Differential oxidation conditions of substituted cyclobutanols derived from terpenes.

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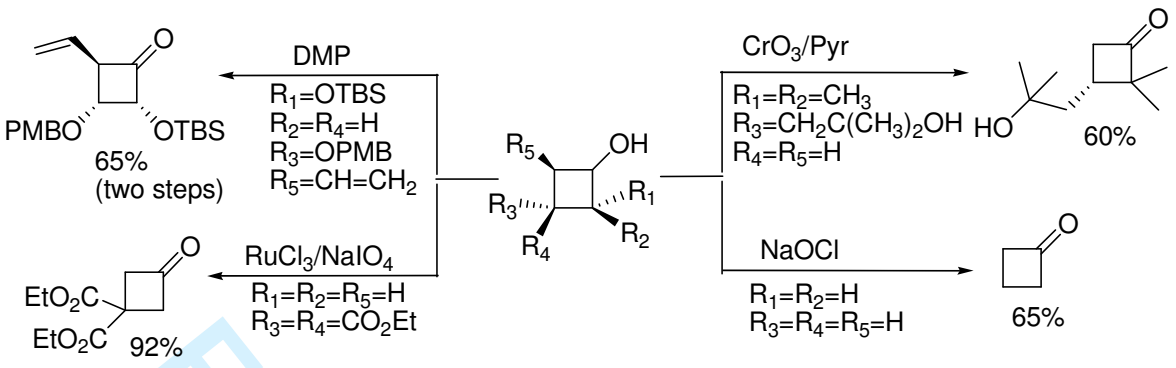
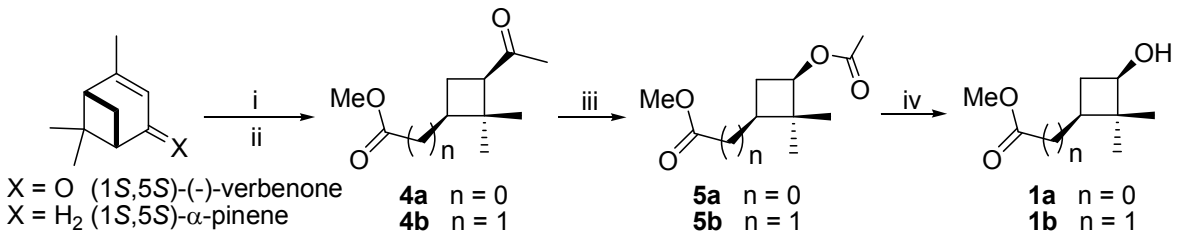
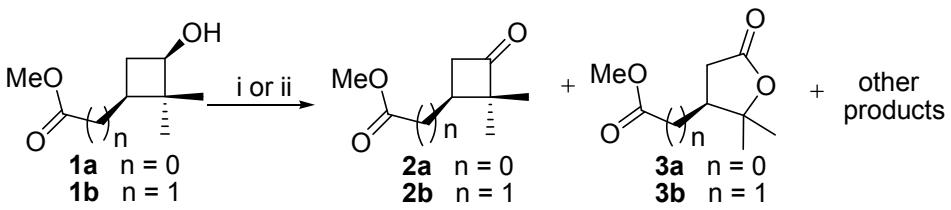


Scheme 1. Reported oxidations of cyclobutanols with different oxidizing agents.



Scheme 2. Synthesis of alcohols **1a** and **1b**. Reagents and conditions: (i) $RuCl_3/NaIO_4$; (ii)CH_2N_2; (iii) *m*-CPBA; (iv) KOH.



Scheme 3. Synthesis of compounds **2** and **3.** Reagents and conditions: (i) $RuCl_3/NaIO_4$; (ii) PDC.

Table 1: Products of the oxidation of **1a** and **1b**.

Entry	Reagent	Products from [Yields(%)]	
		1a	**1b**
1	$RuCl_3/NaIO_4$	**2a**/**3a** 53:47[a]	**2b**/**3b** 61:39[a]
2	PDC	**2a**/**3a** 66:34[a]	**2b**/**3b** 71:29[a]
3	NaOCl	**3a** 70[b]	**3b** 83[b]
4	DMP	**2a** 93[b]	**2b** 78[b]

a: Calculated from NMR spectra integrations.

b: Isolated yield.

Differential oxidation conditions of substituted cyclobutanols derived from terpenes.

Juan A. Caturelli Kuran and Albertina G. Moglioni.*

Departamento de Farmacología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, Buenos Aires, (C1113AAD), Argentina.

E-mail: amoglio@ffyb.uba.ar

Abstract

The use of different oxidants for homochiral cyclobutanols afforded dissimilar products depending on the agent used. Dess-Martin periodinane permited the obtention of the homochiral cyclobutanones and sodium hypochlorite produced only one of the two possible regioisomeric γ-butyrolactones.

Keywords: γ-butyrolactones; cyclobutanols; cyclobutanones; oxidation; regioselectivity

INTRODUCTION

Oxidation of alcohols is one of the most fundamental reactions in organic chemistry. A great variety of metal and non-metal-based stoichiometric reagents have been developed to oxidize primary and secondary alcohols to the corresponding aldehydes, ketones and carboxylic acids.[1] Among alcohols, cyclobutanols as precursors of cyclobutanones acquire a great importance, not yet as academic curiosities but as building blocks of strained peptides[2] or carbocyclic nucleosides.[3,4]

The chemical reactivity of cyclobutanones is different from that of other large cyclic ketones, due to their ring strain of ca. 25 kcal/mol. This feature allows the synthetic chemist to use various strategies to obtain natural products and biologically active compounds.[5] Cyclobutanones have been used in ring enlargement reactions for the construction of large rings, being themselves and their derivatives valuable precursors of important antiviral and anticancer agents, like carbovir and neplanocin.[6-9]

Ruthenium tetroxide is known to be a very powerful oxidizing agent.[10] This well-defined complex containing Ru (VIII) is a rather non-selective oxidant, often causing multiple bond rupture.[11] A catalytic amount of RuO_4 using $NaIO_4$ as reoxidant has been used for the successful preparation of cyclobutanic synthons.[12] Attempts to oxidize cyclobutanols leading to complex product mixtures have also been reported.[13]

A large number of very mild oxochromium(VI)-amine reagents have been developed.[14] The use of pyridinium dichromate (PDC) for the oxidation of alcohols started after Corey and Schmidt described the potential of this reagent.[15] PDC permits the oxidation of primary and secondary alcohols containing acid-sensitive groups into the corresponding aldehyde or

ketone.[16] Oxidation of cyclobutanols has been reported using Ru(VIII)[17] and Cr(VI)[18] based reagents (Scheme 1).

