Syntheses of Cannabinoid Metabolites: Ajulemic Acid and HU-210

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Article

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Abstract: Cannabinoid metabolites have been reported to be more potent than the parent compounds. Among them, Ajulemic acid (AJA) is a synthetic analogue of Δ⁹-THC-11-oic which will be a good template structure for discovery of more potent analogues. Herein, we optimized the key allylic oxidation step to introduce the C-11 hydroxy group with high yield. And a series of compounds were prepared with this condition applied including HU-210, 11-Nor-Δ⁸-Tetrahydrocannabinol-9-carboxylic acid and Δ⁹-THC-COOH.

Keywords: Phytocannabinoids; metabolites; ajulemic acid; riley oxidation

1. Introduction

Phytocannabinoids and their synthetic analogues are prime candidates for pharmaceutical innovation, exemplified by molecules such as Δ⁹ -tetrahydrocannabinol (Δ⁹-THC, **1**, Figure 1) are known to possess potent analgesic and anti-inflammatory properties. And **1** was first identified in 1964 by Gaoni and Mechoulam as the principle bioactive component of marijuana (hashish), which has been used for centuries as both a therapeutic and recreational drug. More generally, cannabinoid-based chemical probes and leads are essential for continued exploration of the endocannabinoid system. 1 Prior to the 1980s, cannabinoids were hypothesized to produce their effects by nonspecific interactions with cell membranes. The absolute stereochemistry of **1** was established in 1967 2, and more than 2 decades passed before it was identified as a modulator of the cannabinoid receptor 3.

The main metabolic pathways involved hydroxylations or oxygenations. It is well-known that the nature of substituents at the C-1, C-3, and C-9 positions play a critical role in efficient binding to the cannabinoid receptors 4. SAR studies of the C-3 side chain demonstrated that a seven-carbon homologue was optimal for activity and that branched alkyl groups also led to improved binding affinity 5. For example, the dimethylheptyl analogue **3** which is an oxygenation product of **2** exhibits an approximately 50-fold improvement in activity relative to **1** 6. The relative importance of the C-1 hydroxyl differs between the two cannabinoid subtypes. Synthetic cannabinoid **3** 7. possesses two hydrogen donors and exhibits significantly enhanced affinity for both the CB2 and the CB1 receptors, producing many of the same pharmacological effects as **1** 8.

Compound **4** is a synthetic analog of Δ⁹-THC-11-oic acid, the major metabolite of the psychoactive component of marijuana, Δ⁹-THC. Δ⁹-THC-11-oic acid 9 has no psychotropic activity and is present in the tissues of the millions of recreational users of Cannabis long after the mood altering effects are gone 10. Its analgesic properties suggested that it would be a good template structure for discovery of more potent analogs. AJA is such an analog, and is a 'first-in-class' chemical entity designed to have increased anti-inflammatory properties and reduced psychotropic activity compared to its THC parent 11. This compound was found to be well tolerated in a phase I clinical

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trial and subsequently completed a phase II studies wherein this molecule demonstrated efficacy in reducing chronic neuropathic pain without any major adverse effects 12.

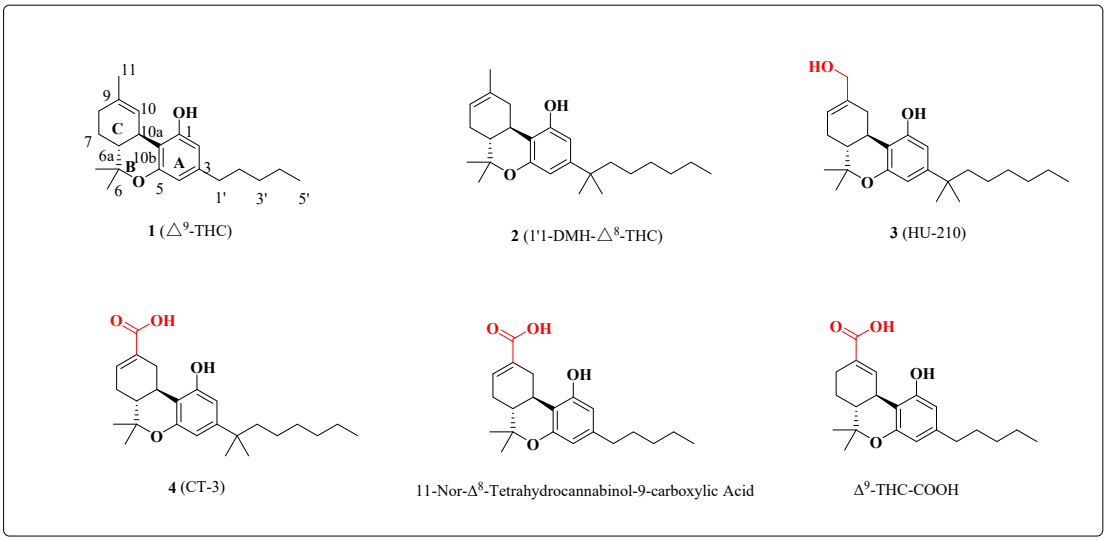
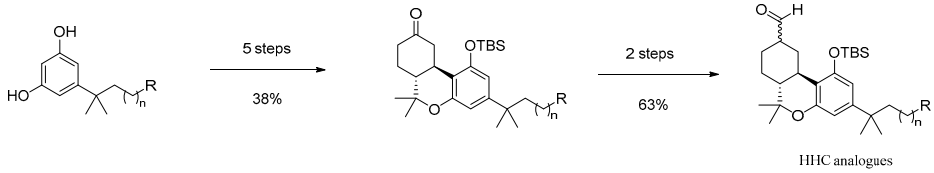


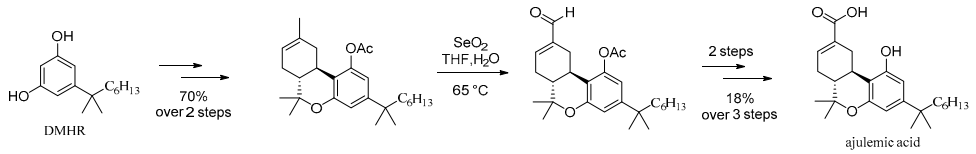
Figure 1. General structural information of cannabinoid metabolites with oxygen at C-11 cite.

