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An Intramolecular Pyranone Diels–Alder Cycloaddition Approach to Cannabinol

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Abstract: The natural product cannabinol was synthesized using an intramolecular pyranone Diels–Alder cycloaddition reaction as the key step. This strategy is well adapted to access cannabinol analogues.

Keywords: cannabinol; cycloaddition; natural products; pyranones; total synthesis

Introduction

Cannabinoids comprise a class of more than 70 natural products isolated from the plant *Cannabis sativa*.[1] Besides the well-known recreational use of the cannabis plant as a psychotropic drug, other medicinal applications include antiemetic,[2] analgesic,[3] anticonvulsant,[4] and antibiotic[1c,5] properties. The biological activities of cannabinoids arise due to their interaction with two G-protein coupled cellular receptors, the central cannabinoid receptor CB_1 and the peripheral cannabinoid receptor CB_2.[6] Because CB_1 and CB_2 show differences in their function, agonists that can selectively bind to one of the receptors are desirable.[7]

Δ^9-Tetrahydrocannabinol (THC; **1**) (Figure 1) has been identified as the primary active ingredient of *Cannabis sativa*. On aromatization of the cyclohexene ring, it gives cannabinol (CBN; **2**) which has shown potent antibacterial activity.[8] More importantly, derivatives of **2** have been found to bind selectively to the CB_2 receptor.[7b,9] Therefore, synthetic routes towards cannabinol and its derivatives have been of great interest. Besides oxidative aromatization of tetrahydrocannabinols,[7a,b,10] other strategies for the synthesis of cannabinols include formation of the biaryl moiety by nucleophilic aromatic substitution or cross-coupling reactions followed by pyran formation,[9,11] and construction of the second phenyl ring starting from a suitably substituted arene by various cyclization reactions including an Ru-catalyzed microwave-mediated [2+2+2]cyclotrimerization reaction[12] and a multicomponent domino reaction.[13] Recently, Minuti and co-workers have developed a high pressure-promoted Diels–Alder reaction of 1-phenylbuta-1,3-dienes with methyl propiolate for the synthesis of phenylcyclohexadienes, which was also applied to the formal synthesis of cannabinol (**2**).[14] However, the very high pressure (9×10^3 bar) required to secure a good yield of the products and the necessity for a separate oxidation step to produce the biaryls is rather inconvenient. Herein, we report our strategy for the synthesis of cannabinol (**2**), featuring an intramolecular pyranone Diels–Alder cycloaddition reaction[15] of compound **4** as the key step to build up the tricyclic motif **3** (Scheme 1).

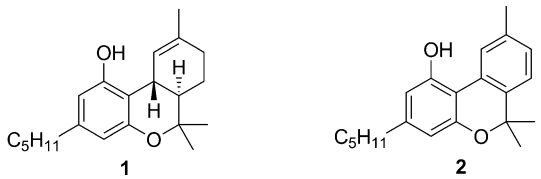
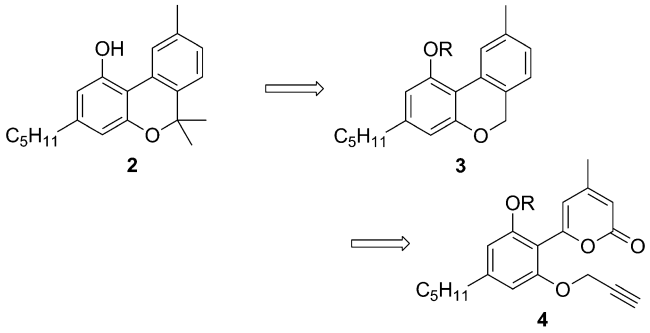


Figure 1. Δ^9-Tetrahydrocannabinol (**1**) and cannabinol (**2**).

