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Regiodivergent Synthesis of *ortho*- and *para*-Cannabinoquinones

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We would like to dedicate this article to Prof. Marco D'Ischia for his remarkable work on the oxidation of phenolic natural products

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Abstract: Spurred by the remarkable biological profile of cannabinoquinoids, we have systematically investigated the periodinane oxidation of their resorcinolic precursors, discovering that the regiochemistry of oxidation, a critical maneuver for bioactivity, depends not only on the nature of the oxidant (λ^3 - vs λ^5 -iodanes), but also on post-oxidative prototropic- and valence tautomeric equilibria that isomerize *ortho*-quinones to *para*-quinones. By complementary selection of the periodinane oxidant and by freezing prototropic equilibrium with *O*-methylation, isomeric *ortho*- and *para*-quinones could be obtained from mono- and diphenolic cannabinoids, setting the stage for the exploration of novel areas of the biological space, and establishing a blueprint for the extension of this strategy to other classes of bioactive alkylresorcinols.

Introduction

The development of a deep-violet color upon treatment of hashish with bases under aerobic conditions was first re-reported in 1911, at the outset of studies on cannabinoids.^[1] This chromatic oxidative reaction (Beam test) was then extensively used as a forensic assay for narcotic cannabis (hashish, marijuana), even though, as studies progressed, it became clear that only non-narcotic diphenolic cannabinoids like cannabidiol (CBD, **1a**, Figure 1) and cannabigerol (CBG, **2a**) develop a color under the conditions of the assay.^[2] The hydroxylated *para*-quinone structures **3a** and **4a** were assigned to the colored pigments formed by oxidation of, respectively, CBD and CBG (**3a** and **4a**, respectively),^[2] but the nature of the quinones obtained from monophenolic cannabinoids like Δ^9 -tetrahydrocannabinol (Δ^9 -THC, **5a**) and cannabinol (CBN, **6a**) was long debated.^[3] In these compounds, the tautomeric interconversion of *o*- and *p*-hydroxyquinoid forms is locked (Scheme 1), and both structures can, in principle, exist (see *infra*). These uncertainties were eventually clarified by an X-ray study of the quinones formed by λ^3 -iodane [phenyliodine (III)bis(trifluoroacetate), PIFA] oxidation of Δ^8 -THC (**5b**) and CBN (**6a**), unambiguously assigning a *p*-

quinone structure to both oxidation products (**7b** and **8a**, respectively).^[3] A *p*-quinone structure was then assigned by default to all cannabinoquinoids next reported by isolation^[4,5] or by semi-synthesis.^[6,7]

(Insert Figure 1 here)

Figure 1. Examples of cannabinoids and cannabinoquinoids.

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(Insert Scheme 1 here)

Scheme 1. Tautomeric interconversion of hydroxy *o*- and *p*-cannabinoquinoids (R^1 = alkyl, R^2 = terpenyl).

After an initial and then faded excitement for the selective anti-cancer activity of cannabinoquinoids,^[3] interest was re-kindled by the discovery of the immunomodulating properties of VCE.004.8 (**9**),^[7] a 2-aminoalkylderivative of cannabidiolquinone (CBDQ, **3a**) currently undergoing Phase II clinical development under orphan drug designation in EU and USA and fast track status in USA for systemic sclerosis, an autoimmune disease.^[8] An improved and scalable synthesis of CBDQ (**3a**) was developed using SIBX,^[9] a non-explosive formulation of the λ^5 -iodane iodoxybenzoic acid (IBX) as the oxidant,^[10] while the electrochemical version of the oxidation of cannabinoids to cannabinoquinoids was investigated in the context of the development of a marijuana breathalyzer based on the formation of the quinone **7a** from Δ^9 -THC (**5a**).^[11] These developments provided a rationale to systematically explore the chemical and biological space of cannabinoquinoids.

Results and Discussion

Cannabinoquinones are chemically unstable, and *O*-methylation was investigated as a stabilizing maneuver alternative to the aza-Michael addition/dehydrogenation strategy that led to the discovery of VCE004.8.^[7] Two alkylation strategies were investigated, namely, the direct methylation of CBDQ (**3a**), the SIBX oxidation product of CBD,^[9] or, alternatively, the SIBX oxidation of *O*-methyl CBD (**1b**), a natural constituent of cannabis.^[12] Despite the use of the same iodane oxidant, the two strategies afforded a different quinone as the only reaction product (**3b** and **10**, respectively) (Scheme 2). *O*-Methylation of cannabinoquinoids is associated to modulation properties on the NRF2-BACH1 axis, a phenotype not expressed by their corresponding natural phytocannabinoids and quinones.^[13] The relevance of this profile for the management of neurodegenerative diseases^[13] made the clarification of the structure of the methylation products and of the regiochemical aspects of their synthesis a critical issue.

