex **13**.

Introduction

The biological activity of a number of ester derivatives of cephalotaxine (**1**) is remarkable, as illustrated by homoharringtonine (HHT) (**2**) (Omacetaxine mepesuccinate® (Fig. 1) [1]. HHT (**2**) has an IC_{50} of 0.017 μg/mL against the cell line P-388 [2] and demonstrated clinical activity in chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) through binding to the ribosome thus inhibiting protein synthesis [3] and promoting cell death by apoptosis [4]. The activity of HHT (**2**) has been demonstrated by more than 50 clinical studies, primarily sponsored by the National Cancer Institute (NCI) in the United States, and in China. HHT (**2**) is used for the treatment of leukemia in China and has received its approval in Europe as an orphan drug and was approved by the FDA in October 2012 as a treatment for acute myeloid leukemia for patients who are resistant to two tyrosine kinase inhibitors [5]. Thanks to this clinical importance, and due to its unique pentacyclic structure, the alkaloid core cephalotaxine (**1**) became an attractive target for ~~the~~ chemists. Since the publication of its first synthesis by Weinreb and Semmelhack in 1972 [6], 24 racemic syntheses, 19 enantioselective syntheses of (−)-cephalotaxine (natural configuration) and one of the (+)-enantiomer have been published [7].

In our attempt to complete the total synthesis of (−)-cephalotaxine **1**, the tetracyclic pyrrolobenzazepine unit **3**, which could be regarded as a potential precursor of cephalotaxine **1** missing only two carbon atoms (C1−C2) of elaboration of the D ring, was prepared with a 16.2% overall yield in a concise eight-step sequence from inexpensive safrole [8]. However, nucleophilic addition to this compound, a prerequisite to the formation of the D ring of **1**, was not possible [9]. This unexpected reactivity was explained by the almost null partial charges at C_3 and C_5 positions, which were accurately determined experimentally by high-resolution X-ray diffraction studies at 100 K. We have therefore envisaged the substitution of the A ring by an electron withdrawing chromium tricarbonyl substituent to reverse this unusual electronic distribution (Fig. 2), hoping that this would allow the addition of a nucleophile

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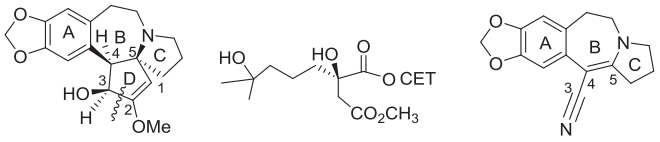


Fig. 1. Cephalotaxine **1**, homoharringtonine **2** and the tetracyclic pyrrolobenzazepine **3**.

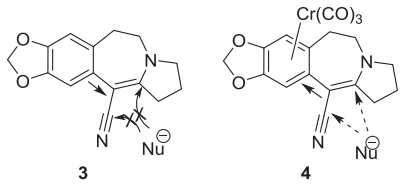


Fig. 2. Expected electronic modifications upon modifying the aromatic ring substitution of benzazepine **3**.

bringing the two missing carbon atoms needed to complete the D cycle of the cephalotaxine **1** skeleton.

Indeed, the neutral [(η^6-arene)$Cr(CO)_3$] motif has been taking a growing place in organometallic chemistry as well as in organic synthesis [10]. The electrophilicity of an arene is dramatically enhanced by coordination to a tricarbonyl metal entity ($M(CO)_3$; M = Cr, Mn^+), allowing several transformations which cannot be carried out on the metal-free arene ring. Thus there has been widespread interest in the chemistry of arene-metal complexes and, among them, (η^6-ArH)$Cr(CO)_3$ complexes have been extensively studied [11–14]. These complexes are used in many synthetic applications including diastereoselective and enantioselective synthesis, chiral ligand design [15,16] and total synthesis [17]. In particular, it has been shown that nucleophilic attack of $Cr(CO)_3$ substituted arenes bearing a conjugated double bond led to a stabilized benzyl anion through addition of the nucleophile at the β position [18–21].

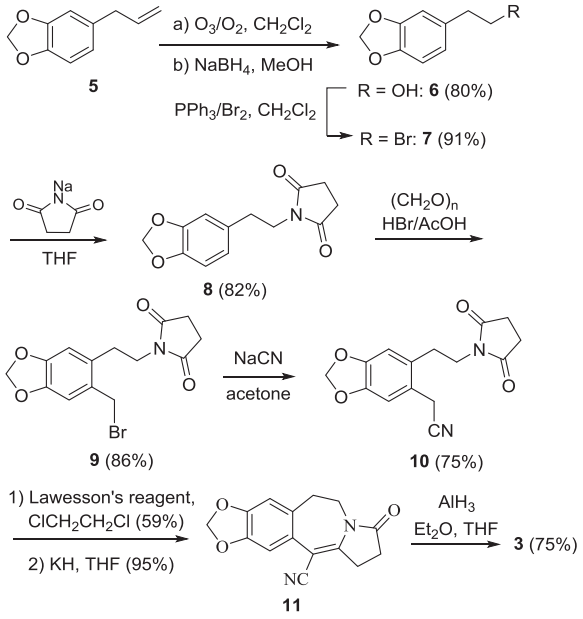
We report herein on the unexpected results dealing with the formation of a pentacarbonyl chromium carbonyl species starting from tetracyclic pyrrolobenzazepine unit **3**.