Results and Discussion

Our synthesis started with regioselective acylation of the known olivetol dimethyl ether **5**[16] to produce α,β-unsaturated ketone **6** (Table 1). Friedel–Crafts acylation of **5** with crotonoyl chloride in DCM or toluene gave a mixture of the desired 2-acylation prod-

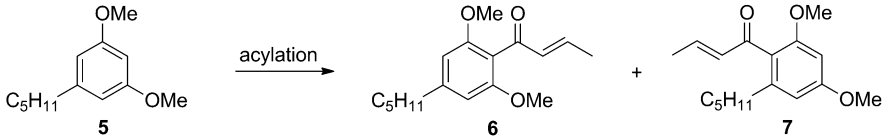


Scheme 1. Retrosynthetic analysis of cannabinol (**2**).

uct **6** and the isomeric 4-acylation product **7** in a ratio of 1:2, from which only a disappointing 20% yield of **6** was isolated (entries 1 and 2). The ratio of **6** to **7** could be improved to 2:3 by subjecting **5** to crotonic acid in the presence of TFAA and $FeCl_3$ (entry 3).[17] Addition of 1,10-phenanthroline to the reaction mixture to reduce the reactivity of $FeCl_3$ in the hope that the 2-acylation product **6** could be obtained in improved yield resulted, however, in exclusive formation of compound **7** (in 58% isolated yield) (entry 4). Although the desired product **6** was not obtained, the high regioselectivity was noteworthy. We then treated **5** with *n*-butyllithium (1.2 equiv.) in the presence of TMEDA to effect *ortho*-lithiation[11c,18] and subsequently treated the resulting organolithium with crotonoyl chloride (1.4 equiv.) (entry 5). To our delight, **6** was the only product formed although the reaction was not complete. After stirring the reaction mixture at ambient temperature for 3 h, **6** was isolated in 10% yield together with substantial amount of the unreacted **5** recovered. The quantity of reactants was then explored. After some experiments, it was found that the reaction was complete when the amounts of *n*-butyllithium and crotonoyl chloride were increased to 4.0 and 4.5 equivalents, respectively, and **6** was isolated in 81% yield.

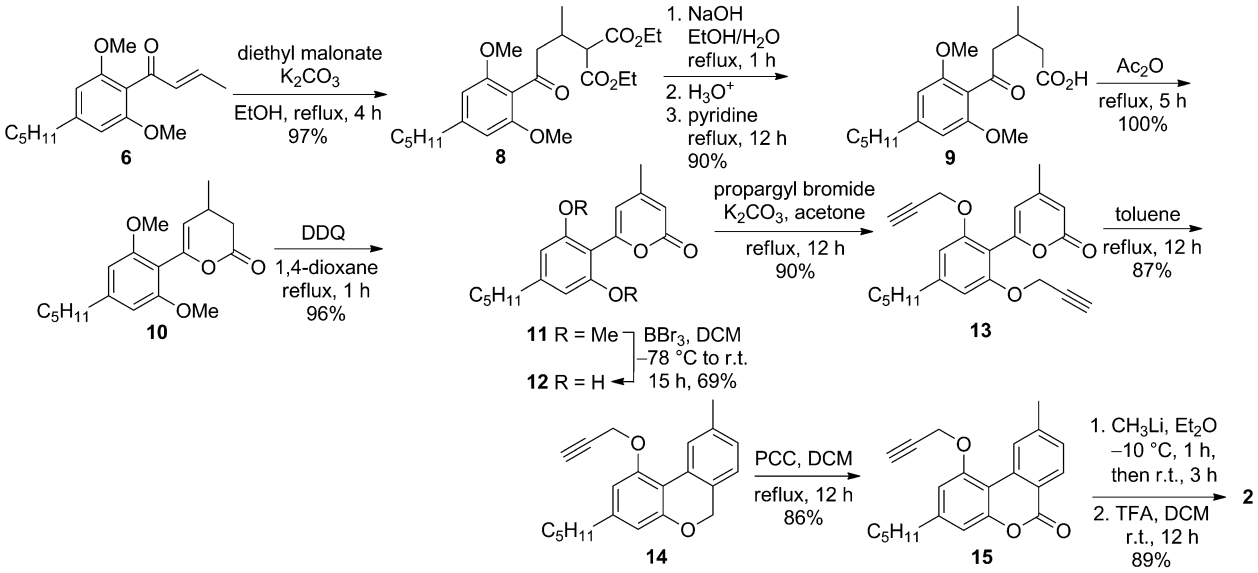
Having **6** in hand, we then finished our total synthesis of cannabinol (**2**) (Scheme 2). Michael addition of **6** with diethyl malonate provided **8** in excellent yield. Ester hydrolysis followed by decarboxylation in refluxing pyridine afforded keto acid **9**, which cyclized on treatment with acetic anhydride to give dihydropyranone **10**. Subsequent oxidation of **10** with DDQ gave pyranone **11** in excellent yield. Next, in order to get access to precursor **4** ($R = CH_3$) for the key intramolecular pyranone Diels–Alder cycloaddition reaction, one of the methyl protecting groups of **11** needed to be replaced with a propargyl group. Quite a number of methods for the monodeprotection of aryl dimethyl ethers have been developed in the literature and applied in natural product synthesis.[19] However, this proved to be difficult in our hands. Usually, the dideprotection product **12** itself or a mixture with the desired monodeprotection product (structure not shown) was obtained. Finally, we decided to remove both methyl protecting groups and react the resulting bis-phenol **12** with propargyl bromide to obtain the dipropargyl ether **13**. The extra propargyl group could be removed later at a suitable stage after the cycloaddition reaction had been carried out. The dideprotection with BBr_3 proceeded as expected to give **12** in 69% isolated yield. After dipropargylation, **13** was ready for the key intramolecular pyranone Diels–Alder cycloaddition reaction, which proceeded smoothly in refluxing toluene and delivered pyran **14** in excellent yield. Next, selective oxidation of the benzylic methylene group with PCC furnished pyranone **15** in 86% isolated yield. Finally, addition of CH_3Li followed by treatment of the crude reaction mixture with TFA furnished the natural product can-