There are few reports on the synthesis of cannabinoid metabolites. which vary from five to seven steps (Figure 2). Jiang et al. reported a synthetic route to synthesize the HHC analogues with seven steps in 24% overall yields 13. And Tepper et al developed a synthetic route to synthesize the AJA within five steps but only in 13% overall yields 14. Considering the rapid change in the illicit drug market, a concise synthetic where the combination of a simple replacement of the phenol protecting group (Figure 2) and the optimization of the riley oxidation condition give a better yield (43% overall). Therefore, a synthetic route for the synthesis of a key intermediate, which subsequently can be used to synthesize the cannabinoid metabolites was developed. The synthesis method to the intermediate is carried out on a multigram scale.

1. Syntheses of cannabinoid metabolites analogues (Jiang et al): 13



2. Syntheses of cannabinoid metabolites ajulemic acid (Tepper et al): 14



3. This work:

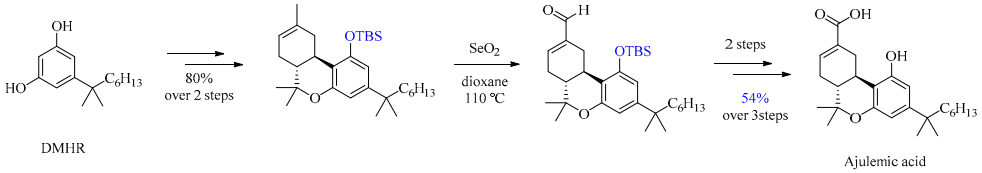


Figure 2. Overview of the Syntheses of the C-11 oxygenation intermediates.

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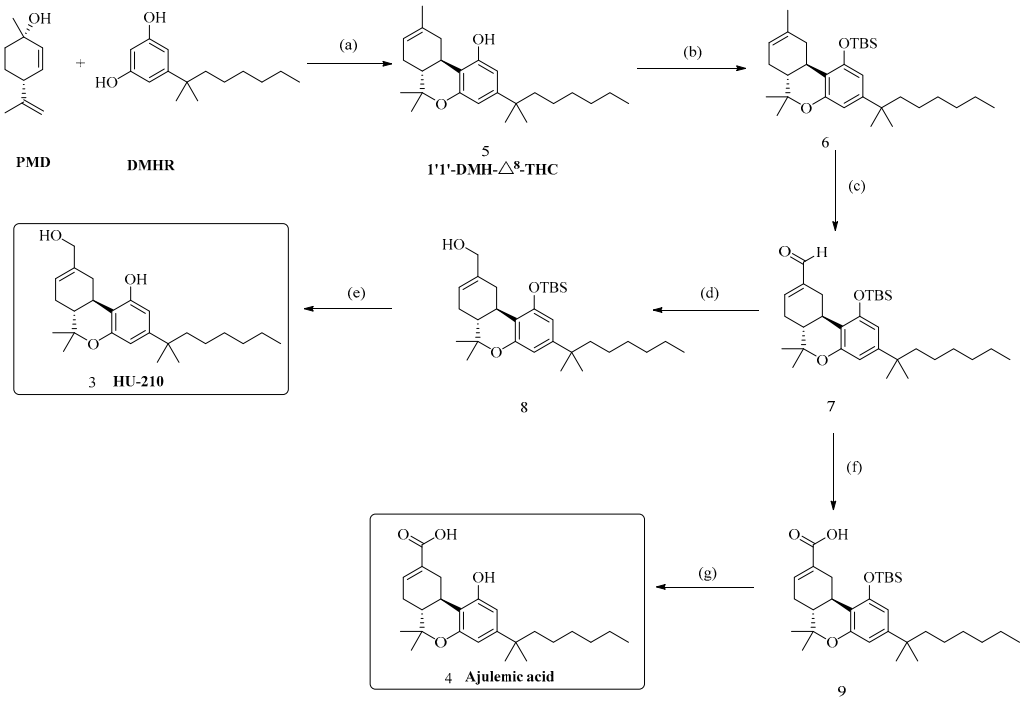
2. Results and discussion

The route to synthetic the ajulemic acid by Tepper was optimized with the change of the SeO_2 mediated condition to improve the yield of the key allylic oxidation step. Our synthesis started with preparation of the tricyclic intermediate (**5**) 15 as shown in Scheme 1. Commercial available starting materials *p*-menthadienol (PMD) and 1,1-dimethylheptyl resorcinol (DMHR) were under the acid condition to promote the cyclization to obtain the tricyclic skeleton of the cannabinoid metabolites in 72% yield. Thus, further protection of the phenol group with a TBS group afforded the key tricyclic intermediate (**6**) in 97% yield. 11To install the C11 hydroxyl group, (**6**) was subjected to a SeO_2-mediated allylic oxidation, and product (**7**) bearing an aldehyde group at C11 was obtained in 65% yield. Then reduction of the new generated aldehyde group with $NaBH_4$ afforded the hydroxy group in 89% yield, The resultant (**8**) was then reacted with 1M TBAF in THF to give product HU-210 in 93% yield. We then turned our attention to (**7**) for the total syntheses of ajulemic acid. To this end, (**7**) was first converted to acid (**9**) with treatment by Pinnick oxidation in 90% yield, further treatment of (**9**) with TBAF in THF to give product ajulemic acid in 92% yield.