(insert Scheme 2 here)

Scheme 2. Chemoselective formation of isomeric *O*-methylcannabinoquinones.

The ¹H NMR spectra of the isomeric quinoids **3b/10** were very similar (See Supporting Information), but two distinctive differences were present in the low-field region of their ¹³C NMR spectra. Thus, the methoxy-substituted olefin carbon (C-5') resonated at δ 164.4 in **10**, and δ 156.8 in **3b**, and also the carbonyl signals were shifted downfield in **10** compared to **3b** (δ 187.8 and 184.1 vs δ 180.6 and 178.6). Due to its more electrophilic nature, an *ortho*-quinone carbonyl is a better electron sink than a *para*-quinone carbonyl for the mesomeric delocalization of the oxygen lone pair of the 5'-methoxy group. The contribution of the dipolar resonance form where C-5' is part of an oxonium ion, is therefore larger in *ortho*-cannabinoquinones compared to *para*-cannabinoquinones (Scheme 3), rationalizing the marked downfield shift of C5' in **10** when compared to **3b**.

(Insert Scheme 3 here)

Scheme 3. Dipolar resonance formulas of methoxy-substituted *ortho*- and *para*-cannabinoquinones (R^1 = n -C₅H₁₁, R^2 = terpenyl).

Additionally, a NOESY correlation between the methoxy group and the single quinone proton (H-4' in **10**, H-2' in **3b**) was observed only in **10**. Overall, these observations identified **3b** as a *para*-quinone, and **10** as an *ortho*-quinone, establishing a simple and clear-cut differentiation between compounds of the two classes, additionally supported by a set of 2D NMR experiments (full NMR assignment of **3b** and **10** is reported as Supporting Information). Similar observations were done for the preparation of *O*-methylcannabigerquinone (*O*-methyl CBGQ) by methylation of the corresponding quinone (CBGQ, **4a**), or, alternatively, by oxidation of *O*-methylcannabigerol (**2b**), providing a second pair of isomeric quinones (**4b** and **11**, respectively) whose spectroscopic features fully matched those of the **3b/10** pair.

SIBX has been reported to selectively oxidize 2-alkylphenols to 2-hydroxycyclohexadienones (*o*-quinols), and some simple phenols lacking *o*-substituents to *o*-quinones,^[15] with the tendency for functionalization of the *ortho*-position being also backed up by DFT calculations.^[16] The opposite site-selectivity observed with CBD (**1a**) and CBG (**2a**)^[10] is presumably the result of tautomeric isomerization of originally formed *o*-quinones (Scheme 1, C) to their more stable and intramolecularly hydrogen-bonded *para*-tautomers (Scheme 1, A). On this basis, the impossibility of tautomeric equilibration could provide a simple explanation as to why the oxidation of the *O*-methyl analogues of CBD and CBG (**1b** and **2b**, respectively) gave exclusively *o*-quinones and not the *p*-quinones obtained from their corresponding resorcinols.

(Insert Figure 2 here)

Figure 2. Additional cannabinoquinoids synthesized. TBDMS = *tert*-butyldimethylsilyl.

A similar chemoselectivity was also observed with monophenolic cannabinoids where one resorcinolic oxygen is linked by an ether bond to the isoprenoid moiety [Δ^8 -THC (**5b**), CBN (**6a**), and their dimethylheptyl analogues (**5c**, **6b**)], that all afforded *o*-quinones as the only reaction products (**13a**, **14a**, **13b**, and **14b**, respectively).^[16] Conversely, the oxidation of Δ^8 -THC (**5b**) and CBN (**6a**) with the λ^3 -periodinane PIFA exclusively afforded the *p*-quinones **7b** and **8a**, in accordance to the literature report.^[3] To demonstrate the post-oxidative tautomerization of hydroxy *o*-quinones to hydroxy *p*-quinones, an attempt was done to oxidize the monosilyl ether of CBD (**1c**) to the *o*-quinone **12**, that was expected to next generate the *p*-quinone **3a** by desilylation. However, the acidity of SIBX led to silyl loss in the course of the reaction, and **3a** was, instead, directly obtained.

A tautomeric equilibrium of different type could underlie the exclusive formation of the *p*-quinones **16a** and **16b** from the SIBX oxidation of cannabichromene (CBC, **15a**) and its dimethylheptyl analogue (**15b**) (Figure 3).

(Insert figure 3 here)

Figure 3. Quinones formed from the oxidation of cannabichromene-type cannabinoids. (geranyl = (*E*)-Me₂C=CH-CH₂-(Me)CH=CH-CH₂).