Hypervalent iodine reagents are becoming increasingly appreciated for their mild and highly chemoselective oxidizing properties. Their use has been limited due to lack of stability and poor solubility.[1] Unlike other iodine (V) compounds, Dess-Martin periodinane (DMP) is a stable compound with high solubility in most organic solvents.[19] DMP has several advantages over Cr- and Ru-based oxidants, including milder conditions, higher yields, simplified workups, and tolerance to sensitive functional groups.[20] DMP is especially useful for the oxidation of optically active epimerization-sensitive substrates, such as cyclobutanic compounds, without loss of enantiomeric excess.[21]

Sodium hypochlorite, a readily available, clean and cheap reagent, has been already reported as an efficient reagent for the oxidation of cyclobutanols to the corresponding ketones.[22]

As part of our ongoing investigations, directed to the obtention of enantiopure cyclobutane building blocks,[2,23] it was necessary to found optimized conditions for the oxidation of 2,2,3-trisubstituted cyclobutanols. Herein, we report our results in the oxidation of (1*S*,3*R*)-methyl 3-hydroxy-2,2-dimethylcyclobutanecarboxylate **1a** and methyl 2-((1*R*,3*R*)-3-hydroxy-2,2-dimethylcyclobutyl)acetate **1b** using different oxidizing agents, aimed at producing the corresponding cyclobutanones.

RESULTS AND DISCUSSION

Cyclobutanols **1a** and **1b** were obtained from (1*S*,5*S*)-α-pinene or (1*S*,5*S*)-(-)-verbenone (Scheme 2) via the corresponding methyl esters **4a** and **4b**, which were obtained through a previously described pathway.[24]

Esters **4a** and **4b** were treated with *m*-chloroperbenzoic acid in methylene chloride in absence of light for 3 days to render diesters **5a** and **5b** in fairly good yield. Cyclobutanols were obtained by controlled hydrolysis of the corresponding acetates using cold potassium hydroxide in methanol. The compounds **1a** and **4a** were already described by us[24] and the spectroscopical data of compounds **1b** and **4b** were in accordance with that reported previously for their enantiomers.[25]

Despite the unselective nature of RuO_4 as an oxidant, there are reports of the oxidation of cyclobutanic compounds using ruthenium-based oxidants.[17] We performed the reaction in an heterogeneous phase with a catalytic amount of RuO_4 using $NaIO_4$ as reoxidant. However, reproducibility was not obtained due to the variability in yields of the desired product **2a**. The isolation of this product from the reaction mixture was difficult because some byproducts were present (Scheme 3).

The same results were obtained when the oxidation of cyclobutanol **1b** was attempted (Table 1, entry 1).

PDC has been successfully used in the oxidation of a structurally-related primary alcohol,[23] hence we decided to try it on the oxidation of **1a** and **1b**. The reaction was carried out in methylene chloride at room temperature. In this case, cyclobutanones **2a** and **2b** were obtained

together with other products (Scheme 3). The yields obtained, using this oxidizer, are shown in Table 1, entry 2.

Taking into account the results obtained using metal-based reagents, the search for efficient reaction conditions persisted. To this end, we evaluated sodium hypochlorite as an oxidant for compounds **1a** and **1b**. The reaction, performed in acetic acid with aqueous NaOCl at 0 ºC, produced only one compound in each case. These products resulted different to the ones expected (Table 1, entry 3). As confirmed by NMR spectroscopy, these compounds were the same as the main byproducts observed in the Ru- and Cr-based reactions. Analysis of mono- and bidimensional ^{1}H and ^{13}C NMR spectra allowed us to establish the structure of these new products.

HSQC NMR data for compound **3a** (Figure 1) showed the methylenic hydrogen atoms at 3.07 ppm and 2.69 ppm both joined to the δ 31.7 ppm carbon atom. In the case of **3b**, the two methylenic carbon atoms appeared in the ^{13}C-NMR spectrum at 35.1 and 34.4 ppm. The spatial orientation of the geminal groups at the ring was assigned by NOESY spectra to the γ-butyrolactones **3**. (Figure 2).

Considering that two different regioisomeric γ-butyrolactones could have been obtained, the chemical shifts for the methylenic carbon atoms confirmed that the reaction proceeds by a Baeyer-Villiger-like (BV) rearrangement[26] rendering **3a** or **3b** as a sole product.

Little is known about the BV oxidation of cyclic ketones to lactones by hypochlorous acid.[27] HOCl resembles peroxyacids in being both a weak acid and an oxidizing agent. Hegedus et al.

synthesized (+)-cerulenin via a BV oxidation of cyclobutanones using *m*-chloroperbenzoic acid.[28] There are some precedents in the treatment of a cyclobutanone with ruthenium tetroxide in the presence of aqueous hypochlorite. The products reported were the two possible lactones.[13] However, to the best of our knowledge this is the first time a γ-butyrolactone is reported as the only product in the NaOCl-oxidation of cyclobutanols derived from terpenes. With this in mind, the obtention of only one regioisomeric γ-butyrolactone can be rationalized through the migration of the quaternary carbon atom, over the secondary one, on the intermediate cyclobutanones **2**.

Moreover, we assayed the oxidation of cyclohexanol using sodium hypochlorite. Although, in this case only the cyclohexanone was obtained. The different ring strain energies between these cycloalkanones (cyclohexanone; 3 kcal/mol vs cyclobutanone; 25 kcal/mol)[29] could explain this differential behavior.