Scheme 1. Synthesis of ajulemic acid and HU-210. Reagents and conditions: (a) 1. *p*-TSA, toluene; 80 °C for 1h; yield of 82%. (b) TBSCl, imidazole, and N, N-dimethylformamide (DMF); room temperature for overnight duration; yield of 97%; (c) SeO_2, dioxane; 110 °C for 1 h; yield of 65%. (d) $NaBH_4$, and MeOH; 0 °C for 50 min; yield of 89%. (e) TBAF, and tetrahydrofuran (THF); room temperature for 2 h; yield of 93%; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH and H_2O(4:1); room temperature for 1 h; yield of 90%; (g) TBAF, and tetrahydrofuran (THF); room temperature for 2 h; yield of 92%.

In the initial attempt, the acetyl protecting group of the tricyclic intermediate phenol **10** lead to a low yield of the allylic oxidation step. We tried a variety of conditions including SeO_2/THF/H_2O 14, SeO_2/AcOH/DCM 16, SeO_2/*t*BuOOH/salicylic acid/DCM 17, SeO_2/*t*BuOOH/DCM 18 and SeO_2/dioxane. The result shown that there was a byproduct （**12**） observed which is a regio-selected isomer. Also, there was another byproduct （**13**） shown in the Table 1 which is an aromatic product. Fortunately, SeO_2 mediated riley oxidation in dioxane at 110 °C gave a moderate yield. When the acetyl group was replaced with the silyl ether protected group, the yield of the allylic oxidation was improved obviously due to the well decrease of the by-products.

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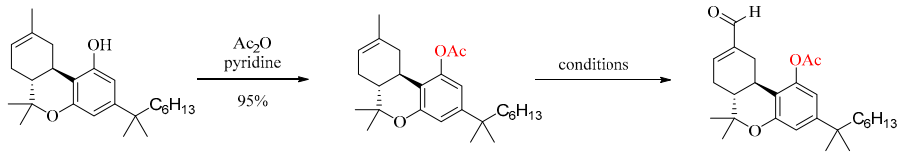
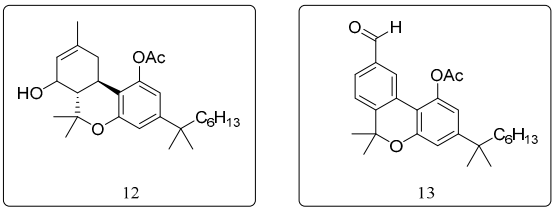
Table 1. The optimization of the riley oxidation (see SI).



5 10 11

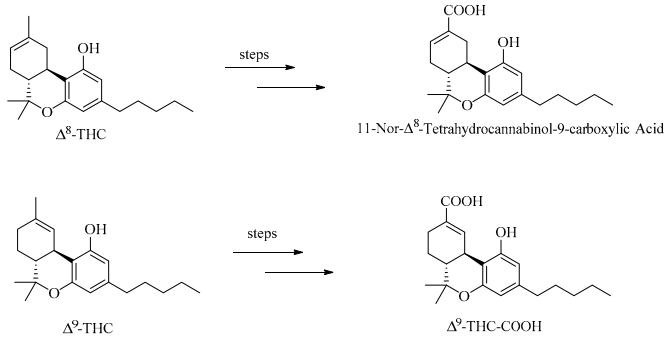
Entry	substrate	condition	product	yield[a]
1	**5**	SeO_2, DCM	**11**	15 %
2	**5**	SeO_2,THF, H_2O, 65 °C	**11**	25%
3	**5**	SeO_2, *t*BuOOH, DCM	**11**	8 %
4	**5**	SeO_2/BuOOH, Salicylic acid	**11**	12 %
5	**5**	SeO_2, AcOH, dioxane	**11**	N.A
6	**5**	SeO_2, dioxane, reflux	**11**	39 %
7	**6**	SeO_2, dioxane, reflux	**7**	65%

[a] Isolated yield.



12 13

The optimized condition was then applied for the syntheses of 11-Nor-Δ⁸-Tetrahydrocannabinol-9-carboxylic Acid and Δ⁹-THC-COOH (Figure 1). To this end, this method was successfully to obtain the metabolites through a four-steps strategy from the Δ⁸-THC and Δ⁹-THC, respectively (Scheme 2).



Scheme 2. Syntheses of 11-Nor-Δ⁸-Tetrahydrocannabinol-9-carboxylic Acid and Δ⁹-THC-COOH with the same operation.

3. Materials and Methods

3.1. General Information

All solvents and reagents used in this study were purchased from commercial sources and used without further purification. Thin-layer chromatography (TLC) was performed using SIL G/UV 254 silica-glass plates. Flash chromatography was carried out using Silica Gel 60 (200-400 mesh) utilizing solvent systems defined in the experimental procedure for each synthesized molecule. NMR spectra were obtained using a JEOL JNM-ECZ600R 600 MHz spectrometer at room temperature. NMR spectra were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^1H NMR = 7.26 ppm, ^{13}CNMR = 77.16 ppm; Acetone- d_6: ^1H NMR = 2.05 ppm, ^{13}C NMR = 206.3 ppm; DMSO-d_6: ^1H NMR =2.50 ppm, ^{13}C NMR = 39.52 ppm; CD_2Cl_2: ^1H NMR = 5.32 ppm, ^{13}C NMR = 54.0 ppm; MeOD-d_4 : ^1H NMR = 3.31 ppm, ^{13}CNMR = 49.0 ppm; The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.High-resolution mass spectroscopy (HRMS) was carried out on a Vion IMS TOF-Q mass spectrometer. Deuterium incorporation was determined by HRMS.