Cannabichromene (CBC, **15a**) shows a remarkable reactivity associated to valence tautomerism,^[17] and the regiochemistry of the oxidation could be the result of this tautomeric manifold,

declined in terms of electrocyclic opening of the *o*-quinone chromene ring to an alkylidientrione, re-aromatization isomerization of the proximal olefin double bond, and eventual electrocyclization on the α -dicarbonyl system to a *p*-quinone (Scheme 4). This mechanistic rationale was backed up by the formation of a mixture of the *o*-quinone **17** and *p*-quinone **16c** from the oxidation of **15c**, the bis-prenylogue analogue of **15b**. The mixture could be resolved by gravity column chromatography, but the *o*-quinone **17** could not be stored and isomerized spontaneously to **16c**.

(Insert Scheme 4 here)

Scheme 4. Possible mechanism for the isomerization of *o*-CBCQ to *p*-CBCQ (**16a**) by chromene-alkylidientrione valence tautomerism ($R_1 = nC_5H_{11}$, $R_2 =$ isoprenyl).

Some mechanistic hypotheses on the observed regioselectivity of periodinane oxidation are worth discussing.^[18] The reaction is started by ligand exchange on iodine and formation of an aryloxyiodonium species (Scheme 5). Next, assuming a two-electrons process,^[18] an iodonium (III) intermediate could undergo nucleophilic attack by an external water molecule (or by trifluoroacetic acid), preferentially at the less encumbered *para*-position. Elimination of *o*-iodobenzoic acid and formation of a hydroquinone could next follow, with ligand exchange on iodine and elimination, this time triggered by phenol deprotonation, eventually affording a *p*-quinone (Scheme 5, A).^[19,20] With an iodonium (V) intermediate, the oxidation can occur intramolecularly by [2,3]-sigmatropic rearrangement of the iodine-oxygen bond, a process isosterically equivalent to the orthologue *N*-S sigmatropic shift in the Gassman indole synthesis (Scheme 5, B).^[21] β -Elimination of iodobenzoic acid will next afford an *o*-quinone, either directly as in Scheme 5, or after isomerization of the *o*-quinol ester to a catechol ester.^[22] Longer [2,*n*] sigmatropic shifts of heteroatomic bonds, as in the semidine rearrangement,^[23] are apparently disfavored in aryloxydiodonium (V) species, since, with the exception of **17**, mixture of regioisomeric quinones were never observed as primary oxidation products. λ^3 -Periodinanes can only react with the intermolecular mechanism, and therefore normally generate *p*-quinones because steric effects shield the *o*-position from nucleophilic attack.

(Insert Scheme 5 here)

Scheme 5. Possible mechanism for the formation of *p*-quinones and *o*-quinones from aryloxyiodonium (III) and aryloxyiodonium (V) intermediates (A and B) from, respectively, PIFA and SIBX.

Ortho- and *para*-cannabinoquinoids showed differences not only in their color, particularly marked in the quinones from CBN because of aryl conjugation (See the Graphical Abstract) but, as expected, also in their stability. The *o*-quinone of CBG (**11**) was unstable at room temperature, possibly due to polymerization induced by the presence of the nucleophilic isoprenyl terminal bond, but could be fully characterized, as could **17**, despite its quick valence isomerization to **16c**. All the other *o*-cannabinoquinoids (**10**, **12**, **13a**, **13b**, **14a**, **14b**) showed acceptable shelf life, although lower than the one of their corresponding *p*-isomers.

Conclusion

The complementary use of λ^3 - and λ^5 -iodanes, as such or associated to *O*-methylation to block post-oxidative tautomeric equilibria, represents an interesting diversification strategy for phenolic lead structures. This opportunity, as well as the possibility to use SIBX for the synthesis of *p*-quinones, has so far overlooked, despite its mechanistic rationale and its potential to provide a blueprint to explore novel areas of the biological space associated to phenolic lead structures.

Experimental Section

General: IR spectra were recorded on an Avatar 370 FT-IR Techno-Nicolet apparatus. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were measured on Bruker Avance 400 MHz spectrometer or on a Bruker Avance 500 MHz. Chemical shifts were referenced to the residual solvent signal (CDCl_3 : $\delta_{\text{H}} = 7.21$, $\delta_{\text{C}} = 77.0$). Homonuclear ^1H connectivities were determined by the Correlation spectroscopy (COSY) experiment. One-bond heteronuclear ^1H - ^{13}C connectivities were determined with the

heteronuclear single quantum coherence (HSQC) spectroscopy experiment. Two- and three-bond ^1H - ^{13}C connectivities were determined by gradient two-dimensional (2D) heteronuclear multiple bond correlation (HMBC) experiments optimized for a $^2J = 9$ Hz. Low- and high-resolution electrospray ionization mass spectrometry (ESI-MS) data were determined on an LTQ OrbitrapXL (Thermo Scientific) mass spectrometer. Reactions were monitored by thin-layer chromatography (TLC) on Merck 60 F254 (0.25 mm) plates, visualized by staining with 5% H_2SO_4 in EtOH and heating. Organic phases were dried with Na_2SO_4 before evaporation. Chemical reagents and solvents were purchased from Sigma-Aldrich and were used without further purification unless stated otherwise. Petroleum ether with boiling point of 40–60 °C was used. Silica gel 60 (70–230 mesh) was used for gravity column chromatography (GCC). All starting cannabinoids were available from previous studies in the area.^[9,13,17]

SIBX Oxidation of cannabinoids.