Finally, considering the previously cited advantages of DMP as a mild oxidant, we assayed this reagent on the oxidation of alcohols **1a** and **1b**. This reaction was performed in methylene chloride at room temperature. Notably, it took only one hour to afford cyclobutanones **2a** and **2b** as the only product with high yields, 78-93%. (Table 1, entry 4). The unequivocal assignment of their structures was made by bidimensional NMR, HSQC and NOESY spectra, and is shown in Figure 2.

In summary, we found that DMP is the only reagent capable of affording cyclobutanones **2a** and **2b** from 2,2,3-trisubstituted cyclobutanols derived from terpenes (**1a** and **1b)** without byproducts. Additionally, sodium hypochlorite allowed the effective preparation of homochiral γ-butyrolactones **3a** and **3b**, useful starting materials for the preparation of nucleosidic

compounds,[30] from the same substrates, without the isolation of the corresponding ketones **2a** and **2b**.

EXPERIMENTAL

All the reactions were carried out in oven-dried flasks. Flash column chromatography was performed on Kieselgel 60 silica. Commercially available reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over Na_2SO_4. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, or 2.2 % v/v ethanolic *p*-anisaldehyde.

Optical rotations were recorded on a Perkin-Elmer 343 polarimeter with a 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Nicolet 380 FT-IR spectrometer as a thin film on NaCl plates. NMR spectra were recorded on a Bruker Avance 500 spectrometer in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm. High resolution mass spectra were obtained on a Bruker micrOTOF-Q II™ spectrometer. (1*S*,5*S*)-α-pinene and (1*S*,5*S*)-(-)-verbenone were purchased from Acros Organics and were used without purification.

Sample Experiments

(1S)-Methyl 2,2-dimethyl-3-oxocyclobutanecarboxylate (2a)[24]: DMP (1.38 g, 3.25 mmol, 1.3 equiv) was added to a solution of **1a** (410 mg, 2.6 mmol) in CH_2Cl_2 (10 mL) at 0 ºC.

The resultant solution was stirred at 0 °C for 1 h. The white precipitate was filtered then 10 % (w/v) aq $Na_2S_2O_3$ (6 mL) was added and the product mixture was stirred for 15 min. The organic layer was separated, washed with satd aq $NaHCO_3$ (2x7mL) and brine (2x7mL), then dried and concentrated under vacuum to afford **2a** (380 mg, 94%). $[\alpha]_D$ + 17.7 (*c* 1.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (s, 3H), 1.26 (s, 3H), 2.92 (dd, *J*= 9.0 Hz, 7.4 Hz, 1H), 3.05 (dd, *J*= 17.9 Hz, 8.9 Hz, 1H), 3.48 (dd, *J*= 17.9 Hz, 7.3 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3, 23.0, 40.5, 44.7, 51.9, 64.3, 172.5, 211.1; IR: 2956, 2871, 1784, 1728, 1437, 1354, 1178, 1065 cm^{-1}. HRMS calcd for $C_8H_{13}O_3$ (MH+) m/z 157.0859, found m/z 157.0859.

Methyl 2-((3S)-tetrahydro-5,5-dimethyl-2-oxofuran-4-yl)acetate (3b): NaOCl {17% (w/v) in H_2O, 4 mL, 9 mmol, 15 equiv} was added dropwise to a solution of **1b** (100 mg, 0.58 mmol) in AcOH (2 mL) at 0 ºC. The resultant solution was stirred at 0 °C for 2 h, and then extracted with CH_2Cl_2 (15 mL). The organic extract was washed with satd aq $NaHCO_3$ (2x10mL), then dried and concentrated under vacuum to afford **3b** as a pale yellow oil (90 mg, 83 %). $[\alpha]_D$ -22.3 (*c* 0.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.48 (s, 3H), 2.35 (d, *J*= 10.1 Hz, 1H), 2.38 (dd, *J*= 10.2 Hz, 1.7 Hz, 1H), 2.52 (dd, *J*= 15.8 Hz, 4.9 Hz, 1H), 2.72 (m, 1H), 2.84 (dd, *J*= 17.4 Hz, 8.2 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 27.3, 34.4, 35.1, 41.5, 52.1, 85.8, 171.8, 174.9; IR: 2976, 1774, 1736, 1438, 1377, 1313, 1267, 1171 cm^{-1}. HRMS calcd for $C_9H_{14}O_4Na$ m/z 209.0790, found m/z 209.0784.

Acknowledgements

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Supporting Information: Full experimental detail and ^{1}H and ^{13}C NMR spectral can be found via the "Supplementary Content" section of this article's webpage.

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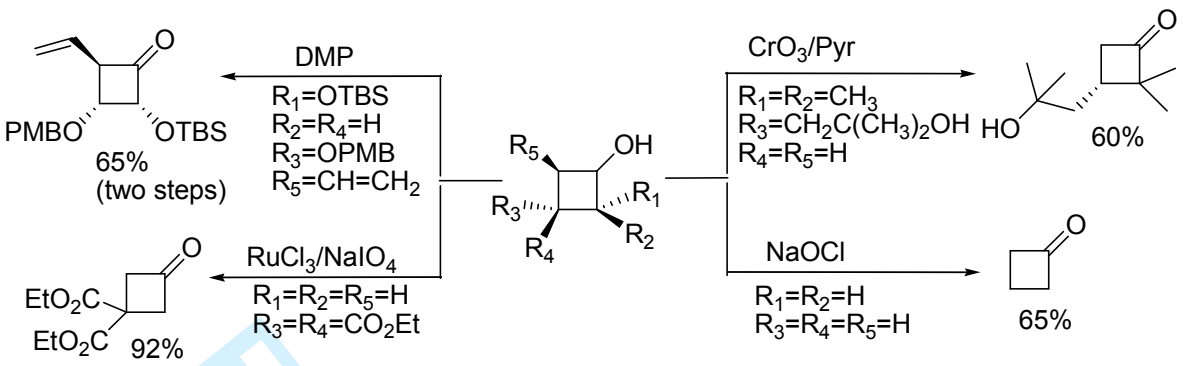

