The Diels-Alder Approach towards Cannabinoid Derivatives and Formal Synthesis of Tetrahydrocannabinol (THC)

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Based on the Diels-Alder reaction of vinylchromenes with electron-poor dienophiles, we developed a strategy for the synthesis of tetrahydrocannabinol derivatives. Substituted vinylchromenes could be converted with several dienophiles to successfully isolate several complex molecules. These molecules already contain the cannabinoid-like base structure and further processing of one such derivative led to a precursor of Δ9-tetrahydrocannabinol. The most challenging step towards this precursor was an epoxidation step that was ultimately achieved via dimethyl dioxirane.

1. Introduction

Since their discovery more than 50 years ago,[1] cannabinoids,[2] a group of around 60 secondary metabolites found in Cannabis sativa, have received plenty of attention due to their immense pharmacological capabilities. Their mode of action is based on their effect on the endocannabinoid system, i.e. the cannabinoid-receptors, and new details are still uncovered.[3]

The most prominent compound, 2Δ-tetrahydrocannabinol (1, THC, Figure 1),[2] is responsible for the psychoactive effects of C. sativa and has antiemetic and appetizing properties so that it can be used for the treatment of e.g. anorexia in acquired immune deficiency syndrome (AIDS)-patients[4] and nausea as a side effect of chemotherapy.[3] Furthermore, it has proven to have analgesic effects and can be used in pain management in multiple sclerosis and neuropathic pain[6] or for the treatment of the tics in Tourette’s syndrome.[7]

More than 20 total syntheses[8] for THC and its derivatives have been reported. However, it can be cost-effectively produced by the extraction of several Cannabis strains or semi synthetically by the extraction of Cannabidiol (2, CBD, Figure 1) and a subsequent ring-closing procedure.[9] In this context, synthetic efforts are not focused on THC but rather on analog compounds that show stronger and/or more selective effects. Research on cannabinoids is going strong and a journal dedicated solely to give a platform to discuss all aspects of cannabinoids has been created.[10] Furthermore, the search for compounds to selectively address certain targets within the endocannabinoid system is ongoing.

The design of novel compounds is often based on the structure of THC (1); referred to as classical cannabinoids.[11] However, non-related structures have been developed that can influence the endocannabinoid system just as effectively. A prominent example of non-classical cannabinoids is Rimonabant (3, Figure 1). It shows inverse agonistic effects on the CB-receptors and had been developed as an appetite suppressant to combat chronic obesity.[12] Unfortunately, rimonabant

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Figure 1. The phytocannabinoids THC (1) and CBD (2), non-classical cannabinoid Rimonabant (3), and the classical cannabinoids Nabilone (4), HU-210 (5), and HU-211 (6).
showed severe psychiatric side effects and was consequently suspended.\cite{13}

Of the cannabinoids based on the THC structure, one of the most functional is the synthetic compound Nabilone (4, Figure 1). Traded by the name of Cesamet\textsuperscript{®} it shows similar activity to THC and is used just like THC for the treatment of nausea as a side effect of chemotherapy and against anorexia in AIDS patients. Additionally, it has been shown that it can be beneficial for the relief of pain and functional movement in fibromyalgia patients.\cite{14} Not only has Nabilone (4) a better bioavailability, moreover, the ratio of analgesic to psychoactive effect is shifted towards the analgesic aspect when compared to THC (1). The same clinical trial suggested that nabilone (4) can enhance the positive mood while cognitive impairment is on a low level.\cite{15}

Still considered to be the most potent cannabinoid known is HU-211 (5, Figure 1), a synthetic cannabinoid created by the group of Mechoulam.\cite{16} It is the reduced form of HU-210 (6, Figure 1) which already exhibits a longer-lasting activity that is 100 to 800 fold higher when compared to THC (1). HU-210 promotes neurogenesis and thereby exhibits anxiolytic and antidepressant effects.\cite{17}

Strategies to synthesize classical cannabinoids cover a broad range of approaches. Minami and Coworkers have shown that vinyl chromenes 7 (Scheme 1A) can undergo Diels-Alder reactions.\cite{18} However, they had to employ high reaction temperatures and found that the resulting double bond isomerized. In our last publication on the topic we reported that the Diels-Alder reaction could be successfully implemented with maleic anhydride for derivatives 10 that did not bear the hydroxy group (Scheme 1B).\cite{19} Subsequently, the Diels-Alder products were successfully transformed into THC derivatives.