Oxidation of *O*-methyl CBD (1b**) as representative:** To a cooled (ice bath) solution of *O*-methyl CBD (**1b**, 200 mg, 0.61 mmol, $R_f = 0.47$, petroleum ether-EtOAc 95:5 as eluant) in ethyl acetate (10 mL), SIBX (39 wt. %, 1.44 g, 2.01 mmol, 3.3 molar equiv.) was added in small portions. At the end of the addition, the cooling bath was removed, and the suspension was stirred at room temperature, following the course of the reaction by TLC (R_f **10** = 0.19, petroleum ether-EtOAc 95:5). After 18 h, the reaction mixture was filtered over a pad of Celite. The filtration cake was washed with EtOAc (10 mL), and the pooled filtrates were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (4 × 15 mL) and next with brine. After drying and evaporation, the residue was purified by GCC on silica gel (10 g, petroleum ether-EtOAc 95:5 as eluant) to obtain 98 mg (47%) **10**. In all other iodane (SIBX, PIFA) oxidations, a similar difference in R_f values between reactants and reaction products was observed. The reaction yield is provided along with the description of their physical state for each product.

ortho-O-Methylcannabidiolquinone (Me-CBDQ, **10):** Dark red oi (47%)l, FT-IR (cm^{-1}): $\nu = 2955, 2924, 2857, 1643, 1431, 1107, 886$. ^1H NMR (CDCl_3 , 400 MHz) $\delta = 6.83$ (bs, H-4'), 5.06 (bd, $J = 2.5$ Hz, H-2), 4.56 (bs, H-9a), 4.52 (bs, H-9b), 3.87 (s, 5'-OMe), 3.65 (m, H-3), 2.67 (dt, $J = 9.2, 3.0$ Hz, H-4), 2.41 (t, $J = 7.5$ Hz, H-1''), 2.17 (m, H-6a), 2.04 (m, H-6b), 1.95 (m, H-5), 1.64 (bs, H-7), 1.61 (bs, H-10), 1.50 (m, H-2'), 1.32 (overlapped, H-3''), 1.30 (overlapped, H-4''), 0.89 (t, $J = 6.9$ Hz, H-5'). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 180.6$ (C-1'), 178.6 (C-2'), 164.4 (C-5'), 148.7 (C-8), 142.6 (C-4'), 133.0 (C-1), 128.0 (C-3'), 124.2 (C-6'), 123.6 (C-2), 110.4 (C-9), 45.1 (C-4), 31.8 (C-1'), 31.5 (C-3''), 30.6 (C-5), 30.4 (C-6), 30.2 (C-2''), 29.3 (C-3), 24.0 (C-7), 22.5 (C-4''), 18.5 (C-10), 14.5 (C-5''). ESI-MS m/z 343 $[\text{M}+\text{H}]^+$; HRESI-MS: m/z calcd. for $\text{C}_{22}\text{H}_{31}\text{O}_3$ $[\text{M}+\text{H}]^+$ 343.2273, found 343.2279.

ortho-O-Methylcannabigerolquinone (Me-CBGQ, **11):** Dark red oi (37%). FT-IR (cm^{-1}): $\nu = 2956, 2925, 2855, 1655, 1638, 1345, 1107$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 6.89$ (bs, 1H), 5.08 (m, 2H), 3.97 (s, 3H), 3.05 (d, $J = 7.4$ Hz, 2H), 2.37 (t, $J = 7.4$ Hz, 2H), 2.04 (m, 2H), 1.98 (m, 2H), 1.72 (bs, 3H), 1.67 (bs, 3H), 1.50 (bs, 3H), 1.49-1.32 (m, 6H), 0.90 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 180.6, 178.9, 163.3, 142.4, 136.1, 134.3, 131.3, 127.7, 124.3, 120.7, 56.6, 39.7, 31.4, 29.7, 27.9, 26.7, 25.7, 22.4, 21.6, 17.7, 16.1, 13.9$. HRESI-MS: m/z calcd. for $\text{C}_{22}\text{H}_{33}\text{O}_3$ $[\text{M}+\text{H}]^+$ 345.2430, found 345.2430.