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3.2. Experimental Section

3.2.1. Synthesis of compound (5)

To a 3-neck round bottom flask was charged DMHR (5 g, 21.18 mmol, 1 equiv), *p*- toluenesulfonic acid (0.728 g, 3.83 mmol, 0.2 equiv) and toluene (150 ml). To this was added PMD (3.54 g, 23.29 mmol, 1.1 equiv) over 1 h, followed by a toluene (8 ml) rinse while maintaining the batch temperature at 15–30 °C. The batch was heated to 70–80 °C under partial vacuum, and a Dean–Stark trap filled with toluene was used to remove water azeotropically. And the reaction was quenched by addition of a saturated solution of NH_4Cl (15 ml). and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (20 mL), and dried with Na_2SO_4.The solvent was removed in vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/ethyl acetate = 50/1) to give **5** (6.45 g, 82% yield) as a yellow oil. R_f = 0.7 (silica gel, EtOAc/hexanes= 1/10). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.40 (d, J = 1.8 Hz, 1H), 6.23 (d, J = 1.8 Hz, 1H), 5.44 (dt, J = 5.0, 1.4 Hz, 1H), 3.20 (dt, J = 17.2, 3.0 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.14 (d, J = 4.1 Hz, 1H), 1.95 – 1.77 (m, 3H), 1.71 (q, J = 1.3 Hz, 3H), 1.50 (ddd, J = 11.3, 6.1, 2.6 Hz, 2H), 1.40 (s, 3H), 1.26 – 1.16 (m, 13H), 1.12 (s, 3H), 1.07 (td, J = 8.9, 8.4, 4.1 Hz, 2H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.65, 154.55, 150.17, 134.90, 119.47, 110.29, 108.17, 105.54, 44.98, 44.61, 37.45, 36.10, 31.93, 31.63, 30.17, 28.88, 28.81, 28.01, 27.75, 24.76, 23.65, 22.82, 18.66, 14.24. IR (film, cm^{-1}): 3384, 2958, 2927, 2856, 1622, 1413, 1034, 965, 838; HRMS (ESI) calcd for $C_{25}H_{38}O_2$ $[M+H]^+$: m/z 371.2945, found: 371.2944.

3.2.2. Synthesis of compound (6)

To a solution of **5** (5.79 g, 15.65 mmol, 1.0 equiv) in dry DMF (100 mL) at room temperature was added dry imidazole (4.75 g, 69.77 mmol, 4.46 equiv) and TBSCl (7.07 g, 46.9 mmol, 3.0 equiv) and the resultant mixture was stirred at the same temperature for 18 h. The mixture was quenched by addition of a saturated solution of NH_4Cl (10 mL), and water (200 ml) was added to the mixture. The mixture was extracted with ethyl acetate (3 x 50 mL). Combined organic layers were washed with brine (25 mL), and dried over Na_2SO_4. The solvent of the organic phase was concentrated in vacuo, and the residue was purified by a flash column chromatography (hexane/EtOAc: 50/1) to give **6** (7.34 g, 97% yield) as a colorless oil. R_f =0.7 (hexane/EtOAc: 20/1). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.41 (d, *J* = 1.9 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 5.45 – 5.35 (m, 1H), 3.30 – 3.20 (m, 1H), 2.61 – 2.53 (m, 1H), 2.22 – 2.09 (m, 1H), 1.84 – 1.77 (m, 3H), 1.69 (d, *J* = 2.0 Hz, 3H), 1.50 (ddd, *J* = 10.3, 5.5, 1.2 Hz, 2H), 1.38 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 8H), 1.19 (dd, *J* = 7.1, 3.5 Hz, 4H), 1.10 (s, 3H), 1.07 – 1.03 (m, 2H), 1.01 (s, 9H), 0.84 (t, *J* = 7.1 Hz, 3H), 0.26 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.71, 154.30, 149.40, 135.15, 119.36, 114.19, 109.83, 108.66, 45.34, 44.72, 37.44, 36.15, 32.24, 31.97, 31.74, 30.18, 29.06, 28.81, 28.19, 27.64, 26.13, 24.83, 23.54, 22.80, 18.47, 14.27, 14.23, -3.41, -4.24; HRMS (ESI) calcd for $C_{31}H_{52}O_2Si$ $[M+H]^+$: m/z 485.3809, found: 485.3818.