Results and discussion

*Preparation of the organic ligand **3***

Compound **3** was synthesized from safrole **5** in a concise eight-step sequence with an overall yield of 16.2% (Scheme 1).

The synthesis of compound **6** was accomplished by reductive ozonolysis of the vinylic side chain terminus of safrole **5** [22]. Nucleophilic substitution of the resulting alcohol function by bromine yielded **7** in 72.8% yield from safrole (2 steps). The C ring of cephalotaxine **1** was introduced by nucleophilic substitution of the bromide atom of **7** by the sodium salt of succinimide providing compound **8** in 82% yield. Bromomethylation of **8** afforded **9**, which was then converted into the nitrile **10** in 64.5% yield from **8**. After transformation of the succinimide moiety of **10** into a monothioimide using Lawesson's reagent (59%), anionic cyclization was achieved using potassium hydride affording the enamidonitrile **11** in high yield (95%) and subsequent reduction of the remaining imide function gave the desired product **3** in 75% yield, ending the eight-step sequence in 16.2% overall yield from safrole **5**.[7,8]



Scheme 1. Synthesis of the organic ligand **3**.

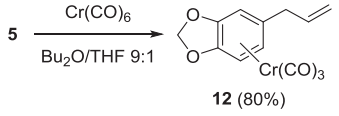
Synthesis of the organometallic complexes

Two general methods are known in literature for synthesis of arene chromium complexes. The first one is the thermally-promoted exchange from hexacarbonyl chromium complex $Cr(CO)_6$ but low yields are usually encountered due to thermal autocatalytic decomposition of the chromium carbonyl group caused by relatively long reaction times [23]. The second one is based on simple thermal conditions using a chromium tricarbonyl transfer agent ($Cr(CO)_3L_3$) [24].

We first prepared the chromium tricarbonyl safrole derivative **12** in order to compare the different structural data with those of the desired target. This compound was previously synthesized by Caro et al. to investigate its reactivity in basic media but has never been described to date [25]. The safrole chromium tricarbonyl complex **12** was prepared starting from chromium hexacarbonyl and safrole in Bu_2O/THF (9:1) under gentle reflux (Scheme 2) in 80% yield. We also tried a less conventional method under microwave activation without success [26].

Compound **12** was characterized by ^{1}H NMR spectroscopy by a pronounced magnetic shielding of its aromatic protons [^{1}H NMR (400 MHz, CD_3COCD_3): 5.14, 5.83 and 5.92 ppm] in comparison with the free corresponding safrole [^{1}H NMR (400 MHz, CD_3COCD_3): 6.65, 6.70 and 6.75 ppm] and consistent with an η^6 coordination mode with loss of the double-bond character in the ring. The two carbonyl stretches of this complex in the IR spectra, 1860 and 1941 cm^{-1}, are consistent with C_{3v} symmetry.

The determination of the $Cr(CO)_3$ tripod orientation with respect to the carbon atoms of the aromatic ring is important and well documented in the solid state. The electronic effects of electron donating groups usually force the $Cr(CO)_3$ tripod to adopt an eclipsed conformation with respect to the donor groups [11]. In the



Scheme 2. Synthesis of chromium tricarbonyl safrole **12**.

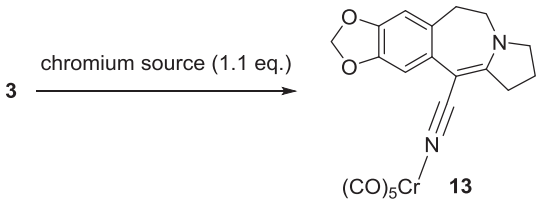
present case this influence should be exerted by the alkoxy groups of the dioxole ring and by the allyl chain, although the positive mesomeric effect of the dioxole is expected to be quite moderate due to limited orbital overlapping. Projection of the $Cr(CO)_3$ tripod to the plane of the arene ring clearly showed that it deviates from the eclipsed conformation as evidenced by the dihedral angles formed by the corresponding H–C of the aromatic ring and the Cr–C of the Cr–CO moieties (H4–C4–Cr–C12: 16.7°; H6–C6–Cr–C13: 17.0° and H3–C3–Cr–C11: 32.7°) and is thus closer to a staggered one (Fig. 3) [29].

We next turned our attention toward the introduction of the chromium carbonyl motif onto compound **3** (Table 1).

Several attempts were made to synthesize the pyrrolobenzazepine chromium tricarbonyl complex **4**. Firstly, we used the thermal method used for the synthesis of **12** (Table 1, entries 1 and 2), however no reaction occurred and compound **3** was almost fully recovered. The microwave assisted procedure reported by Lee et al. [26] (Table 1, entry 3) was not a success either. Since the harsh thermal conditions were probably responsible for the failure of the complex formation, we decided to use a reactant that can transfer the chromium tricarbonyl group under milder conditions. The first transfer agent we decided to use was ~~the~~ naphthalene chromium tricarbonyl [$Cr(CO)_3$(naphthalene)] [30] employed *inter alia* by Schinzer et al. in an approach to the cephalotaxine framework [17]. Reacting this reagent with compound **3** at room temperature (entry 4) in THF or in a mixture of THF and Et_2O (3/1) (entry 5) gave no significant results but, using less THF (entry 6) allowed isolation of a chromium carbonyl compound after 24 h at room temperature.