ortho- Δ^8 -Tetrahydrocannabinolquinone (THCQ, 13a): Dark red oil (51%). FT-IR (cm^{-1}): $\nu = 2956, 2925, 2852, 1639, 1584, 1388, 1184, 1112$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 6.49$ (bs, 1H), 5.30 (bs, 1H), 3.10 (m, 1H), 2.49 (dt, $J_1 = 11.0$ Hz, $J_2 = 4.9$ Hz, 1H), 2.35 (t, $J = 7.7$ Hz, 2H), 2.12 (m, 1H), 1.83 (m, 1H), 1.75-1.20 (overlapped m, 6H), 1.45 (s, 1H), 1.21 (s, 6H), 0.91 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 181.2, 177.7, 162.9, 143.3, 134.4, 118.6, 114.9, 82.1, 43.6, 35.2, 31.4, 29.8, 28.7, 27.4, 27.1, 26.9, 23.3, 22.4, 19.4, 13.9$. HRESI-MS: m/z calcd. for $\text{C}_{21}\text{H}_{29}\text{O}_3$, $[\text{M}+\text{H}]^+ 329.2122$, found 329.2122.

3'-Depentyl-3'-(α,α -dimethylheptyl)-ortho- Δ^8 -tetrahydrocannabinol quinone (DMH-THCQ, 13b): Dark red oil (54%). FT-IR (cm^{-1}): $\nu = 2956, 2925, 2856, 1589, 1379, 1112, 919$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 6.38$ (bs, 1H), 5.31 (bs, 1H), 2.98 (m, 1H), 2.39 (dt, $J_1 = 11.1$ Hz, $J_2 = 5.0$ Hz, 1H), 2.02 (m, 1H), 1.74 (m, 1H), 1.67-1.49 (overlapped m, 8H), 1.37 (s, 1H), 1.27-0.89 (overlapped m, 16H), 0.78 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 180.7, 177.8, 162.9, 149.8, 134.7, 134.5, 118.6, 114.9, 82.2, 43.5, 40.6, 38.5, 35.1, 31.8, 29.8, 29.7, 27.3, 27.2, 27.1, 27.0, 25.1, 23.3, 22.7, 19.5, 14.1$. HRESI-MS: m/z calcd. for $\text{C}_{25}\text{H}_{37}\text{O}_3$, $[\text{M}+\text{H}]^+ 385.2672$, found 385.2677.

ortho-Cannabinolquinone (CBNQ, 14a): Purple oil (58%). FT-IR (cm^{-1}): $\nu = 2955, 2924, 2855, 1649, 1382, 1145, 1110, 811$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.30$ (s, 1H), 7.09 (d, $J = 8.9$ Hz, 1H), 7.02 (d, $J = 7.9$ Hz, 1H), 6.63 (bs, 1H), 2.40 (t, $J = 7.7$ Hz, 1H), 2.36 (s, 3H), 1.69 (s, 6H), 1.56 (m, 2H), 1.32 (m, 2H), 0.90 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 180.2, 175.3, 163.3, 144.7, 138.1, 133.8, 131.8, 128.9, 125.7, 122.3, 111.0, 82.7, 53.6, 31.6, 29.8, 29.0, 28.3, 27.4, 22.4, 21.4, 13.9$. HRESI-MS: m/z calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_3$, $[\text{M}+\text{H}]^+ 325.1798$, found 325.1791.

3'-Depentyl-3'-(α,α -Dimethylheptyl)-ortho-cannabinolquinone (14b): FT-IR (cm^{-1}): $\nu = 2955, 2924, 2856, 1649, 1376, 1145, 1110, 813$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.33$ (s, 1H), 7.12 (d, $J = 8.9$ Hz, 1H), 7.04 (d, $J = 7.9$ Hz, 1H), 6.63 (bs, 1H), 2.39 (s, 3H), 1.73 (s, 6H), 1.70 (overlapped m, 2H) 1.33-0.99 (m, 14H), 0.87 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 179.9, 176.4, 163.1, 151.2, 137.9, 134.1, 131.8, 128.9, 125.7, 124.6, 122.3, 110.8, 82.7, 40.6, 38.8, 31.7, 29.7, 29.7, 28.4, 27.3, 25.1, 22.6, 21.3, 14.0$. HRESI-MS: m/z calcd. for $\text{C}_{25}\text{H}_{33}\text{O}_3$, $[\text{M}+\text{H}]^+ 381.2430$, found 381.2437.