In this publication, we report the successful transfer of the strategy to substrates, which fulfill the requirements of the THC framework, a 7-alkyl substitution, and a 5-hydroxy group. The substituted vinyl chromenes 13, methoxy modified versions of 7, serve as synthetic hubs toward further functionalization. Access to the starting substrates 16a/16b is feasible by existing protocols from phenol precursors 14a/14b. This suggests that a large variety of analogs should be accessible by employing the respective phenol derivatives.\cite{20} With the right substitution pattern, we could successfully synthesize a compound that has been reported as an intermediate in a THC total synthesis, thereby our protocol constitutes a formal synthesis.

2. Results and Discussion

Our modular strategy is centered around vinyl chromenes 13 which can undergo Diels-Alder reactions with a variety of dienophiles (Scheme 2).\cite{21} These Diels-Alder products 12 can be further derivatized, which gives the potential to synthesize a large library of cannabinoid compounds. The vinyl chromenes 13 are accessible through several steps from commercially available resorcinol derivatives 14.

At first, the dimethylchromenes 16a and 16b were synthesized (Scheme 3). One feasible pathway is a two-step protocol in which a Friedel-Crafts acylation towards acylbenzenes 15a and 15b is followed by an aldol reaction that has been employed by Ko et al. for other derivatives.\cite{22} The two-step protocol gave sufficient material of the methyl-substituted derivative 16a, while the pentyl substituted derivative 16b was synthesized in a single step by a protocol according to Press et al.\cite{23} Here, olivetol (14b) reacts directly with 3,3-dimethylacryloyl chloride, resulting in dimethylchromene 16b.

Figure 2 shows the confirmation of the structures via X-ray crystallography for 15a, 15b, and 16a.

The dimethylchromenes 16a and 16b, were then transferred to vinyl chromenes 13a and 13b in five synthetic steps (Scheme 4). First, the phenolic hydroxyl groups of 16 are protected as methoxy groups with methyl iodide in good to excellent yields. For larger quantities, dimethyl sulfate in acetone led to similar good results. The hydroxymethylation of methoxy ethers 17 is achieved via lithiation at C-3 and the

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**Scheme 1.** A) Diels-Alder-concept by Minami et al.: a) 10 equiv. acrylic acid methyl ester, 1 equiv. DBU, DMF, 100 °C;\cite{18} B) Diels-Alder-concept by Glaser et al. b) maleic anhydride, CH3CN, r.t., 12 h.\cite{19}

**Scheme 3.** Synthesis of dimethylchromenes 16a and 16b via different protocols. a) FeCl3, 3,3-Dimethylacryloyl chloride, chloroform, 12 h, r.t., 3 h, 40 °C, 16b 52%; b) AlCl3, C5H5Cl, AcCl, 30 min, 40 °C, then 45 min, 75 °C, 15a 77%, 15b 79%; c) acetone, pyridoline, toluene, 110 °C, 14 h, Dean-Stark conditions, 16a 62%, 16b 38%.
addition of N-(hydroxymethyl)phthalimide as an electrophile. A side product formed in this reaction when it was allowed to warm up before quenching and is described in the supporting information. Reduction to diols 19 and subsequent oxidation that also triggers an elimination, leads to α,β-unsaturated aldehydes 20. A Wittig reaction then transforms the aldehydes to the vinyl chromenes 13a and 13b. The structures of 17a and 18a could be confirmed by X-ray crystallography and are shown in Figure 3.

While the vinyl chromenes 13 have been successfully stored at −20 °C and under argon atmosphere for several days, it is recommended to transform them into the Diels-Alder product as soon as possible. At room temperature, it was observed that the vinyl chromene 13b shows signs of degradation, putatively due to polymerization, oxidation, or dimerization. An attempt to isolate and characterize the resulting compounds has not been successful. Diels-Alder reactions were performed with the substrate 13a (Scheme 5). The reaction with methyl maleic anhydride led to a mixture of the regioisomers 21 and 22. With a 34% yield, regioisomer 21 was the main product, whereas only traces of the second regioisomer were found.

Conversion with maleic anhydride led under slightly different conditions to anhydride 23 in 73% yield.

The relative configuration of the Diels-Alder products 21, 22, and 23 were confirmed via X-ray crystallography and are shown in Figure 4.

Especially interesting are the products of vinyl chromene 13b, since they bear the pharmacophoric pentyl side chain analog to THC. The Diels-Alder reactions performed with this compound are compiled in Scheme 6. The reaction with maleic anhydride showed the best result and gave chromene 24 in a quantitative yield. The other employed dienophiles ethyl (E)-4-oxobut-2-enolate, methyl maleic anhydride and bromo maleic anhydride led to smaller yields. However, in contrast to reaction a) two regioisomers can be obtained in those reactions, which makes a column chromatographic step necessary. For reactions b) and c) both regioisomers could be separated while for d) only one regioisomer has been isolated. We assume that the significantly lower overall isolated yields can be explained by loss in the chromatographic step due to the polar character of the products and the possibility of hydrolytic degradation on the stationary phase. Additionally, the longer required reaction times that were needed for complete conversion of reactions b) to d) could allow the rather delicate diene to degrade.