3.2.3. Synthesis of compound (7)

To a stirred solution of **6** (5.74 g, 11.84 mmol, 1.0 equiv) in dry dioxane (200 mL) was added SeO_2 (4.6 g, 41.46 mmol, 3.5 equiv) at room temperature, and resultant mixture was shielded from light and stirred at the 110 °C for 1 h. The mixture was quenched by filtration off through a celite pad, which was washed with DCM (50 mL). The combined filtrate was washed with saturated aq $Na_2S_2O_8$ (3 x 20 mL), and the water phase was extracted with DCM (3 x 50 mL). Combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by a flash column chromatography (hexane/EtOAc: 10/1 to 4/1) to give **7** (3.82 g, 65% yield) as yellowish solid, R_f = 0.3. (hexane/EtOAc: 10/1). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.50 (s, 1H), 6.83 – 6.77 (m, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 3.84 (ddd, *J* = 17.7, 4.3, 2.0 Hz, 1H), 2.60 – 2.48 (m, 2H), 2.19 – 2.10 (m, 1H), 1.90 (td, *J* = 11.6, 4.7 Hz, 1H), 1.80 (q, *J* = 2.1 Hz, 1H), 1.52 – 1.48 (m, 2H), 1.43 (s, 3H), 1.20 (dd, *J* = 15.9, 4.1 Hz, 13H), 1.13 (s, 3H), 1.04 (t, *J* = 4.0 Hz, 1H), 0.97 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 3H), 0.28 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (151 MHz,

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Chloroform-*d*) δ 193.42, 154.90, 154.06, 149.91, 148.69, 142.57, 112.86, 109.85, 108.43, 45.33, 44.70, 37.50, 31.95, 31.45, 30.16, 29.45, 28.98, 28.85, 27.69, 27.61, 26.08, 24.81, 22.79, 18.46, 18.31, 14.23, -3.43, -4.12. HRMS (ESI) calcd for $C_{31}H_{50}O_3Si$ $[M+H]^+$: m/z 499.3602, found: 499.3615.

3.2.4. Synthesis of compound (8)

To a solution of **7** (2.80 g, 5.62 mmol, 1.0 equiv) in MeOH (30 mL) was added $NaBH_4$ (256 mg, 6.74 mmol, 1.2 equiv) at 0 °C in one portion, and the resultant mixture was then stirred at 0 °C for 50 min. The reaction was quenched by addition of an aqueous solution of NH_4Cl (10 mL), and the MeOH in resultant mixture was removed under vacuum, and the resultant residue was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), and dried over Na_2SO_4. The solvent of the extract was concentrated under vacuum, and the residue was purified by a flash column chromatography (hexane/EtOAc: 10/1 to 4/1) to give **8** (2.5 g, 89% yield) as yellowish solid, R_f = 0.5. (hexane/EtOAc: 5/1). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.42 (d, *J* = 1.9 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 5.76 – 5.71 (m, 1H), 4.08 – 3.99 (m, 2H), 3.41 – 3.32 (m, 1H), 2.59 (td, *J* = 11.0, 4.5 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.95 – 1.77 (m, 3H), 1.52 – 1.47 (m, 2H), 1.39 (s, 3H), 1.25 – 1.19 (m, 9H), 1.18 (q, *J* = 3.5 Hz, 3H), 1.11 (s, 3H), 1.07 – 1.02 (m, 2H), 0.99 (s, 9H), 0.84 (t, *J* = 7.1 Hz, 3H), 0.25 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.75, 154.23, 149.57, 138.57, 120.42, 113.78, 109.85, 108.64, 76.42, 66.91, 45.55, 44.70, 37.45, 32.00, 31.95, 30.16, 29.03, 28.80, 27.85, 27.62, 26.13, 24.82, 22.79, 18.45, 18.40, 14.23, -3.43, -4.17. HRMS (ESI) calcd for $C_{31}H_{52}O_3Si$ $[M+H]^+$: m/z 501.3759, found: 501.3744.

3.2.5. Synthesis of compound (10)

To a solution of **5** (5.6 g, 13.5 mmol, 1.0 equiv) in pyridine (100 mL) was added Ac_2O (5.11 ml, 6.74 mmol, 4 equiv) at 0 °C in one portion, and the resultant mixture was then stirred at room temperature for 4 h. The mixture was then added with water (100 mL) and the resultant residue was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with H_2O (3 x 10 mL) and brine (10 mL), and dried over Na_2SO_4. The solvent of the extract was concentrated under vacuum, and the residue was purified by a flash column chromatography (hexane/EtOAc: 10/1) to give **10** (5.93 g, 95% yield) as yellowish solid, R_f = 0.7. (hexane/EtOAc: 10/1). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.69 (d, *J* = 2.2 Hz, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 5.48 – 5.40 (m, 1H), 2.77 – 2.69 (m, 1H), 2.61 (td, *J* = 11.0, 5.0 Hz, 1H), 2.30 (s, 3H), 2.17 – 2.11 (m, 1H), 1.97 – 1.89 (m, 1H), 1.83 – 1.77 (m, 2H), 1.70 (s, 3H), 1.52 (dd, *J* = 8.0, 4.5 Hz, 2H), 1.39 (s, 3H), 1.21 (dd, *J* = 26.3, 3.2 Hz, 12H), 1.12 (s, 3H), 1.08 (ddd, *J* = 11.0, 5.2, 2.7 Hz, 2H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.06, 154.31, 150.27, 149.73, 134.01, 119.89, 115.83, 113.19, 112.27, 44.76, 44.57, 37.59, 36.20, 31.88, 31.86, 30.11, 28.75, 28.67, 27.85, 27.60, 24.68, 23.70, 22.80, 21.44, 18.68, 14.23. HRMS (ESI) calcd for $C_{27}H_{40}O_3$ $[M+H]^+$: m/z 413.6215, found: 413.6214.

3.2.6. Synthesis of compound (11)

To a 100-ml, 3-neck round bottom flask was charged compound **10** (1.23 g, 2.98 mmol, 1 equiv), Selenium dioxide (378 mg, 3.41 mmol, 1.25 equiv), tetrahydrofuran (12.2 ml, 4.3 equiv) and water (0.57 ml, 0.2 equiv). The reactor was heated to 55–65 °C, for 23.5 h. The mixture was quenched by filtration off through a celite pad, which was washed with DCM (20 mL). The combined filtrate was washed with saturated aq $Na_2S_2O_8$ (3 x 10 mL), and the water phase was extracted with DCM (3 x 12 mL). Combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by a flash column chromatography (hexane/EtOAc: 10/1 to 4/1) to give **11** (0.32 g, 25% yield) as yellowish solid, R_f = 0.3. (hexane/EtOAc: 10/1), And also to give two byproducts **12** and **13**.