Unlike compound **12**, this complex displays three ν(CO) infrared bands, 1914, 1870 and 1856 cm^{-1}, consistent with C_{4v} symmetry and the ^1H NMR spectrum shows no shielding of the aromatic protons as expected for a chromium tricarbonyl species like **4** (Fig. 2). Moreover, the ^{13}C NMR spectrum shows 2 peaks, one being around four times higher than the other, consistent with the presence of two types of carbonyl functions. The most reasonable structure for **13** at that stage excluded the formation of an (η^6-arene)$Cr(CO)_3$ motif in favor of a $Cr(CO)_5$ unit linked to the nitrile group. Crystals of compound **13** were grown using slow diffusion multisolvent technique in a mixture of ethyl acetate and pentane and its structure confirmed by an X-ray diffraction study. Many reflexions were visibly excluded during the integration with the initial unit cell A [$a = 6.7983(5)$, $b = 22.3141(19)$, $c = 7.2583(5)$ Å, $\beta = 116.708(8)°$]. There were also many statistically disordered atomic sites so twin deconvolution was attempted. The original cell (cell A) was found along with a second cell of double the volume, $a = 7.3815(13)$, $b = 22.311(3)$, $c = 11.9765(12)$, $ß = 94.190(9)°$ (Cell B). This appears to be related to the first cell by a doubling of the 6.8 Å axis. Indeed, the smaller cell may be transformed to a different setting in which β is 95.039(34)° *vs* $a = 6.113(5)$, $b = 22.3141(19)$, $c = 7.2583(5)$ Å, $ß = 95.04(3)°$ (Cell A). This cell is clearly independent of the larger one even though the *b* axis is the same. TwinSolve was used to index, integrate and scale the data using both Cell A and Cell B [31]. Since the cells really represent polymorphs, only data that were not overlapped were output. This is the primary reason for the low completeness of the data. In cell B, each pyrrolobenzazepine chromium carbonyl complex presents a different orientation of the azepine ring, due to the freedom degree of the ethane segment C9–C10 and C29–C30 respectively, as evidenced by the corresponding dihedral angles C9–C10–C11–C17 (58.72°) and C29–C30–C31–C37 (−64.63°) (Fig. 4). Whatever the resolution of the crystal structure, the coordination of the metal to the nitrogen atom of the nitrile function instead of to the electron rich benzodioxole arene is evidenced in both crystal cells of compound **13**.

Table 1
Tentative optimization process for the synthesis of a chromium carbonyl derivative from **3**.



Entry	Reaction conditions	3	13
1	Bu_2O/THF (9:1), $Cr(CO)_6$, 160 °C, 24 h	96%	–
2	Bu_2O/THF (9:1), $Cr(CO)_6$, 100 °C, 72 h	95%	–
3	THF, $Cr(CO)_6$, 160 °C, 100 W, 15 bar, 1 h	94%	–
4	THF, [$Cr(CO)_3$(naphthalene)], r.t., 12 h	96%	–
5	Et_2O/THF (1:3), [$Cr(CO)_3$(naphthalene)], r.t., 24 h	93%	Traces
6	Et_2O/THF (9:1), [$Cr(CO)_3$(naphthalene)], r.t., 24 h	–	67%
7	Acetone, [$Cr(CO)_3$(tmtach)], 50 °C, 5 h	–	53%

Competition between these two functions for the coordination to a chromium carbonyl group have been reported using $Cr(CO)_6$ as the metallic source. In the case of electron poor arenes, the coordination was shown to occur at the nitrile [32,33] while Rose et al. reported the formation of an arene complex despite the presence of a nitrile group, in the case of a more electron rich phenyl group [34].

The following mechanism could explain the formation of compound **13**, bearing five carbonyl groups, from a chromium tricarbonyl derivative. First, and as previously described [35], the chromium source [$Cr(CO)_3$(naphthalene)] undergoes solvolysis to afford [$S_3Cr(CO)_3$]. This compound could then lead, by reaction with oxygen donors (THF or acetone), to the ultimate formation of Cr_2O_3 and hence releasing of CO molecules in the solvent which lead to the concomitant formation of higher carbonylated species $S_2Cr(CO)_4$ **14** [35] or, by reaction with **3**, to the species **15**. Delivery of two extra carbonyl ligands to this last compound could arise

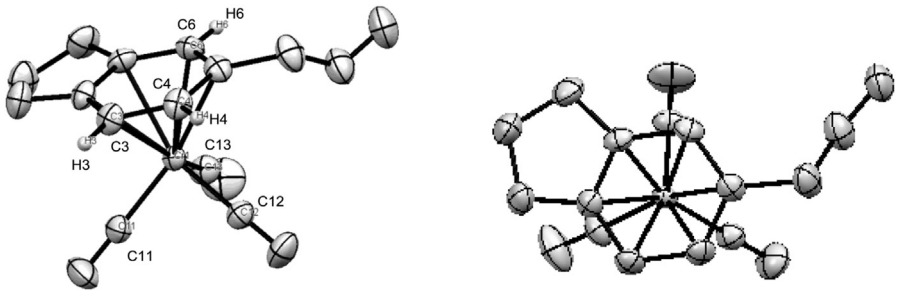


Fig. 3. Thermal ellipsoid plot of the molecular structure of chromium tricarbonyl safrole **12**. For clarity, most of the H atoms and flexibility of the allyl chain terminus in the cell have been omitted for clarity. The ellipsoids enclose 50% of the electronic density. Fig. 3 was drawn with the Mercury program [27] in the ORTEP style [28].