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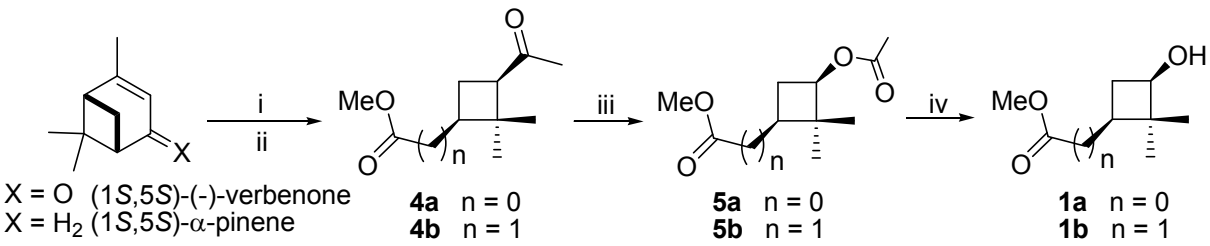

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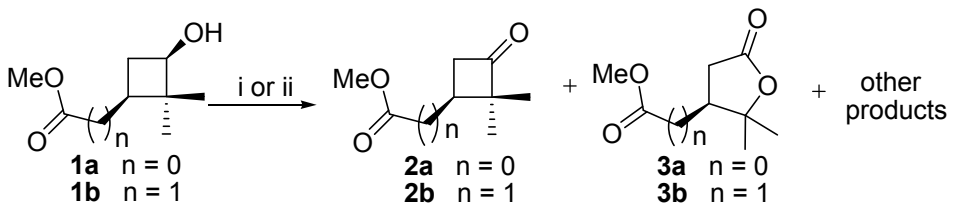

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3	NaOCl	**3a** 70[b]	**3b** 83[b]
4	DMP	**2a** 93[b]	**2b** 78[b]

a: Calculated from NMR spectra integrations.

b: Isolated yield.

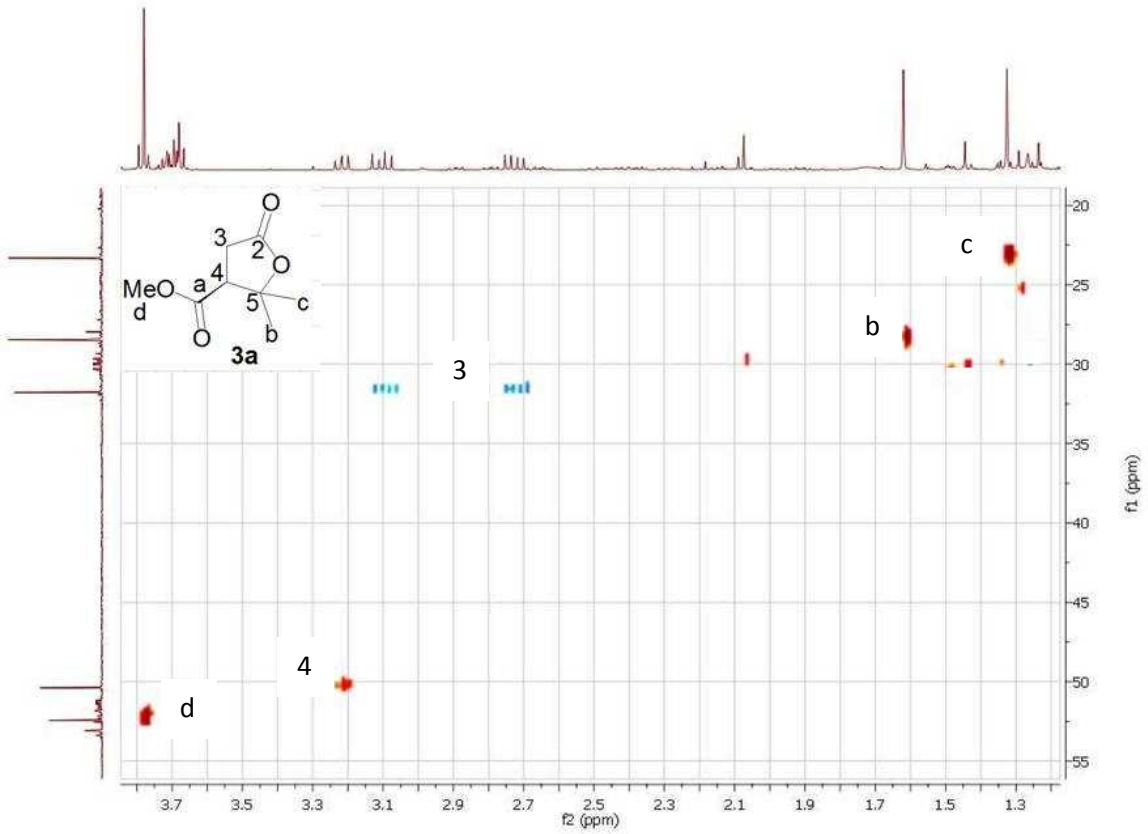


Figure 1. HSQC NMR spectrum of γ-butyrolactone **3a**.