para-Cannabichromenquinone (CBCQ, 16a): Red oil (59%). FT-IR (cm^{-1}): $\nu = 2957, 2926, 2852, 1648, 1580, 1324, 1078, 969, 891$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 6.48$ (d, $J = 10.2$ Hz, H-1), 6.42 (s, H-2'), 5.57 (d, $J = 10.2$ Hz, H-2), 5.09 (bt, $J = 8.5$ Hz, H-6), 2.42 (t, $J = 8.5$ Hz, H-1'), 2.07 (m, H-5), 1.95 (m, H-4a), 1.66 (bs, H-8), 1.63 (overlapped, H-4b), 1.58 (bs, H-9), 1.50 (m, H-2''), 1.48 (s, H-10), 1.32 (overlapped, H-3''), 1.30 (overlapped, H-4''), 0.89 (t, $J = 6.9$ Hz, H-5''). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 184.6$ (C-1'), 181.8 (C-4'), 150.9 (C-5'), 147.8 (C-3'), 132.5 (C-7), 131.1 (C-2'), 128.5 (C-2), 123.3 (C-6), 115.1 (C-1), 114.9 (C-6'), 82.6 (C-3), 41.5 (C-4), 31.5 (C-3''), 30.2 (C-2''), 28.4 (C-1''), 27.2 (C-10), 25.5 (C-8), 22.7 (C-4''), 22.3 (H-5), 17.6 (C-9), 14.2 (C-5''). HRESI-MS: m/z calcd. for $\text{C}_{21}\text{H}_{29}\text{O}_3$, $[\text{M}+\text{H}]^+ 329.2117$, found 329.2122.

3'-Depentyl-3'-(α,α -dimethylheptyl)cannabichromenquinone (CBCQ, 16b): Red oil (57%). FT-IR (cm^{-1}): $\nu = 2957, 2924, 2856, 1648, 1080$. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 6.47$ (d, $J = 10.0$ Hz, 1H), 6.42 (bs, 1H), 5.56 (d, $J = 10.0$ Hz, 1H), 5.09 (bt, $J = 7.8$ Hz, 1H), 2.11 (m, 2H), 1.89 (m, 1H), 1.77-1.52 (m, 4H), 1.67 (bs, 3H), 1.49 (s, 3H), 1.32-0.97 (m, 16H), 0.86 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 184.7, 181.4, 153.2, 151.3, 132.2, 132.1, 128.6, 123.3, 115.2, 114.2, 83.2, 41.5, 40.7, 38.7, 31.7, 29.7, 27.6, 27.3, 25.6, 25.1, 22.6, 22.5, 17.6, 14.0$. HRESI-MS: m/z calcd. for $\text{C}_{25}\text{H}_{37}\text{O}_3$, $[\text{M}+\text{H}]^+ 385.2743$, found 385.2739.

3'-Depentyl-3'-(α,α -dimethylheptyl)geranyl-para-cannabichromenquinone (CBCQ, 16c): Red oil (51%). FT-IR (cm^{-1}): $\nu = 2956, 2923, 2855, 1649, 1449, 1181, 1080$. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.47$ (d, $J = 10.0$ Hz, 10H), 6.42 (s, 1H), 5.57 (d, $J = 10.0$ Hz, 1H), 5.11 (m, 3H), 2.13-1.96 (m, 10H), 1.74-1.59 (m, 16H), 1.49 (s, 3H), 1.29-1.18 (m, 12 H), 1.05 (m, 2H), 0.87 (t, $J = 6.9$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 184.71, 181.45, 153.22, 151.35, 135.97, 135.05, 132.18, 131.27, 128.67, 124.38, 124.08, 123.14, 115.22, 114.25, 83.21, 41.55, 40.76, 39.72, 39.65, 38.71, 31.71, 29.77, 27.65, 27.63, 27.30, 26.76, 26.54, 25.71, 25.14, 22.62, 22.45, 17.70, 16.01, 14.06$.

3'-Depentyl-3'-(α,α -dimethylheptyl)geranyl-ortho-cannabichromenquinone (CBCQ, 17): Purple oil (5%). ^1H NMR (400 MHz, CDCl_3): $\delta = 6.53$ (s, 1H), 6.49 (d, $J = 10.1$ Hz, 1H), 5.34 (d, $J = 10.1$ Hz, 2H), 5.11 (m, 3H), 2.15-1.96 (m, 10H), 1.74-1.54 (m, 16H), 1.49 (s, 3H), 1.3-1.14 (m, 12H), 1.05 (m, 2H), 0.87 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 180.38, 174.72, 163.44, 151.24, 136.06, 135.13, 132.74, 131.31, 124.38, 124.36, 124.01, 123.18, 123.09, 115.71, 109.98, 84.60, 41.88, 40.64, 39.72, 39.68, 39.00, 31.75, 29.78, 27.77, 27.43, 27.40, 26.76, 26.53, 25.71, 25.13, 23.83, 22.65, 22.50, 17.70, 16.03, 14.07$. We were not able to collect IR and mass spectra due to the fast interconversion of 17 in 16c.