Table 1. Regioselective acylation of olivetol dimethyl ether **5**.



Entry	Reagents and conditions	**6**/**7**[a]	Yield [%] of **6**[b]
1	crotonoyl chloride, $AlCl_3$, CH_2Cl_2, reflux	33:67	20
2	crotonoyl chloride, $AlCl_3$, toluene, reflux	33:67	20
3	crotonic acid, TFAA, $FeCl_3$, DCM, r.t.	40:60	35
4	crotonic acid, TFAA, $FeCl_3$, 1,10-phenanthroline, DCM, r.t.	0:100	0
5	(a) *n*-BuLi (1.2 equiv.), TMEDA, Et_2O, −78 °C to r.t.; (b) crotonoyl chloride (1.4 equiv.), −78 °C to r.t.	100:0	10
6	(a) *n*-BuLi (4.0 equiv.), TMEDA, Et_2O, −78 °C to r.t.; (b) crotonoyl chloride (4.5 equiv.), −78 °C to r.t.	100:0	81

[a] Determined by ^1H NMR integration of the crude reaction mixture.
[b] Isolated yield.



Scheme 2. Total synthesis of cannabinol (**2**).

nabinol (**2**) with simultaneous removal of the propargyl protecting group, so that an extra deprotection step was not necessary. A separate study on phenyl propargyl ether indicated that the propargyl deprotection reaction was effected by MeLi rather than TFA. A number of methods for propargyl ether deprotection have been reported.[20] However, there is no literature precedent involving an organolithium reagent as depropargylation agent. Thus, our work has provided a new entry to propargyl ether deprotection. Detailed studies are currently underway and the results will be published elsewhere.

Conclusions

In summary, we have developed a novel approach to the total synthesis of the natural product cannabinol. The key step involves an intramolecular pyranone Diels–Alder cycloaddition reaction to build up the benzo[*c*]chromene framework. This strategy is well adapted to access broadly substituted C-ring analogues of cannabinol by using other α,β-unsaturated acyl chlorides or propargyl bromide derivatives.