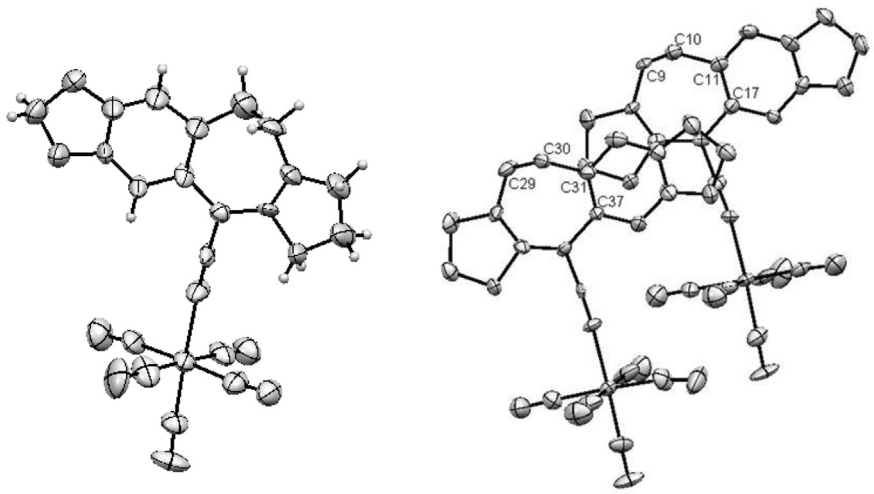
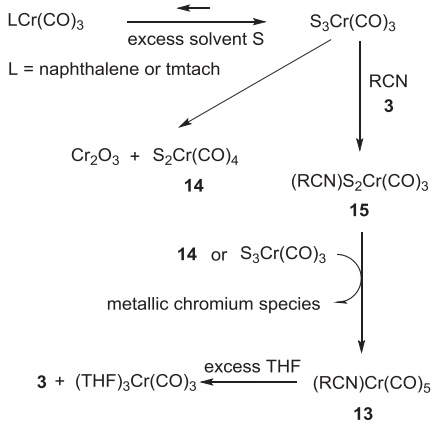


Fig. 4. Thermal ellipsoid plot of the molecular structure of chromium carbonyl complex **13**. Left: cell A; right cell B (two conformations in the unit cell), the ellipsoids enclose 50–35% of the electronic density.

from **14** or [$S_3Cr(CO)_3$] with concomitant formation of metallic chromium species. Compound **3** is indeed too much sterically hindered to envisage the formation of a complex of type [$(RCN)_3Cr(CO)_3$]. The effect of THF concentration on the course of the reaction is due to its chelating properties, which allow it to compete with the other ligands (arene, cyano…) relative to chromium complexation. THF is for instance mandatory for the successful arene complexation of a $Cr(CO)_3$ unit starting from the reagent $Cr(CO)_6$, and its role in that case is attributed to the displacement of CO ligand(s) from $Cr(CO)_6$ [23]. For the reaction using [$Cr(CO)_3$(naphthalene)] as a transfer agent, a too high THF concentration in the medium (THF or Et_2O:THF 1:3, Table 1, entries 4 and 5) would lead to decomplexation of complex **13** with THF resulting in an inefficient process. This was evidenced first by the observed characteristic yellow color of the reaction medium during the reaction that vanished progressively to give the characteristic green color of metallic chromium species and second, with the successful synthesis of complex **13** when the THF concentration is reduced (Table 1, entry 6) (Scheme 3). In order to confirm this hypothesis, another transfer agent, trimethyltriazacyclohexane chromium tricarbonyl [(tmtach)$Cr(CO)_3$], known to easily displace arene groups from arene chromium tricarbonyl complexes, was used [36]. This compound is also prone to decomposition in polar solvent at room temperature under exposure to atmosphere leading to green precipitates, indicative of carbonyl decomplexation and formation of metallic chromium species. It was prepared from chromium hexacarbonyl and trimethyltriazacyclohexane (tmtach) using the thermal procedure to furnish an orange brownish powder which was used as the metallic source in the transfer reaction (Table 1, entry 7). The carbonyl complex **13** was obtained after 12 h at room temperature in THF in 60% yield.

The crystal data and details of the structure determinations for **12** and **13** are summarized in Table 2.



Scheme 3. Complexation–decomplexation equilibria and reasonable mechanism for the synthesis of complex **13**.