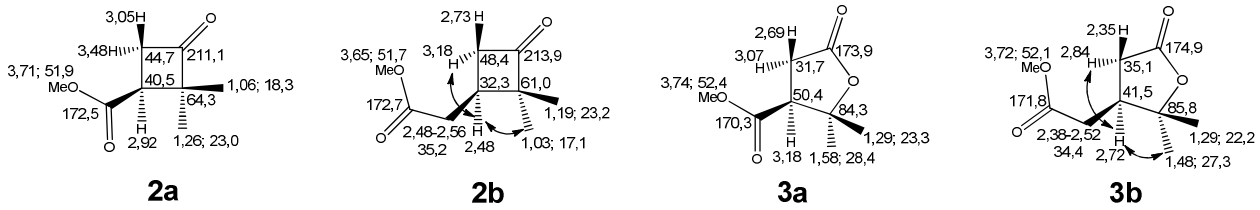
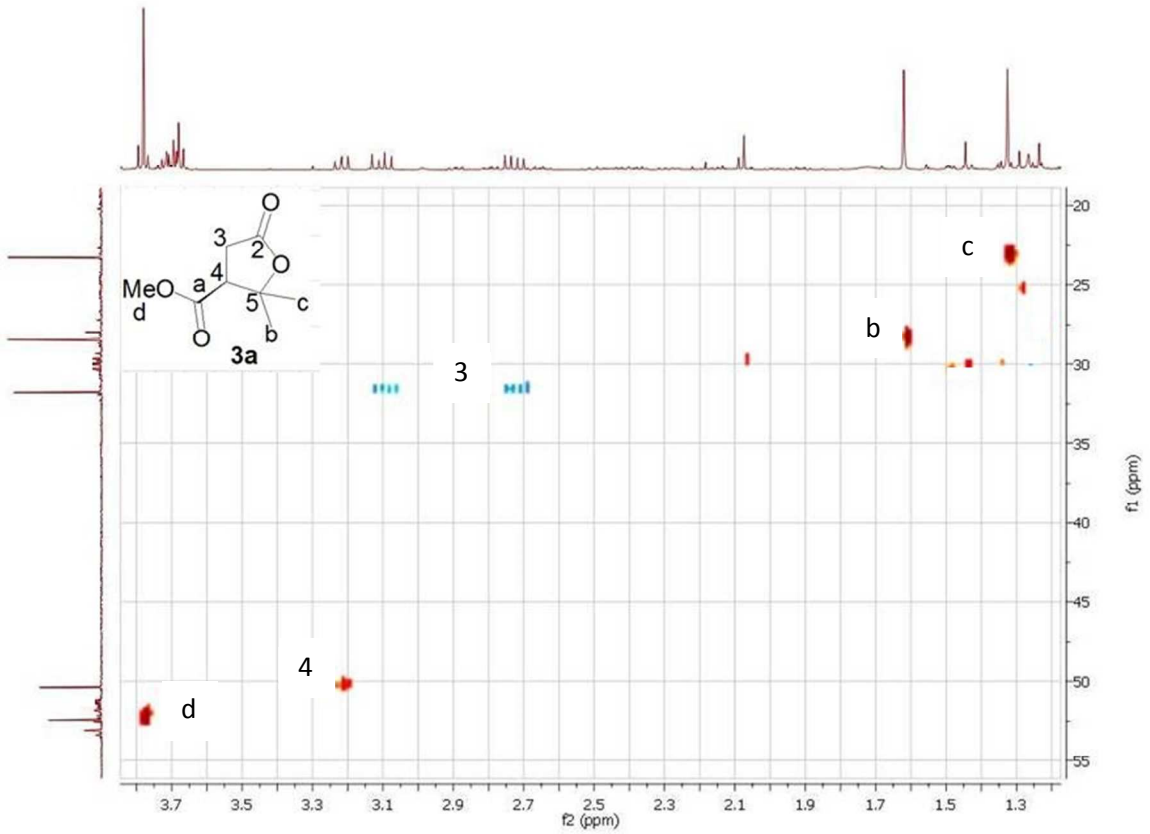


Figure 2. Structural assignment of cyclobutanones **2a**, **2b** and γ-butyrolactones **3a**, **3b**. NOE correlations are shown by doble arrow.



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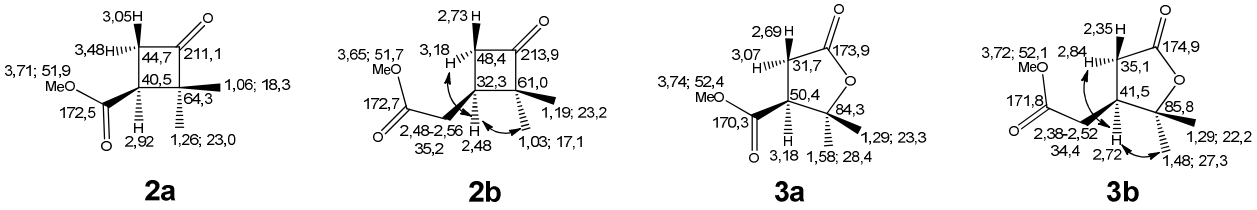

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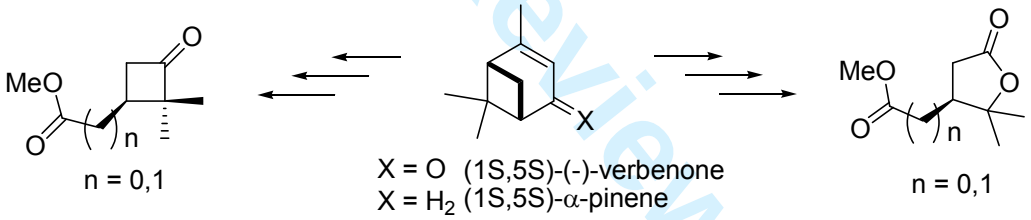
Juan A. Caturelli Kuran and Albertina Moglioni.*

Departamento de Farmacología. Facultad de Farmacia y Bioquímica. Universidad de Buenos Aires. Junín 956, Buenos Aires, C1113AAD, Argentina.

Email: amoglio@ffyb.uba.ar



Supporting Information

Supporting Informations

Differential oxidation conditions of substituted cyclobutanols derived from terpenes.

Juan A. Caturelli Kuran and Albertina G. Moglioni.*

Departamento de Farmacología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, Buenos Aires, (C1113AAD), Argentina.

Table of Contents:

Supporting Information

General Methods:

All the reactions were carried out in oven-dried flasks. Flash column chromatography was performed on Kieselgel 60 silica. Commercially available reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over Na_2SO_4. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, or 2.2 % v/v ethanolic *p*-anisaldehyde.