Experimental Section

General

Solvents were dried according to standard procedures where needed. Melting points were determined on a XT4A hot-stage apparatus and are uncorrected. IR spectra were obtained using an IFS25 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AV300 or AV400 instrument. Mass spectra were recorded on a Micromass Q-TOF mass spectrometer.

(*E*)-1-(2′,6′-Dimethoxy-4′-pentylphenyl)but-2-en-1-one (6)

To a solution of olivetol dimethyl ether **5** (337 mg, 1.62 mmol) and TMEDA (0.3 mL, 1.94 mmol) in dry THF (10 mL) at −78 °C under nitrogen, was added *n*-butyllithium (1.6 M solution in hexane, 4 mL, 6.47 mmol). After addition, the mixture was allowed to warm to ambient temperature and stirred for 0.5 h before being cooled to −78 °C again. Crotonoyl chloride (0.7 mL, 7.29 mmol) was added dropwise. The resulting mixture was allowed to warm to ambient temperature and stirred for a further 0.5 h, and then quenched with saturated aqueous ammonium chloride (30 mL). The mixture was extracted with ethyl acetate (3× 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (10% ethyl acetate in petroleum ether) to give **6** as an orange oil; yield: 362 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 6.9$ Hz, 3H), 1.30–1.35 (m, 4H), 1.56–1.64 (m, 2H), 1.89 (dd, $J = 6.9$ Hz and 1.5 Hz, 3H), 2.58 (t, $J = 7.8$ Hz, 2H), 3.75 (s, 6H), 6.32 (dq, $J = 15.6$, 1.5 Hz, 1H), 6.37 (s, 2H), 6.62 (dq, $J = 15.6$, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 18.4, 22.6, 31.1, 31.5, 36.7, 55.9, 104.2, 116.0, 134.1, 145.9, 146.3, 157.2, 195.7 ppm; IR (neat): $\nu_{max} = 1658$, 1606, 1578, 1455, 1414, 1235, 1126 cm^{-1}; HR-MS (ESI): $m/z = 277.1802$, calcd. for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804.

Diethyl 2-[4′-(2″,6″-Dimethoxy-4″-pentylphenyl)-4′-oxobutan-2′-yl]malonate (8)

To a solution of ketone **6** (4.5 g, 16.4 mmol) in dry ethanol (100 mL) was added diethyl malonate (5.3 g, 32.8 mmol) and anhydrous K_2CO_3 (0.5 g, 3.3 mmol). The resulting mixture

was heated to 80 °C for 4 h, then cooled and quenched with 2 M aqueous HCl (10 mL). The bulk of ethanol was evaporated under vacuum. The residue was partitioned between H_2O (100 mL) and ethyl acetate (30 mL). The separated aqueous phase was extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with brine (3× 40 mL), then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (15% ethyl acetate in petroleum ether) to give **8** as an orange oil; yield: 6.97 g (97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.9 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.25 (t, J = 7.2 Hz, 6H), 1.29–1.36 (m, 4H), 1.55–1.65 (m, 2H), 2.56 (t, J = 7.5 Hz, 2H), 2.72–2.99 (m, 3H), 3.45 (d, J = 6.3 Hz, 1H), 3.76 (s, 6H), 4.18 (q, J = 7.5 Hz, 4H), 6.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 17.4, 22.6, 29.3, 31.1, 31.6, 36.8, 49.0, 55.8, 56.4, 61.1, 61.2, 104.1, 117.8, 146.5, 156.7, 168.7, 168.9, 203.7; IR (neat): ν_{max} = 1749, 1731, 1706, 1607, 1580, 1457, 1416, 1128 cm^{-1}; HRMS (ESI): m/z = 459.2350, calcd. for $C_{24}H_{36}NaO_7$ $[M+Na]^+$: 459.2359.