PIFA Oxidation of cannabinoids

Oxidation of cannabichromene (CBC) as representative: To a stirred solution of CBC (**15a**, 150 mg, 0.48 mmol), a solution of bis(trifluoroacetoxy)iodobenzene (PIFA, 641 mg, 1.49 mmol, 3.1 molar equiv.) in $\text{MeCN-H}_2\text{O}$ 6:1 (2 mL) was added dropwise. The progress of the reaction was monitored by TLC. After completion of the reaction (20 minutes), the mixture was diluted with EtOAc (10 mL) and washed with saturated Na_2CO_3 (4 $\times$ 15 mL) and next with brine. After drying and evaporation, the residue was purified by GCC on silica gel (10 g, petroleum ether–EtOAc 95:5 as eluant) to give 86 mg (55%) CBCQ (**16a**), identical to the product obtained from the SIBX oxidation.

Methylation of cannabinoquinoids

Methylation of CBDQ (3a) as exemplificative: To a stirred solution of CBDQ (**3a**, 200 mg, 0.61 mmol, in dry DMF (5 mL), NaHCO_3 (102 mg, 1.22 mmol, 2 molar equiv) was added. The resulting solution was stirred at room temperature for 5 minutes, and then methyl iodide (282 μL , 3.04 mmol, 5 mkol. eq) was added dropwise. The solution was stirred at room

temperature overnight, and then worked up by dilution with EtOAc (15 mL). The organic phase was washed with 2M NaOH (3x 15 mL) and next with brine. After drying and evaporation, the residue was purified by GCC on silica gel (10 g, petroleum ether as eluant) to obtain 160 mg (76%) **3b**.

para-O-Methylcannabidiolquinone (Me-CBDQ, 3b): Dark orange oil, (76%). FT-IR (cm⁻¹): ν = 2956, 2926, 2857, 1649, 1260, 890. ¹H NMR (CDCl₃, 400 MHz): δ = 6.37 (bs, H-2'), 5.09 (bd, J = 2.5 Hz, H-2), 4.54 (bs, H-9a), 4.50 (bs, H-9b), 3.87 (s, 5'-OMe), 3.72 (m, H-3), 2.67 (dt, J = 9.2, 2.5 Hz, H-4), 2.36 (t, J = 7.5 Hz, H-1''), 2.17 (m, H-6a), 1.97 (overlapped, H-6b), 1.94 (overlapped, H-5), 1.67 (bs, H-7), 1.61 (bs, H-10), 1.50 (m, H-2''), 1.32 (overlapped, H-3''), 1.30 (overlapped, H-4''), 0.89 (t, J = 6.9 Hz, H-5''). ¹³C NMR (CDCl₃, 100 MHz): δ = 187.9 (C-1'), 184.1 (C-4'), 156.8 (C-5'), 148.2 (C-8), 147.3 (C-3'), 135.5 (C-6'), 133.2 (C-1), 132.5 (C-2'), 122.8 (C-2), 110.9 (C-9), 45.3 (C-4), 31.3 (C-1''), 31.5 (C-3''), 30.6 (C-5), 30.4 (C-6), 30.2 (C-2''), 29.1 (C-3), 24.2 (C-7), 22.5 (C-4''), 18.1 (C-10), 14.5 (C-5''). HRESI-MS: *m/z* calcd. for C₂₂H₃₁O₃ [M+H]⁺ 343.2273, found 343.2279.

para-O-methylcannabigerolquinone (CBGQ, 4b): Orange oil (35%). FT-IR (cm⁻¹): ν = 2926, 2857, 1650, 1445, 1265, 1199, 1107, 894. ¹H NMR (CDCl₃, 400 MHz): δ = 6.89 (bs, 1H), 4.98 (m, 2H), 3.90 (s, 3H), 3.06 (d, J = 7.3 Hz, 2H), 2.31 (td, J₁ = 7.9 Hz, J₂ = 1.4, 2H), 1.97 (m, 2H), 1.89 (m, 2H), 1.66 (bs, 3H), 1.58 (bs, 3H), 1.50 (bs, 3H), 1.42 (m, 2H), 1.26 (m, 4H), 0.83 (t, J = 6.9 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 188.2, 184.1, 155.6, 147.6, 137.1, 132.2, 131.9, 131.4, 124.2, 120.0, 60.9, 39.7, 31.5, 29.7, 28.6, 27.5, 26.6, 25.7, 22.4, 17.7, 16.1, 13.9. HRESI-MS: *m/z* calcd. for C₂₂H₃₃O₃ [M+H]⁺ 345.2430, found 345.2422.