Conclusion

In order to modify the reactivity of a pyrrolobenzazepine unit toward nucleophilic attack, we envisaged its transformation into an arene chromium tricarbonyl complex. Unexpectedly, the reaction conditions used led to a chromium pentacarbonyl complex where the metal was linked to the nitrogen atom of the organic framework. The study of the nucleophilic attack of this complex is now under progress and will be reported in due course.

Experimental section

General

TLC analyses were carried out on aluminum sheets precoated with silica gel (60 F254) and visualized with UV light, staining at 100 °C was performed using Kägi–Misher reagent. Purification by column chromatography was performed using 70–230 mesh silica gel (Merck). NMR spectra were recorded with a Bruker Advance DRX 500 FT spectrometer [400 MHz (^{1}H) and 100 MHz (^{13}C)] or a Bruker AH 300 FT spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C)]. Chemical shifts are expressed in ppm downfield from TMS. Data are reported as follows: chemical shift [multiplicity (s: singlet, d: doublet, dd: double doublet, ddd: double double doublet, dm: double multiplet, dt: double triplet, t: triplet, td triple doublet, tm, triple multiplet, tt: triple triplet, q: quartet, quint: quintuplet, m: multiplet, br: broad), coupling constants (*J*) in Hertz, integration]. The numbers of attached proton(s) in the ^{13}C NMR spectra were elucidated by use of JMOD experiments and are described as: (CH_3) primary, RCH_3; (CH_2) secondary, R_2CH_2; (CH) tertiary, R_3CH; (C) quaternary, R_4C. Reference peaks for the NRM spectra in $CDCl_3$: 7.26

Table 2
Crystallographic data of **12** and **13**.

	Compound **12**	Compound **13**
Empirical formula	$C_{13}H_{10}CrO_5$	$C_{20}H_{14}CrN_2O_7$
Formula weight	298.21	446.33
Temperature (K)	293(2)	193(2)
Wavelength (Å)	0.71073	1.54187
Crystal system	Monoclinic,	Monoclinic,
Space group	P 2_1/c	P 2_1
Unit cell dimensions (Å)	$a = 8.343(1)$	$a = 7.3815(13)$
	$b = 8.120(1)$	$b = 22.311(3)$
	$c = 19.535(3)$	$c = 11.9765(12)$
(°)	$\beta = 107.51(4)$	$\beta = 94.190(9)$
Volume (Å^3)	1262.1(3)	1967.1(5)
Z, Z'	4,	2, 2
Calculated density (mg/m^3)	1.569	1.507
Absorption coefficient (mm^{-1})	0.919	5.202
F(000)	608	912
Crystal size (mm)	0.40 × 0.30 × 0.20 m	0.20 × 0.13 × 0.07
θ range for data collection (°)	3.52 to 27.45	3.701 to 65.075
Limiting indices	$-10 \le h \le 10$, $-10 \le k \le 9$, $-25 \le l \le 25$	$-8 \le h \le 7$, $-20 \le k \le 26$, $-14 \le l \le 9$
Reflections collected	9315	6632
Independent reflections	2847 [R(int) = 0.0237]	4502 [R(int) = 0.0575]
Completeness to θ max	98.5%	88.2%
	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.83 and 0.74	0.19 and 0.69
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2842/21/182	4499/40/541
Goodness-of-fit on F^2	1.028	1.077
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0390$,	$R1 = 0.1029$,
	$wR2 = 0.1008$	$wR2 = 0.2567$
R indices (all data)	$R1 = 0.0589$,	$R1 = 0.1287$,
	$wR2 = 0.1136$	$wR2 = 0.2770$
Extinction coefficient	0.019(3)	–
Flack parameter	–	0.04(2)
Largest diff. peak and hole (e Å^{-3})	0.341 and −0.370	0.725 and −0.505

(^{1}H) and 77.16 (^{13}C); CD_3COCD_3: 2.05 (^{1}H) and 29.84 (^{13}C). High-resolution mass spectra were obtained with a WATERS HPLC Alliance coupled to a LCT Premier instrument. Elemental analyses were carried out on a Flash EA 1112 CHNS/O Thermo Electron instrument and are expressed as percentage values. Melting points were measured on an Electrothermal Digital melting point capillary apparatus; the values are reported in °C and are uncorrected. For air-sensitive reactions, all glassware was oven-dried (120 °C) over a 24 h period and cooled under a stream of argon. All commercially available reagents were used as supplied. THF was distilled from sodium benzophenone ketyl and stored under argon. Diisopropylamine was distilled from potassium hydroxide. Air-sensitive reagents were transferred by syringe or with a double-ended needle. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C) homogeneous material. Ozonolysis was carried out using a Fischer ozone generator 500 apparatus. For compound **12**, the X-ray diffraction data were collected on an Enraf-Nonius Kappa-CCD diffractometer using graphite-monochromated Mo-Kα ($\lambda = 0.71073$ Å) radiation at ambient temperature. Diffraction images were recorded according to a $\varphi + \omega$ scan profile data strategy derived by the COLLECT software package [37]. Intensities were integrated, then reduced and merged after semi-empirical absorption correction using HKL-2000 software [38]. The structure solution was carried out by direct methods (SHELXS-97) [39] and refined on F^2 by means of full-matrix least-squares methods (SHELXL-97) [38]. All non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms, located from difference Fourier maps, were refined using a riding model with $U_{iso} = 1.2U_{eq}$ of the parent atom. Positional disorder involving the terminal C of the vinyl group was suggested with a fixed occupancy ratio (0.85:0.15) implicating the use of soft similar distance, rigid-bond, and anisotropic displacement restraints (SADI sd (0.002), DELU sd (0.005), and SIMU sd(0.03). For compound **13** the X-ray diffraction data were collected using a Rigaku MM007 HF copper rotating-anode generator Cu-Kα ($\lambda = 1.54187$ Å) with Osmic VariMAX HF optics and a RAPID II Image Plate Detector at 193(2) K. A total of 63 oscillation images with 5° rotation per image and 60-s exposure per degree of oscillation were measured with the CrystalClear software package32 from a monoclinic unit cell. Intensities were reduced and merged after empirical absorption correction as well as correction for Lorentz and polarization effects using FS_Process from the CrystalClear suite. TwinSolve was used to index, integrate and scale the data using both Cell A and Cell B. The unoverlapped data from Cell B were input to Olex2 [40] and used for subsequent solution by direct methods (SHELXD) [38] and refinement (see Table 2). Similar-ADP restraints sd (0.4) and rigid-bond restraints (sd 0.1) were applied for the following atoms C9/C11–N2–C20–C19. ORTEP drawings were made using ORTEP3 [28] as implemented within Mercury. [27]