5-(2′,6′-Dimethoxy-4′-pentylphenyl)-3-methyl-5-oxo-pentanoic Acid (9)

A mixture of diethyl malonate **8** (7.5 g, 17.2 mmol) and sodium hydroxide (6.8 g, 172 mmol) in ethanol (100 mL) and water (57 mL) was refluxed for 1 h, and then cooled. The bulk of the ethanol was evaporated under vacuum. The residue was partitioned between 2 M aqueous HCl (60 mL) and ethyl acetate (50 mL). The separated aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was dissolved in pyridine (172 mL). The resulting mixture was heated to reflux for 12 h, and then cooled. The bulk of pyridine was evaporated under vacuum. The residue was partitioned between 2 M aqueous HCl (60 mL) and ethyl acetate (60 mL). The separated aqueous phase was extracted with ethyl acetate (2× 60 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under vacuum to give keto acid **9** as an orange oil; yielkd: 4.9 g (90%), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.9 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H), 1.29–1.35 (m, 4H), 1.57–1.65 (m, 2H), 2.24 (m, 1H), 2.50–2.86 (m, 6H), 3.76 (s, 6H), 6.35 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.9, 22.6, 26.3, 31.0, 31.5, 36.7, 40.7, 51.1, 55.7, 104.1, 117.7, 146.6, 156.7, 179.1, 204.4; IR (neat): ν_{max} = 1705, 1608, 1582, 1463, 1416, 1369, 1282, 1230, 1130 cm^{-1}; HR-MS (ESI): m/z = 359.1833, calcd. for $C_{19}H_{28}NaO_5$ $[M+Na]^+$: 359.1834.

6-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methyl-3,4-dihydro-2*H*-pyran-2-one (10)

A solution of keto acid **9** (3.2 g, 9.51 mmol) in acetic anhydride (50 mL) was heated to reflux for 5 h. The cooled mixture was evaporated under vacuum. The residue was partitioned between water (100 mL) and ethyl acetate (40 mL). The separated aqueous phase was extracted with ethyl acetate (2×40 mL). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate (5×50 mL) and brine (3×50 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (10% ethyl acetate in petroleum ether) to give dihydropyranone **10** as an orange oil; yield: 3.0 g (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.28–1.35 (m, 4H), 1.57–1.64 (m, 2H), 2.41 (m, 1H), 2.57 (t, J = 7.8 Hz, 2H), 2.72–2.84 (m, 2H), 3.78 (s, 6H), 5.23 (d, J = 3.3 Hz, 1H), 6.36 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.2, 22.6, 26.4, 31.1, 31.6, 36.9, 36.9, 56.1, 104.2, 109.6, 113.3, 144.0, 146.4, 158.7, 170.1; IR (neat): ν_{max} = 1763, 1688, 1607, 1577, 1459, 1416, 1236, 1128, 1023 cm^{-1}; HR-MS (ESI): m/z = 319.1901, calcd. for $C_{19}H_{27}O_4$ $[M+H]^+$: 319.1909.

6-(2′,6′-Dimethoxy-4′-pentylphenyl)-4-methyl-2*H*-pyran-2-one (11)

DDQ (5.8 g, 19.1 mmol) was added to a solution of dihydropyranone **10** (4.1 g, 12.7 mmol) in dry 1,4-dioxane (100 mL). The resulting mixture was heated to reflux for 1 h and cooled. The bulk of solvent was evaporated under vacuum. The residue was diluted with DCM (40 mL), and then filtered. The filter cake was washed with DCM (20 mL). The filtrate was washed successively with saturated aqueous sodium bicarbonate (3×40 mL) and brine (3×40 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (17% ethyl acetate in petroleum ether) to give pyranone **11** as a yellow solid; yield: 3.9 g (96%); mp 91–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.9 Hz, 3H), 1.28–1.38 (m, 4H), 1.57–1.67 (m, 2H), 2.17 (d, J = 1.5 Hz, 3H), 2.58 (t, J = 7.8 Hz, 2H), 3.76 (s, 6H), 6.02 (m, 1H), 6.10 (d, J = 1.5 Hz, 1H), 6.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 21.6, 22.6, 31.0, 31.6, 36.9, 56.0, 104.1, 108.8, 111.1, 111.6, 147.6, 155.9, 156.0, 158.5, 164.1; IR (KBr): ν_{max} = 1720, 1649, 1608, 1577, 1561, 1468, 1418, 1238, 1129 cm^{-1}; HR-MS (ESI): m/z = 339.1554, calcd. for $C_{19}H_{24}NaO_4$ $[M+Na]^+$: 339.1572.