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Keywords: quinones • oxidation • phytocannabinoids • iodanes • tautomerism

- [1] W. Beam, *Fourth Report Wellcome Tropical Research Lab. Chem Sect. Khartoum* **1911**, B25.
- [2] R. Mechoula, Z. Ben-Zvi, Y. Gaoni. *Tetrahedron* **1968**, *24*, 5615-5624.
- [3] N. M. Kogan, R. Rabinowitz, P. Levi, D. Gibson, P. Sandor, M. Schlesinger, R. Mechoulam. *J. Med. Chem.* **2004**, *47*, 3800-3806.
- [4] M. M. Radwan, M. A. ElSohly, D. Slade, S. A. Ahmed, L. Wilson, A. T. El-Afly, I. Khan, S. A. Ross. *Phytochemistry* **2008**, *69*, 2627-2633.
- [5] A. S. Husni, C. R. McCurdy, M. M. Radwan, A. S. Ahmed, D. Slade, S. A. Ross, M. A. ElSohly, J. S. Cutler. *Med. Chem. Res.* **2014**, *23*, 4295-4300.
- [6] A. G. Granja, F. Carrillo-Salinas, A. Pagani, M. Gómez-Cañas, R. Negri, C. Navarrete, M. Mecha, L. Mestre, B. L. Fiebich, I. Cantarero, M. A. Calzado, M. L. Bellido, J. Fernan-dez-Ruiz, G. Appendino, C. Guaza, E. Muñoz. *J. Neuroimmune Pharmacol.* **2012**, *7*, 1002-1016.
- [7] C. del Río, C. Navarrete, J. A. Collado, M. L. Bellido, M. Gómez-Cañas, M. R. Pazos, J. Fernández-Ruiz, F. Pollastro, G. Appendino, M. A. Calzado, I. Cantarero, E. Muñoz, *Sci. Rep.* **2016**, *6*:21703. doi: 10.1038/srep21703.
- [8] <https://sclerodermanews.com/2018/02/20/emerald-health-scleroderma-treatment-orphan-drug-designation/> (accessed on September 4, 2020).

- [9] D. Caprioglio, D. Mattoteia, F. Pollastro, R. Negri, A. Lopa-triello, G. Chianese, A. Minassi, J. A. Collado, E. Munoz, O. Tagliatela-Scafati, G. Appendino. *J. Nat. Prod.* **2020**, *83*, 1711-1715.
- [10] L. Ozanne, L. Pouységu, D. Depernet, B. François, S. Quideau. *Org. Lett.* **2003**, *5*, 2903-2906. For an acidity study on IBX, see: M. J. Gallen, R. Goumont, T. Clark, F. Terrier, Craig M. Williams. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 2929-2934.
- [11] E. R. Darzi, N. K. Garg. *Org. Lett.* **2020**, *22*, 3951-3955.
- [12] D. Caprioglio, G. Allegrone, F. Pollastro, S. Valera, A. Lopatriello, A. Collado, E. Muñoz, G. Appendino, O. Tagliatela-Scafati. *Planta Med.* **2019**, *85*, 981-986.
- [13] L. Casares, J. D. Unciti, M. E. Prados, D. Caprioglio, M. Higgins, G. Appendino, A. T. Dinkova-Kostova, E. Muñoz, L. de la Vaga. *Redox Biol.* **2020** (in press).
- [14] D. Magdziak, A. A. Rodriguez, R. W. Van de Water, T. R. R. Pettus. *Org. Lett.* **2002**, *4*, 285-288.
- [15] A. Kaur, A. Ariafard. *Org. Biomol. Chem.* **2020**, *18*, 1117-1129.
- [16] The oxidation of CBN with SIBX was reported to provide a *p*-quinone (ref. 9), whose structure, in the light of this study, should be reversed to the one of an *o*-quinone.
- [17] D. Caprioglio, D. Mattoteia, A. Minassi, F. Pollastro, A. Lopatriello, E. Muñoz, O. Tagliatela-Scafati, G. Appendino. *Org. Lett.* **2019**, *21*, 6122-6125.
- [18] R. M. Moriarty, O. Prakash. *Org. Reactions*, **2001**, *57*, 327-415.
- [19] Y. Tamura, T. Yakura, H. Tohma, K. Kikuchi, Y. Kita. *Synthesis* **1989**, 126-127.
- [20] R. Barret, M. Daudon. *Tetrahedron Lett.* **1990**, *34*, 4871-4872.
- [21] P. T. Gassman, T. van Bergem, D. P. Gilbert, B. W. A. Cue Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495-5508.
- [22] Calculations have shown that the isomerization of a quinol ester to a catechol ester is exergonic (see ref. 16).
- [23] D. V. Banthorpe, C. Ingold, J. Roy. *J. Chem. Soc. B*, **1968**, 64-66.

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Post-oxidative prototropic- and valence tautomeric equilibria are responsible for the exclusive formation of *p*-quinones in the λ^5 -iodane oxidation of cannabinoids. *O*-Methylation prevents prototropic equilibration and, by complementary timing of oxidation and methylation steps, isomeric *ortho*- and *para*-cannabinoquinoids could be obtained.