Optical rotations were recorded on a Perkin-Elmer 343 polarimeter with a 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Nicolet 380 FT-IR spectrometer as a thin film on NaCl plates. NMR spectra were recorded on a Bruker Avance 500 spectrometer in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm. High resolution mass spectra were obtained on a Bruker micrOTOF-Q II™ spectrometer. (1*S*,5*S*)-α-pinene and (1*S*,5*S*)-(-)-verbenone were purchased from Acros Organics and were used without purification.

Experimental Procedure and Product Characterization

Representative procedure A: Ru-based oxidation of cyclobutanols

A solution of RuO_4 in CCl_4 was prepared by mixing a solution of $RuCl_3$ hydrate (Ru content 45%, 178 mg, 0.86 mmol) in CCl_4 (100 mL) with a solution of $NaIO_4$ (900 mg, 4.2 mmol) in H_2O (100 mL). The two-phase system was stirred overnight, then the organic layer was separated and the aqueous layer was extracted with CCl_4 (2 x 30 mL). The combined organic extracts were used in the subsequent oxidation.

Supporting Information

The RuO_4 solution (5.38 μmol/mL, 0.13 mol %) was added dropwise (5.2 mL) to a solution of the requisite cyclobutanol (1.0 equiv) in $CHCl_3$ (20 mL), then a solution of $NaIO_4$ (2.2 equiv) in H_2O (20 mL) was added. The two-phase system was stirred for 24 h at rt. The organic layer was run off and the aqueous layer was extracted with CH_2C1_2. The combined organic extracts were washed with brine, then dried and concentrated under vacuum to provide a mixture of **2** and **3** as a yellow oil.

Representative procedure B: Cr-based oxidation of cyclobutanols

PDC (1.1 equiv) was added to a solution of the requisite cyclobutanol (1.0 equiv) in CH_2Cl_2 (81 mL). The resultant solution was bubbled with nitrogen and stirred for 4 h at rt. Celite® (3g) was added and stirring was continued for 5 min. The solution was vacuum filtered through Celite®. The clear organic solution was washed with brine, then dried and concentrated under vacuum to afford a mixture of **2** and **3** as a yellow oil.

Representative procedure C: NaOCl-mediated oxidation of cyclobutanols

NaOCl (14 equiv) was added dropwise to a solution of the requisite cyclobutanol (1.0 equiv) in AcOH (6 mL) at 0 ºC. The resultant solution was stirred at 0 °C for 2 h, and then extracted with CH_2Cl_2. The organic extract was washed with satd aq $NaHCO_3$, then dried and concentrated under vacuum.

Representative procedure D: DMP-mediated oxidation of cyclobutanols

DMP (1.3 equiv) was added to a solution of requisite cyclobutanol (1.0 equiv) in CH_2Cl_2 (10 mL) at 0 ºC. The resultant solution was stirred at 0 °C for 1 h. The white precipitate was filtered then 10

% (w/v) aq $Na_2S_2O_3$ (6 mL) was added and the product mixture was stirred for 15 min. The organic layer was separated, washed with satd aq $NaHCO_3$ and brine, then dried and concentrated under vacuum.

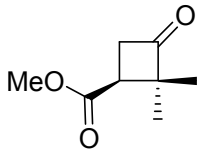
Methyl 2-((1R)-2,2-dimethyl-3-oxocyclobutyl)acetate (2b): Following *general procedure D*, reaction of **1b** (270 mg, 1.57 mmol) and DMP (840 mg, 1.98 mmol) afforded **2b** as an oil (210 mg, 79%). $[\alpha]_D$ = - 1.4 (*c* 0.65, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (s, 3H), 1.19 (s, 3H), 2.48 (m, *J*= 7.4 Hz, 4.9 Hz, 2H), 2.56 (dd, *J*= 10.5 Hz, 8.5 Hz, 1H), 2.73 (dd, *J*= 17.9 Hz, 6.6 Hz, 1H), 3.18 (dd, *J*= 17.6 Hz, 8.2 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.1, 23.2, 32.3, 35.2, 48.4, 51.7, 61.0, 172.7, 213.9; IR: 2956, 2924, 2852, 1778, 1736, 1464, 1186 cm^{-1}. All spectroscopical data are in accordance with that described for its enantiomer.[1]

(3S)-Methyl tetrahydro-5,5-dimethyl-2-oxofuran-4-carboxylate (3a): Following *general procedure C*, reaction of **1a** (320 mg, 2.02 mmol) and NaOCl {17% (w/v) in H_2O, 12 mL, 27 mmol} afforded **3a** as a pale yellow oil (242 mg, 70 %). $[\alpha]_D$ = +4.0 (*c* 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.58 (s, 3H), 2.69 (dd, *J*= 17.9 Hz, 8.7 Hz, 1H), 3.07 (dd, *J*= 17.9 Hz, 9 Hz, 1H), 3.18 (t, *J*= 9 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.3, 28.4, 31.7, 50.4, 52.4, 84.3, 170.3, 173.9; IR: 2956, 1780, 1735, 1437, 1361, 1172, 1120 cm^{-1}. All spectroscopical data are in accordance with that described for its enantiomer.[2]