6-(2′,6′-Dihydroxy-4′-pentylphenyl)-4-methyl-2*H*-pyran-2-one (12)

To a solution of pyranone **11** (3.4 g, 10.9 mmol) in dry DCM (20 mL) at −78 °C under argon, was added boron tribromide (1.0 M solution in DCM, 11.4 mL, 11.4 mmol). After addition, the mixture was allowed to warm to ambient temperature and stirred for 15 h before being quenched with ice-cooled water (50 mL). The bulk of DCM was evaporated under vacuum. The residue was extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate (3× 40 mL) and brine (3×40 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (3% methanol in DCM) to give pyranone **12** as a colorless solid; yield: 2.2 g (69%); mp 191–193 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.87 (t, J = 6.9 Hz, 3H), 1.25–1.34 (m, 4H), 1.47–1.56 (m, 2H), 2.15 (s, 3H), 2.40 (t, J = 7.8 Hz, 2H), 6.01 (s, 1H), 6.20 (s, 3H), 9.54 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 14.4, 21.6, 23.6, 31.8, 32.5, 36.9, 108.0, 111.2 112.8, 148.4, 157.8, 158.3, 159.7, 166.8; IR (KBr): ν_{max} = 3392, 1685, 1630, 1565, 1524, 1451, 1200, 1174, 1049 cm^{-1}; HR-MS (ESI): m/z = 311.1248, calcd. for $C_{17}H_{20}NaO_4$ $[M+Na]^+$: 311.1259.

4-Methyl-6-[4′-pentyl-2′,6′-bis(prop-2″-yn-1″-yloxy)-phenyl]-2*H*-pyran-2-one (13)

To a solution of pyranone **12** (230 mg, 0.8 mmol) in acetone (20 mL) were added potassium carbonate (442 mg, 3.2 mmol) and propargyl bromide (0.33 mL, 4.4 mmol). The resulting mixture was heated to reflux for 12 h and cooled. The bulk of solvent was evaporated under vacuum. The residue was partitioned between ethyl acetate (20 mL) and water (40 mL). The separated aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic extracts were washed with brine (3×30 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (25% ethyl acetate in petroleum ether) to give pyranone **13** as an orange solid; yield: 234 mg (90%); mp 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.9 Hz, 3H), 1.31–1.36 (m, 4H), 1.58–1.66 (m, 2H), 2.17 (s, 3H), 2.49 (t, J = 2.4 Hz, 2H), 2.60 (t, J = 7.8 Hz, 2H), 4.66 (d, J = 2.4 Hz, 4H), 6.02 (s, 1H), 6.13 (s, 1H), 6.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.6, 22.6, 30.8, 31.4, 36.7, 56.8, 76.0, 78.5, 106.9, 110.4, 111.4, 111.8, 147.4, 155.0, 156.0, 156.5, 163.8; IR (KBr): ν_{max} = 3290, 2123, 1732, 1612, 1582, 1565, 1454, 1402 cm^{-1}; HR-MS (ESI): m/z = 387.1552, calcd. for $C_{23}H_{24}NaO_4$ $[M+Na]^+$: 387.1572.

9-Methyl-3-pentyl-1-(prop-2′-yn-1′-yloxy)-6*H*-benzo[*c*]chromene (14)