*2-[(3′,4′-Methylenedioxy)phenyl]ethanol (**6**)*

Caution: care should be taken when manipulating highly toxic ozone and instable ozonides. Reaction is performed under a fume hood at low temperature, in the presence of a protic solvent to stabilize the potentially explosive ozonide, in the form of a hydroperoxyacetal [41]. We experienced no safety issues in the course of performing this reaction in the 1–50 g scale.

In a 2 L three-necked flask fitted with a sintered rod and a calcium chloride guard, safrole (50 g, 308 mmol) was diluted in dichloromethane (1.5 L) and ethanol (0.2 L). A stream of ozone was established (flow rate: 130 L/h, 3% O_3 in O_2) for 3 h at −78 °C. The reaction progress was monitored by TLC analysis. When it showed complete consumption of safrole, the excess ozone was removed by

a stream of oxygen for 5 min, then sodium borohydride (59 g, 1.54 mmol, 5 eq.) was added by portions at −78 °C with vigorous stirring. After coming gradually to room temperature overnight (the acetone/dry ice cold bath was left in place), the mixture was stirred for 3 days until a test with potassium iodide reveals the disappearance of peroxides. After dropwise addition of 10% aqueous H_2SO_4 (350 mL) *via* a connected addition funnel (note the significant gas evolution), water (600 mL) was added to dissolve the salts and the layers were separated. The aqueous layer was extracted with dichloromethane (4 × 250 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure and the resulting oil was distilled under vacuum ($Eb_{0.01}$ = 98 °C) to give piperonyl ethanol (**6**) as colorless oil. Yield: 42 g (80%). IR (film, ν cm^{-1}): 3341, 2882, 1502, 1487. RMN ^1H (300 MHz, $CDCl_3$) δ (ppm): 1.71 (s, 1H, OH), 2.77 (t, J = 6.5 Hz, 2H), 3.79 (t, J = 6.5 Hz, 2H), 5.91 (s, 2H), 6.64–6,77 (m, 3H). RMN ^{13}C (75 MHz, $CDCl_3$) δ (ppm): 38.3 (CH_2), 63.0 (CH_2), 100.3 (CH_2), 107.7 (CH), 108.9 (CH), 121.3 (CH), 132.1 (C), 145.5 (C), 147.2 (C).

*5-(2-Bromoethyl)benzo[d][1,3]dioxole (**7**)*

At 0 °C, triphenylphosphine (15.15 g, 57.75 mmol, 1.2 eq.) was dissolved in CH_2Cl_2 (26 mL), then Br_2 (2.96 mL, 57.75 mmol, 1.2 eq.) was added dropwise *via* a syringe. Piperonyl ethanol (**6**) (8 g, 48.13 mmol) was dissolved in CH_2Cl_2 (3 mL) and added dropwise to the solution. The reaction mixture was stirred at room temperature for two hours, concentrated *in vacuo* and the resulting yellow product washed in a Büchner funnel with Et_2O/Cy (1/1). The filtrate was concentrated *in vacuo* and then purified by vacuum distillation ($Eb_{0.005}$ = 85 °C) to give **7** as a colorless oil. Yield: 10.03 g (91%). IR (film, ν cm^{-1}): 2891, 1501, 1488, 1442, 1292, 1119, 667. ^1H NMR (300 MHz, $CDCl_3$): δ ppm 3.06 (t, J = 7.5 Hz, 2H), 3.51 (t, J = 7.5 Hz, 2H), 5.92 (s, 2H), 6.64–6.77 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 33.1 (CH_2), 39.0 (CH_2), 100.9 (CH_2), 108.2 (CH), 109.9 (CH), 121.6 (CH), 132.5 (C), 146.4 (C), 147.6 (C).