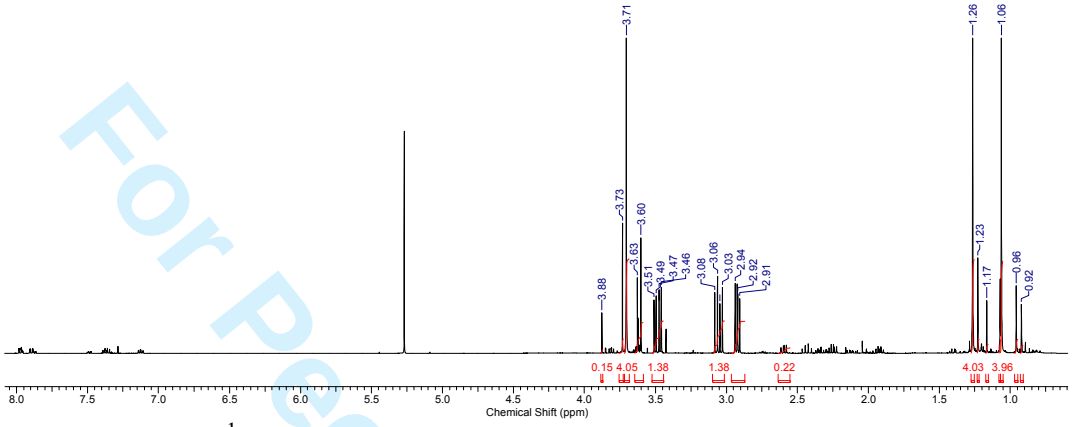
References

1. Pirrung, M. C.; Chang, V. K.; DeAmicis, C. V. Mechanism and synthetic applications of the photochemical generation and X-H insertion reactions of oxacarbenes. *J. Am. Chem. Soc.* **1989**, *111*, 5824–5831.
2. Jacobine, A. M.; Lin, W.; Walls, B.; Zercher, C. K. Formation of γ-lactones through CAN-mediated oxidative cleavage of hemiketals. *J. Org. Chem.* **2008**, *73*, 7409-7412.

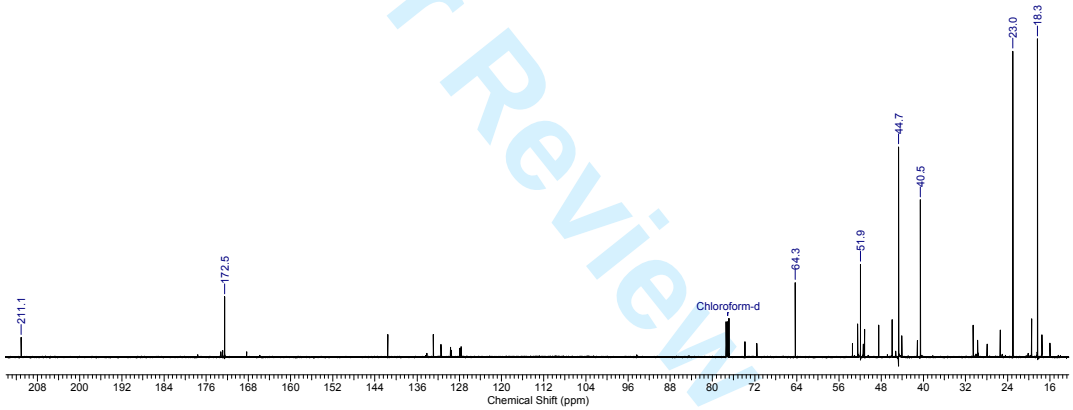
Supporting Information



2a



^{1}H NMR spectrum of **2a** (500 MHz, $CDCl_3$)



^{13}C NMR spectrum of **2a** (125 MHz, $CDCl_3$)

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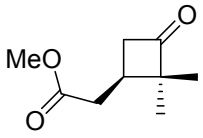
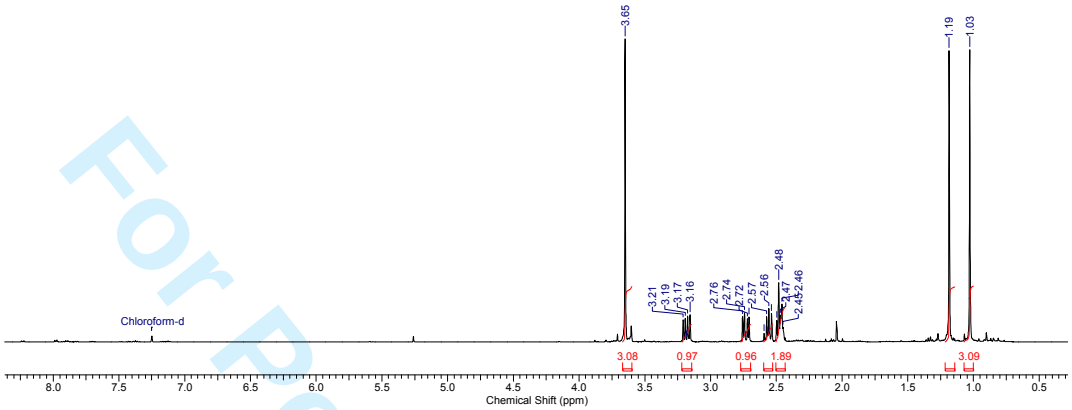


2b



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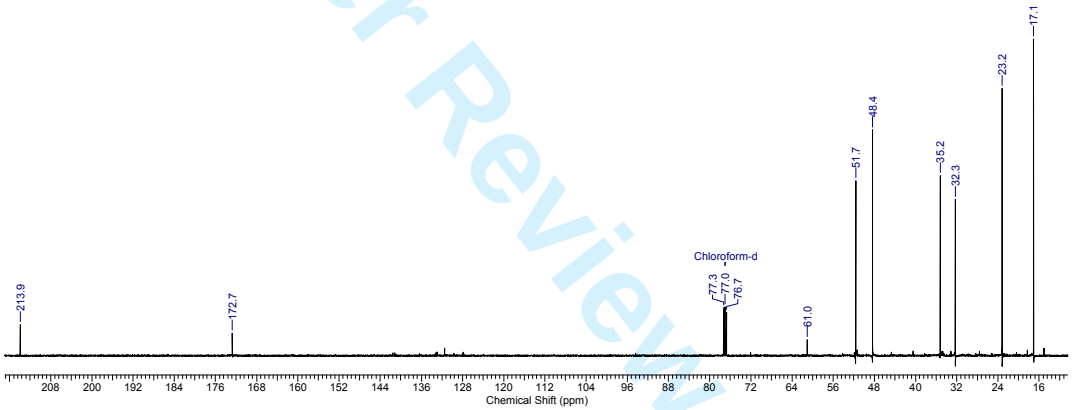