Compound **11**, ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.50 (s, 1H), 6.90 – 6.81 (m, 1H), 6.70 (d, *J* = 1.7 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 3.43 – 3.34 (m, 1H), 2.57 – 2.54 (m, 1H), 2.30 (s, 3H), 2.16 – 2.10 (m, 1H), 1.91 (td, *J* = 11.5, 4.5 Hz, 2H), 1.53 – 1.49 (m, 2H), 1.44 (s, 3H), 1.23 (d, *J* = 2.9 Hz, 8H), 1.19 (t, *J* = 4.0 Hz, 5H), 1.16 (s, 3H), 1.07 (dq, *J* = 9.1, 3.7, 3.3 Hz, 2H), 0.84 (d, *J* = 7.3 Hz, 3H).^{13}C NMR (151 MHz, Chloroform-*d*) δ 193.43, 169.28, 154.03, 150.83, 149.79, 148.81, 141.65, 114.59, 113.21, 112.67, 44.72,

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44.54, 37.66, 31.87, 31.07, 30.09, 29.12, 28.75, 28.63, 27.55, 27.11, 24.67, 22.80, 21.46, 18.55, 14.26, 14.22. HRMS (ESI) calcd for $C_{27}H_{38}O_4$ $[M+H]^+$: m/z 427.2843, found: 427.2838.

Compound **12**, ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.99 (s, 1H), 6.43 (d, *J* = 1.9 Hz, 1H), 6.38 (d, *J* = 2.2 Hz, 1H), 5.68 (dt, *J* = 5.2, 1.7 Hz, 1H), 5.64 – 5.59 (m, 1H), 3.04 – 2.96 (m, 1H), 2.24 (s, 3H), 2.23 – 2.17 (m, 1H), 2.10 (td, *J* = 11.3, 3.8 Hz, 1H), 1.97 – 1.90 (m, 1H), 1.52 – 1.48 (m, 2H), 1.40 (s, 3H), 1.23 (s, 3H), 1.20 (s, 12H), 1.08 – 1.04 (m, 2H), 1.02 (s, 3H), 0.84 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.69, 155.11, 151.56, 134.68, 125.64, 108.70, 107.42, 107.09, 79.86, 75.64, 46.69, 44.43, 37.49, 37.35, 31.87, 30.10, 28.93, 28.80, 28.72, 27.55, 24.67, 22.77, 21.19, 19.19, 18.34, 14.22. HRMS (ESI) calcd for $C_{27}H_{40}O_4$ $[M+H]^+$: m/z 429.2999, found: 429.3000.

Compound **14**, ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.47 (d, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 2.2 Hz, 1H), 5.73 (d, *J* = 6.1 Hz, 1H), 4.39 – 4.32 (m, 1H), 2.80 (dd, *J* = 11.8, 8.5 Hz, 1H), 2.22 – 2.13 (m, 1H), 1.97 – 1.89 (m, 1H), 1.89 – 1.82 (m, 1H), 1.79 (d, *J* = 2.1 Hz, 3H), 1.51 (ddd, *J* = 11.3, 6.0, 2.4 Hz, 2H), 1.38 (s, 3H), 1.27 – 1.16 (m, 13H), 1.09 (s, 3H), 1.08 – 1.05 (m, 2H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.92, 154.69, 151.21, 134.70, 125.84, 108.23, 107.83, 107.60, 77.51, 77.37, 75.21, 44.89, 44.49, 40.95, 37.39, 31.95, 30.18, 28.78, 27.96, 27.87, 24.77, 22.83, 19.28, 18.64, 14.25. HRMS (ESI) calcd for $C_{25}H_{38}O_3$ $[M+H]^+$: m/z 387.2893, found: 387.2899.

Compound **15,** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.94 (s, 1H), 8.57 (d, *J* = 1.4 Hz, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 6.56 (d, *J* = 1.7 Hz, 1H), 6.43 (d, *J* = 1.8 Hz, 1H), 5.97 (d, *J* = 5.0 Hz, 1H), 5.61 (d, *J* = 3.1 Hz, 1H), 1.76 (s, 6H), 1.55 (dd, *J* = 8.0, 4.3 Hz, 2H), 1.26 (s, 6H), 1.20 (q, *J* = 4.9, 4.0 Hz, 6H), 1.09 – 1.06 (m, 2H), 0.84 (s, 3H). HRMS (ESI) calcd for $C_{25}H_{32}O_4$ $[M+H]^+$: m/z 381.2424, found: 381.2428.