*1-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)pyrrolidine-2,5-dione (**8**)*

NaH (11.08 g, 60%, 87.24 mmol, 4 eq.) was washed three times with THF then suspended in THF (13 mL). At 0 °C, a solution of succinimide (10.8 g, 109.0 mmol, 5 eq.) dissolved in DMF (27 mL) was added dropwise to the suspension. The reaction mixture was heated up to 30 °C until all H_2 was released. A solution of the 5-(2-Bromoethyl)benzo[*d*][1,3]dioxole **7** (5 g, 21.81 mmol) was dissolved in THF (4 mL) and added to the sodium succinimidate suspension. The mixture was heated to 50 °C and stirred for 20 h. To the reaction were added water (35 mL) and AcOEt (25 mL), layers were separated and the aqueous layer was extracted three times with AcOEt, dried over $MgSO_4$ and filtrated. The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 1:1) to give the imide **8** as a white solid. Yield: 4.21 g (78%). IR (neat, ν cm^{-1}): 2343, 1777, 1701, 1503, 1485. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.65 (s, 4H), 2.80 (t, J = 7.6 Hz, 2H), 3.63 (t, J = 7.6 Hz, 2H), 5.90 (s, 2H), 6.61–6.72 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 28.1 (2 CH_2), 33.3 (CH_2), 40.1 (CH_2), 101.0 (CH_2), 108.3 (CH), 109.2(CH), 121.8 (CH), 131.6 (C), 146.4 (C), 147.8 (C), 176.9 (2 CO). HRMS (ESI) *m/z* calcd. for $C_{13}H_{13}NO_4Na$ = 270.0742, $(M + Na)^+$ found = 270.0743.

*1-(2-(6-(Bromomethyl)benzo[d][1,3]dioxol-5-yl)ethyl)pyrrolidine-2,5-dione (**9**)*

To the imide **8** (2.376 g, 9.61 mmol) dissolved in glacial acetic acid (8 mL) was added paraformaldehyde (0.991 g, 10.55 mmol, 1.1 eq.). A solution of hydrobromic acid (1.96 mL, 11.53 mmol, 33% HBr in acetic acid) was added dropwise to the mixture. The reaction mixture was stirred at 40 °C for 4 h, then allowed to cool to room temperature and quenched by adding ice. The brownish solid was then filtrated on Buchner funnel and washed several times with water until all the acid was removed and a homogenous beige color was attained. The solid was dissolved in CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo* to furnish the bromoimide (**9**) as beige solid which was directly engaged in the subsequent reaction. Yield: 2.81 g (86%). IR (neat, ν cm^{-1}): 3046, 3038, 2940, 2929, 1770, 1632. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.72 (s, 4H), 2.86–2.91 (m, 2H), 3.68–3.73 (m, 2H), 4.59 (s, 2H), 5.95 (s, 2H), 6.71 (s, 1H), 6.83 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 28.6 (2 CH_2), 30.6 (CH_2), 32.1 (CH_2), 39.5 (CH_2), 101.6 (CH_2), 110.3 (CH), 110.7 (CH), 129.6 (CH), 130.8 (C), 146.9 (C), 148.4 (C), 177.1 (2CO).

*(6-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)benzo[d][1,3]dioxol-5-yl) acetonitrile (**10**)*

Caution: care should be taken when manipulating highly toxic cyanide salts. To the bromoimide **9** (2.803 g, 8.24 mmol) dissolved in acetone (50 mL) was added sodium cyanide (1.61 g, 32.94 mmol, 4 eq.) in fine powder and the reaction mixture was stirred at room temperature for 4 days. It was concentrated *in vacuo*, treated with water (50 mL) and extracted three times with chloroform (3 × 30 mL). The organic layers were combined and dried over $MgSO_4$, filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2:AcOEt = 85:15) to furnish (**10**) as a white solid. Yield: 1.769 g (75%). An analytical sample was recrystallized from Cy:AcOEt = 1:1 mixture. IR (neat, ν cm^{-1}): 2910, 2170, 1772, 1695. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.72 (s, 4H), 2.75–2.81 (m, 2H), 3.59–3.64 (m, 2H), 3.75 (s, 2H), 5.96 (s, 2H), 6.72 (s, 1H), 6.87 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.3 (CH_2), 28.1 (CH_2), 30.8 (CH_2), 39.0 (CH_2), 101.4 (CH_2), 109.5 (CH), 110.4 (CH), 118.1 (CN), 121.5 (C), 129.2 (C), 147.3 (C), 147.7 (C), 177.1 (2 CO). Anal. calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79%. Found: C, 62.65; H, 5.10; N, 9.61%.