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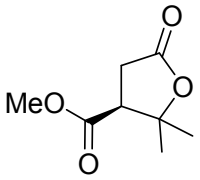
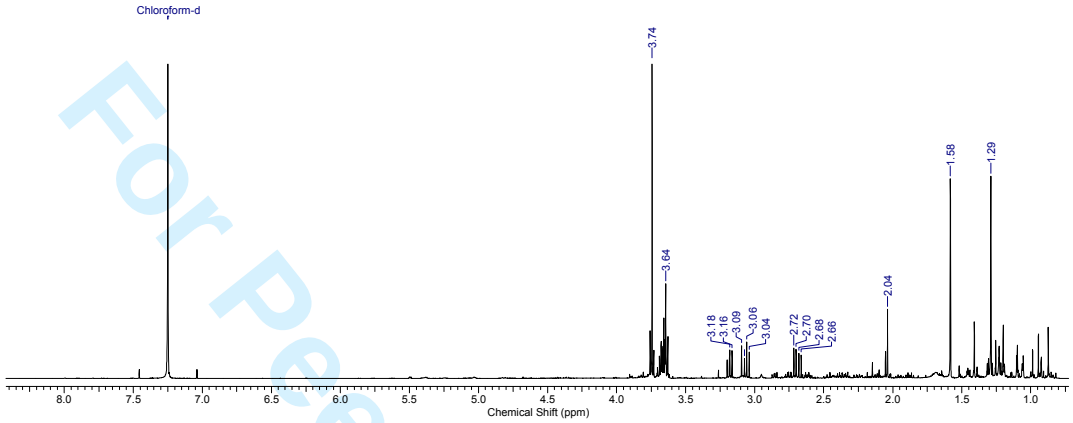


3a



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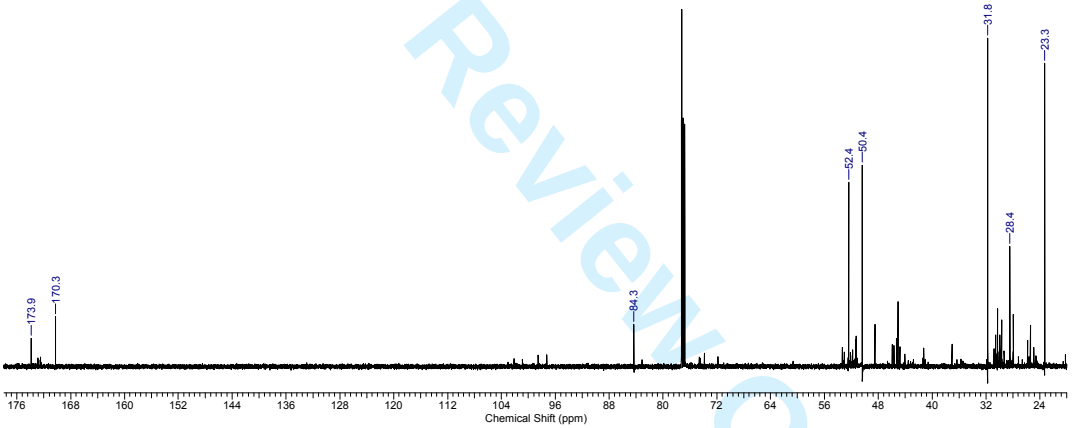

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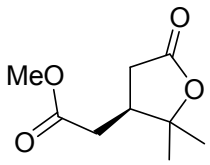
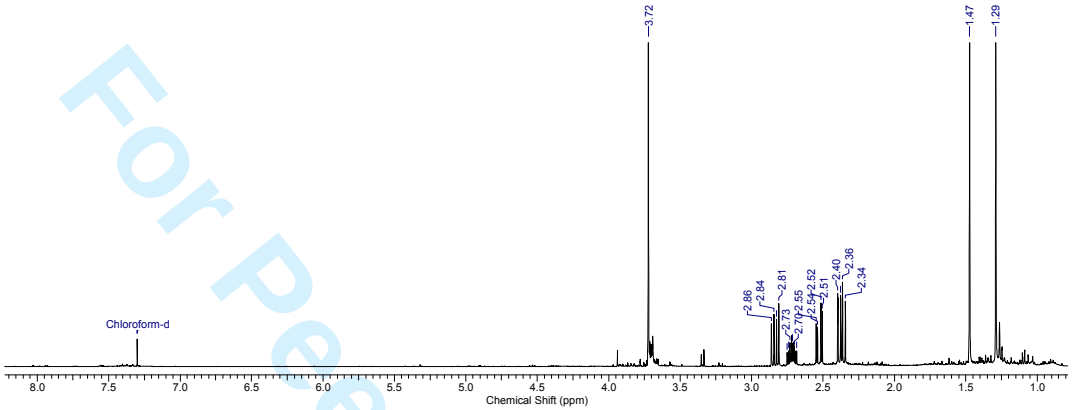


3b



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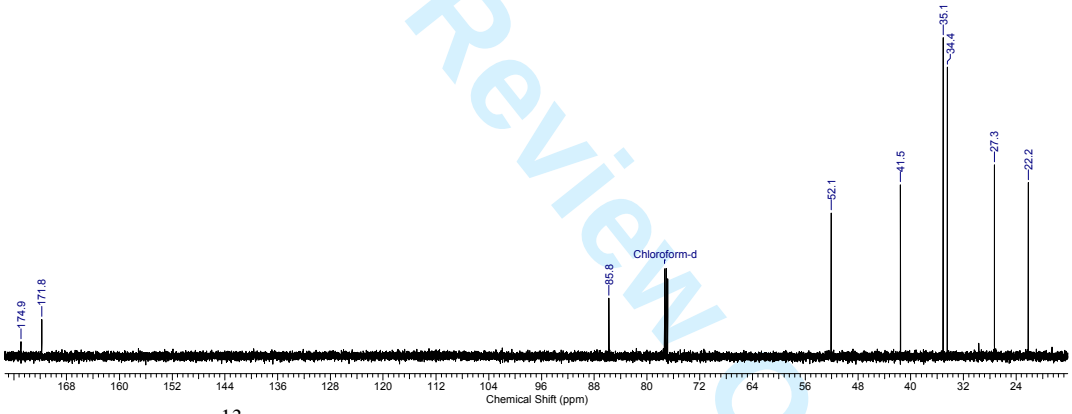

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