3.2.7. Synthesis of compound (3)

To a solution of **8** (2.20 g, 4.40 mmol, 1.0 equiv) in THF (60 mL) was added tetrabutylammonium fluoride (1M in THF, 4.84 mL, 1.1 equiv), and the resultant mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated. aq. NH_4Cl (10 mL), and the resultant mixture was extracted with Et_2O (3 x 10 mL). The organic layers were sequentially washed with water (5 mL) and then with brine (5 mL), and dried over anhydrous $MgSO_4$. The solvent of the extract was removed under vacuum, the residue was subjected to column chromatography on silica gel (hexane/EtOAc: 2/1) to afford **3** (1.57 mg, 93%) as a white solid. R_f = 0.4 (hexane/EtOAc: 2/1). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.39 (d, *J* = 1.8 Hz, 1H), 6.24 (d, *J* = 1.9 Hz, 1H), 5.75 (dd, *J* = 4.0, 2.4 Hz, 1H), 4.07 (q, *J* = 12.7 Hz, 2H), 3.43 (dd, *J* = 15.9, 4.5 Hz, 1H), 2.71 (d, *J* = 4.6 Hz, 1H), 2.22 (s, 1H), 1.92 – 1.80 (m, 3H), 1.49 (ddd, *J* = 11.3, 6.1, 2.7 Hz, 2H), 1.40 (s, 3H), 1.28 – 1.14 (m, 13H), 1.11 (s, 3H), 1.09 – 1.02 (m, 2H), 0.85 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.78, 154.50, 150.30, 138.33, 121.98, 110.03, 107.94, 105.75, 67.22, 45.12, 44.61, 37.42, 31.94, 31.50, 31.44, 30.19, 28.86, 28.79, 27.80, 27.71, 24.76, 22.83, 18.53, 14.24. IR (film, cm^{-1}): 3413, 3223, 2924, 1624, 1580, 1415, 1186, 991, 842; HRMS (ESI) calcd for $C_{25}H_{38}O_3$ $[M+H]^+$: m/z 387.2894, found: 387.2891.

3.2.8. Synthesis of compound (9)

To a mixture of aldehyde **7** (2.69 g, 5.39 mmol, 1.0 equiv), $NaH_2PO_4{\cdot}2H_2O$ (2.59 g, 648 mmol, 4.0 equiv), and 2-methyl-2-butene (3.79 g, 53.9 mmol, 10.0 equiv) in t-BuOH (100 mL) and H_2O (25 mL) was added $NaClO_2$ (1.95 g, 648 mmol, 4.0 equiv) at 0 °C. After being stirred for 1 h at that temperature, the mixture was extracted with EtOAc (3 × 40 mL) and H_2O (15 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated to give the residue, which was purified by column chromatography on silica gel (hexane/EtOAc: 20/1) to afford **9** (2.50 g, 90%) as a yellowish oil. R_f = 0.4 (hexane/EtOAc: 10/1). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.19 – 7.14 (m, 1H), 6.44 (d, *J* = 1.8 Hz, 1H), 6.40 (d, *J* = 1.9 Hz, 1H), 3.90 (ddd, *J* = 17.9, 4.4, 2.1 Hz, 1H), 2.57 (td, *J* = 11.2, 4.3 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.04 (ddt, *J* = 16.4, 11.9, 2.4 Hz, 1H), 1.97 – 1.90 (m, 1H), 1.86 (td, *J* = 11.7, 4.6 Hz, 1H), 1.54 – 1.51 (m, 2H), 1.42 (s, 3H), 1.22 (dd, *J* = 13.7, 5.9 Hz, 13H), 1.13 (s, 3H), 1.10 – 1.04 (m, 2H), 1.01 (s, 9H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.30 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.77, 154.84, 154.13, 149.74, 140.24, 130.98, 112.99, 109.81, 108.50, 75.98, 44.69, 44.53, 37.45, 31.93, 31.79, 30.15, 30.06, 29.01, 28.88, 28.85, 27.57, 26.07, 24.80, 22.77, 18.46, 18.26, 14.21, -3.44, -4.11. HRMS (ESI) calcd for $C_{31}H_{50}O_4Si$ $[M+H]^+$: m/z 515.3551, found: 515.3559.

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3.2.9. Synthesis of compound (4)

To a solution of **9** (1.4 g, 2.72 mmol, 1.0 equiv) in THF (40 mL) was added tetrabutylammonium fluoride (1M in THF, 3.0 mL, 1.1 equiv), and the resultant mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated. aq. NH_4Cl (10 mL), and the resultant mixture was extracted with Et_2O (3 x 10 mL). The organic layers were sequentially washed with water (5 mL) and then with brine (5 mL), and dried over anhydrous $MgSO_4$. The solvent of the extract was removed under vacuum, the residue was subjected to column chromatography on silica gel (hexane/EtOAc: 10/1) to afford **4** (1.0 g, 92%) as a white solid. R_f = 0.6 (hexane/EtOAc: 10/1). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.17 (dt, *J* = 5.1, 2.3 Hz, 1H), 6.40 (d, *J* = 1.8 Hz, 1H), 6.24 (d, *J* = 1.8 Hz, 1H), 3.84 (ddd, *J* = 17.8, 4.8, 2.3 Hz, 1H), 2.68 (td, *J* = 11.3, 4.6 Hz, 1H), 2.50 – 2.38 (m, 1H), 2.10 – 1.95 (m, 2H), 1.85 (td, *J* = 11.7, 4.6 Hz, 1H), 1.50 (ddd, *J* = 8.3, 6.2, 3.5 Hz, 2H), 1.42 (s, 3H), 1.26 – 1.20 (m, 9H), 1.18 (d, *J* = 4.0 Hz, 3H), 1.14 (s, 3H), 1.09 – 1.01 (m, 2H), 0.85 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.30, 154.64, 154.48, 150.56, 140.54, 130.58, 109.23, 108.05, 105.72, 44.61, 44.14, 37.48, 31.92, 31.17, 30.16, 29.89, 28.91, 28.78, 27.68, 24.75, 22.82, 18.46, 14.24. IR (film, cm^{-1}): 3384, 2958, 2927, 2856, 1622, 1412, 1185, 1032, 965, 838; HRMS (ESI) calcd for $C_{25}H_{36}O_4$ $[M+H]^+$: m/z 401.2686, found: 401.2675.