*5,8,9,19-Tetrahydro-8-pyrrolo[2,1-b][3]benzazepine-6H-1,3-dioxolo [4,5-h]-11-carbonitrile (**3**)*

To a solution of enamidonitrile **11** [8] (250 mg, 0.93 mmol) in THF (25 mL) at 20 °C was added a solution of AlH_3 (7 mL) [prepared by dropwise addition of a solution of $AlCl_3$ (1.1 g, 8.2 mmol) in Et_2O (5 mL) to a suspension of $LiAlH_4$ (310 mg, 8.2 mmol) in Et_2O (7.5 mL) at 0 °C under argon atmosphere, stirring of the mixture for 15 min, and decantation of the residual solid]. The resulting mixture was stirred for 30 min and hydrolyzed at 0 °C with a 5 N aqueous ammonia solution (10 mL). The aqueous layer was separated and extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (cyclohexane/ethyl acetate = 1:1) to give enaminonitrile **3** as beige solid. Yield: 177 mg, (75%). M.p.: 193 °C. IR (neat, ν cm^{-1}): 2168, 1629. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.92–1.99 (m, 2H), 2.81 (t, J = 4.5 Hz, 2H), 3.05 (t, J = 7.8 Hz, 2H), 3.45–3.49 (m, 4H), 5.82 (s, 2H); 6.41 (s, H), 6.95 (s, H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.1 (CH_2), 35.6 (CH_2), 36.5 (CH_2), 51.8 (CH_2), 58.2 (CH_2), 74.0 (C), 100.9 (CH_2), 106.7 (CH), 109.1 (CH), 123.6 (CN), 127.9 (C), 130.2 (C), 144.7 (C), 146.7 (C), 157.4 (C). HRMS (ESI) *m/z* calcd. for $C_{15}H_{15}N_2O_2$ = 255.1134, $(M + H)^+$ exp.: 255.1133.

*Tricarbonyl (η^6-safrole)chromium (**12**)*

In a well degazed (freeze–pump–thaw degassing technique) mixture of butyl ether (9 mL) and THF (1 mL) placed in a Schlenk

flask, safrole **5** (1 mL, 6.16 mmol, 2 eq.) and chromium hexacarbonyle (0.677 g, 3.08 mmol, 1 eq.) were refluxed at 150 °C for 20 h protected from light and under argon. The reaction mixture was cooled to room temperature, filtered and the solid was washed with ether and purified by crystallization using the slow diffusion multi-solvent technique with ethyl acetate/pentane to furnish complex **12** as yellow crystals. Yield: 780 mg (85%). M.p.: 59.8 °C. IR (neat, ν cm^{-1}): 1941, 1860. ^1H NMR (400 MHz, CD_3COCD_3): δ ppm: 3.11–3.24 (m, 2H), 5.14–5.23 (m, 2H), 5.14 (s, 1H), 5.83 (s, 1H), 5.92 (m, 1H), 5.94 (m, 1H), 6.19 (s, 1H). ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm: 38.9 (CH_2), 78.9 (CH), 79.2 (CH), 87.7 (CH) 102.0 (CH_2), 107.7 (C), 118.3 (CH_2), 129.2 (C), 131.9 (C), 136.4 (C), 206.1 (3 CO).

*Pentacarbonyl 5,8,9,19-tetrahydro-8-pyrrolo[2,1-b][3]benzazepine 6H-1,3-dioxolo[4,5-h]-11-carbonitrile chromium (**13**)*

Preparation from naphthalene chromium tricarbonyle

To a well degazed (freeze–pump–thaw degassing technique) solution of enaminonitrile **3** (27 mg, 0.106 mmol) in diethyl ether (1.8 mL) and THF (0.2 mL), was added naphthalene chromium tricarbonyle (33.4 mg, 0.127 mmol, 1.2 eq.). The reaction mixture protected from light and under argon was stirred for three days at room temperature. The reaction mixture was concentrated and refilled with nitrogen prior to purification by flash chromatography using ethyl acetate under a flow of nitrogen to give the complex **13** as a yellow solid. Yield: 27.7 mg (67%). For crystallographic studies, the solid was purified by crystallization by the slow diffusion multi-solvent technique using ethyl acetate/pentane to give yellow crystals.

Preparation from [Cr(CO)$_3$(tmtach)]

To a solution of enaminonitrile **3** (81 mg, 0.32 mmol) in acetone (5 mL) was added $Cr(CO)_3$(tmtach) (85 mg, 0.32 mmol, 1 eq.). The reaction mixture was stirred for 5 h at 50 °C protected from light and under argon. The reaction mixture was concentrated then dissolved in $CHCl_3$ (5 mL) and filtered on a pad of silica prior to purification by flash chromatography using ethyl acetate under a flow of nitrogen to give the complex **13** as a yellow solid (75 mg, 53%).

M.p. 180 °C (decomp.). IR (neat, ν cm^{-1}): 1914, 1870 and 1856. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.09 (q, $J = 8$ Hz, 2H), 2.87–2.89 (m, 2H), 3.02 (t, $J = 7.6$ Hz, 2H), 3.56 (d, $J = 4$ Hz, 2H), 3.59 (t, $J = 8$ Hz, 2H), 5.93 (s, 2H), 6.51 (s, 1H), 6.69 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 21.2 (CH_2), 35.6 (CH_2), 36.4 (CH_2), 52.0 (CH_2), 58.7 (C), 74.4 (C)*, 101.3 (CH_2), 106.1 (CH), 109.6 (CH), 126.8 (C)**, 130.3 (C), 133.64 (CN), 145.4 (C), 147.1 (C), 159.2 (C), 214.7 (4 CO), 220.3 (CO).

* observed by indirect HMBC correlation with CH_2 (36.4).

** observed by indirect HMBC correlation with CH_2 (35.6).

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Appendix A. Supplementary material

CCDC 1002364 and 1021537 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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