A solution of pyranone **13** (666 mg, 1.83 mmol) in dry toluene (35 mL) was heated to reflux for 12 h and cooled. The bulk of toluene was evaporated under vacuum. The residue was partitioned between ethyl acetate (40 mL) and water (50 mL). The separated aqueous phase was extracted with ethyl acetate (2×40 mL). The combined organic extracts were washed with brine (3×50 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (5% ethyl acetate in petroleum ether) to give benzo[*c*]chromene **14** as an orange oil; yield: 507 mg (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 6.9 Hz, 3H), 1.34–1.38 (m, 4H), 1.62–1.69 (m, 2H), 2.41 (s, 3H), 2.57–2.61 (m, 3H), 4.82 (d, J = 2.4 Hz, 2H), 4.96 (s, 2H), 6.58 (s, 2H), 7.03–7.08 (m, 2H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.9, 22.7, 30.8, 31.6, 36.2, 56.6, 68.9, 75.7, 78.7, 107.3, 111.0, 111.1, 124.3, 127.1, 127.5, 128.8, 128.9, 137.7, 144.6, 155.6, 156.8; IR (neat): ν_{max} = 3290, 2124, 1613, 1582, 1561, 1454 cm^{-1}; HR-MS (ESI): m/z = 343.1652, calcd. for $C_{22}H_{24}NaO_2$ $[M+Na]^+$: 343.1674.

9-Methyl-3-pentyl-1-(prop-2′-yn-1′-yloxy)-6*H*-benzo[*c*]chromen-6-one (15)

To a solution of benzo[*c*]chromene **14** (78 mg, 0.25 mmol) in dry DCM (10 mL) were added PCC (436 mg, 2.0 mmol) and celite (436 mg). The resulting mixture was heated to reflux for 12 h, and then cooled and filtered. The filter cake was washed with DCM (15 mL). The filtrate was washed with brine (3×30 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (10% ethyl acetate in petroleum ether) to give benzo[*c*]chromenone **15** as a colorless solid; yield: 72 mg (86%); mp 138–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3H), 1.31–1.38 (m, 4H), 1.63–1.70 (m, 2H), 2.53 (s, 3H), 2.63 (t, J = 2.4 Hz, 1H), 2.67 (t, J = 7.8 Hz, 2H), 4.92 (d, J = 2.4 Hz, 2H), 6.76 (d, J = 1.3 Hz, 1H), 6.88 (d, J = 1.3 Hz, 1H), 7.34 (dd, J = 8.1 and 0.9 Hz, 1H), 8.30 (d, J = 8.1 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 22.7, 30.6, 31.5, 36.0, 56.7, 76.3, 78.0, 106.5, 108.8, 111.0, 118.2, 127.5, 129.0, 130.2, 134.5, 145.6, 145.7, 152.7, 156.0, 161.7; IR (KBr): ν_{max} = 3310, 1716, 1621, 1502, 1293, 1111 cm^{-1}; HR-MS (ESI): m/z = 335.1642, calcd. for $C_{22}H_{23}O_3$ $[M+H]^+$: 335.1647.

Cannabinol (2)[12]

Methyllithium (1.6 M solution in diethyl ether, 1.2 mL, 1.9 mmol) was added dropwise to a solution of benzo[*c*]-chromenone **15** (63 mg, 0.19 mmol) in dry diethyl ether (10 mL) at −10 °C under argon. The resulting mixture was stirred for 1 h at −10 °C, before being allowed to warm to ambient temperature and stirred for a further 3 h. The reaction was then cooled to 0 °C. Saturated aqueous ammonium chloride (30 mL) was added and the resulting mixture extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was dissolved in DCM (20 mL). TFA (3 drops) was added and the reaction stirred at ambient temperature for 12 h before being quenched with ice-cooled water. The bulk of DCM was evaporated under vacuum. The residue was partitioned between ethyl acetate (20 mL) and water (30 mL). The separated aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate (3×30 mL) and brine (3×30 mL), and then dried (Na_2SO_4), filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (6% ethyl acetate in petroleum ether) to give cannabinol (**2**) as an orange oil; yield: 52 mg (89%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.9 Hz, 3H), 1.29–1.34 (m, 4H), 1.56–1.65 (m, 8H), 2.38 (s, 3H), 2.50 (t, J = 7.8 Hz, 2H), 5.22 (br s, 1H), 6.29 (d, J = 1.2 Hz, 1H), 6.44 (d, J = 1.2 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H); MS (ESI): m/z (%) = 333 (100) $[M+Na]^+$, 311 (95) $[M+H]^+$.

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