Δ^8-THC, ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.29 (d, *J* = 1.6 Hz, 1H), 6.11 (d, *J* = 1.8 Hz, 1H), 5.44 (dd, *J* = 4.8, 2.6 Hz, 1H), 4.66 (s, 1H), 3.24 – 3.16 (m, 1H), 2.70 (d, *J* = 4.8 Hz, 1H), 2.45 (td, *J* = 7.7, 5.2 Hz, 2H), 2.18 – 2.11 (m, 1H), 1.89 – 1.78 (m, 3H), 1.71 (s, 3H), 1.60 – 1.54 (m, 2H), 1.38 (s, 3H), 1.34 – 1.29 (m, 4H), 1.11 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.00, 154.88, 142.87, 134.90, 119.47, 110.63, 110.26, 107.75, 45.00, 36.14, 35.57, 31.70, 30.75, 28.02, 27.71, 23.64, 22.69, 18.64, 14.17. HRMS (ESI) calcd for $C_{21}H_{30}O_2$ $[M+H]^+$: m/z 315.2319, found: 315.2330.

11-Nor-Δ^8-Tetrahydrocannabinol-9-carboxylic Acid, ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.03 (dd, *J* = 5.2, 2.6 Hz, 1H), 6.18 (d, *J* = 1.6 Hz, 1H), 6.10 (d, *J* = 1.6 Hz, 1H), 3.87 (ddd, *J* = 17.7, 4.5, 2.4 Hz, 1H), 2.60 (td, *J* = 11.2, 4.4 Hz, 1H), 2.43 (d, *J* = 8.6 Hz, 1H), 2.40 (d, *J* = 7.7 Hz, 2H), 2.10 – 1.96 (m, 1H), 1.85 – 1.72 (m, 2H), 1.59 – 1.53 (m, 2H), 1.37 (s, 3H), 1.36 – 1.28 (m, 4H), 1.09 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 170.90, 157.83, 155.76, 143.73, 139.41, 132.43, 110.98, 109.75, 108.54, 77.00, 46.06, 36.62, 32.80, 32.66, 32.05, 31.52, 29.55, 27.91, 23.60, 18.43, 14.40. HRMS (ESI) calcd for $C_{21}H_{28}O_4$ $[M+H]^+$: m/z 345.2060, found: 345.2056.

Δ^9-THC, ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.33 – 6.30 (m, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 6.15 (d, *J* = 1.6 Hz, 1H), 4.80 (s, 1H), 3.21 (dt, *J* = 10.9, 2.6 Hz, 1H), 2.44 (td, *J* = 7.5, 3.5 Hz, 2H), 2.21 – 2.14 (m, 2H), 1.95 – 1.89 (m, 1H), 1.70 (d, *J* = 2.0 Hz, 1H), 1.69 (dq, *J* = 2.3, 1.0 Hz, 3H), 1.59 – 1.54 (m, 2H), 1.42 (s, 3H), 1.41 (s, 1H), 1.33 – 1.28 (m, 4H), 1.10 (s, 3H), 0.90 – 0.87 (m, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.91, 154.30, 142.97, 134.56, 123.85, 110.23, 109.17, 107.68, 77.37, 45.93, 35.61, 33.70, 31.65, 31.30, 30.79, 27.71, 25.15, 23.51, 22.68, 19.41, 14.16. HRMS (ESI) calcd for $C_{21}H_{30}O_2$ $[M+H]^+$: m/z 315.2319, found: 315.2320.

Δ^9-THC-COOH, ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.05 (d, *J* = 2.2 Hz, 1H), 6.20 (s, 1H), 6.11 (s, 1H), 3.35 (d, *J* = 3.4 Hz, 1H), 2.53 (dd, *J* = 18.5, 6.8 Hz, 1H), 2.42 (t, *J* = 7.6 Hz, 3H), 2.04 (dd, *J* = 12.8, 7.3 Hz, 1H), 1.69 – 1.51 (m, 3H), 1.41 (s, 4H), 1.32 (ddd, *J* = 12.7, 10.0, 5.6 Hz, 4H), 1.09 (s, 3H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 171.52, 157.20, 155.95, 144.78, 144.07, 130.08, 109.84, 108.39, 108.19, 77.92, 46.15, 36.64, 35.95, 32.65, 32.06, 27.92, 26.66, 25.50, 23.61, 19.25, 14.40. HRMS (ESI) calcd for $C_{21}H_{28}O_4$ $[M+H]^+$: m/z 345.2060, found: 345.2059.

4. Conclusion

In this study, a straightforward synthetic route was developed for the synthesis of a key intermediate on a multigram scale to be used for the synthesis of cannabinoid metabolites. Optimization of the riley oxidation of the key tricyclic intermediate is significantly improving the yield and make it achievable to apply this condition into the synthesis of different analogues of this skeleton. And this kind of analogue used as a product to meet the different needs in different labs for synthesis of potential cannabinoid metabolites. Similar synthesis strategies could be applied in the synthesis of similar metabolites of other cannabinoids metabolites like 11-Nor-Δ^8-Tetrahydrocannabinol-9-carboxylic Acid and Δ^9-THC-COOH.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. NMR and HRMS spectra for eleven products (compound **5**, compound **6**, compound **7**, compound **8**, compound **10**, compound **11**, compound **12**, compound **14**, compound **15**, compound **3**, compound **9**, compound **4**, compound **12**, Δ^8-THC, Δ^9-THC, 11-Nor-Δ^8-Tetrahydrocannabinol-9-carboxylic Acid, Δ^9-THC-COOH).

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