The Diels-Alder Product 24 was then transformed in several additional steps to chromene 35 (Scheme 7). Several conditions for the hydration of the double bond were tested and complete...
conversion to 30 was observed with 25 mol% Pd/C catalyst loading in a pressurized reactor with a 20 bar hydrogen atmosphere. Subsequently, the anhydride was hydrolyzed followed by an oxidative decarboxylation to alkene 32. The epoxidation of alkene 32 proved to be a challenging endeavor as harsh conditions (e.g., m-CPBA, H₂O₂) resulted in over-oxidation and too mild conditions (e.g., H₂O₂/urea) showed no conversions. The tested reaction conditions are summarized in Table 1. Ultimately it was found that the epoxidation proceeded with the highest yield by employing dimethyl dioxirane (DMDO). The DMDO was freshly prepared according to Taber et al[22]. The absolute cis configuration of epoxide 33 was confirmed via the NOESY technique and a ring-opening reaction performed, which resulted in alcohol 34. This alcohol was then oxidized to literature known α,β-unsaturated ketone 35 which can be described as a precursor for THC since all

![Diagram of molecular structures](image-url)

**Scheme 6.** Diels-Alder reactions with diene 13 b: a) maleic anhydride, ACN, 0 °C to r.t., 16 h, 24, quant.; b) ethyl (E)-4-oxobut-2-enoate, DCM, 0 °C to r.t., 36 h, 25 14%, 26 7%. c) methyl maleic anhydride, ACN, 0 °C to r.t., 60 h, 27 33%, 28 10%; d) bromo maleic anhydride, ACN, 0 °C to r.t., 36 h, 29 17%, second regioisomer was not isolated.

**Scheme 7.** Modification of Diels-Alder product 24. a) 25 mol% Pd/C, 20 bar H₂, EtOAc, 16 h, 25, quant.; b) m-CPBA, pyridine, 55 °C, 2 h, 43%; c) DMDO, Acetone, 0 °C, 2 h, 30%; d) MeLi, THF, –78°C bis r. t. 12 h; f) Dess-Martin periodinane, CH₂Cl₂, 1 h, r. t., 49%.

**Table 1.** Summary of tested epoxidation reactions with alkene 32: A: m-CPBA (70 %), DCM, 0 °C to r.t., 12 h; B: m-CPBA (99 %), DCM, 0 °C to r.t., 12 h; C: TFAA, CO(NH₂)₂·H₂O₂, DCM, 0 °C, 2 h; D: 2.00 equiv. H₂O₂, NaOH, iPrOH, 0 °C, 2 h, r.t., 12 h; E: 1.00 equiv. DMDO, acetone, 0 °C, 2 h, r.t., 12 h; F: 1.50 equiv. DMDO, acetone, 0 °C, 2 h, volatiles removed in high vacuum with a cooling trap.

| Entry | Conditions | Oxidant | Isolated yield 33 [%] |
|-------|------------|---------|-----------------------|
| 1     | A          | m-CPBA 70% | 2                     |
| 2     | B          | m-CPBA 99 % | 9                    |
| 3     | C          | CO(NH₂)₂·H₂O₂  | _[3]_         |
| 4     | D          | H₂O₂    | _[3]_         |
| 5     | E          | DMDO    | 23                   |
| 6     | F          | DMDO    | 28                   |

[a] no product, starting material was lost, [b] no turnover, partial recovery of starting material.
necessary conversions have been reported. The relative configuration of the Diels-Alder products 24 and the dicarboxylic acid 31 was confirmed via X-ray crystallography and is shown in Figure 5.

3. Conclusions

Vinyl chromenes 13 can be synthesized via a multi-step reaction protocol from resorcinol derivatives. The chromenes can then undergo Diels-Alder reactions with electron-poor dienophiles to give classical cannabinoid-like trycyles. Especially the reaction with maleic anhydride to anhydride 24 is highly interesting and gives high yields.

From anhydride 24, a reaction sequence was developed that allowed the conversion to ketone 35, which constitutes the formal synthesis of THC as further reaction protocols have been published. The novel compounds synthesized in this work constitute potential cannabinoid analogs and could be used in structure-activity relationship studies for the development of highly active ligands for the cannabinoid receptors.

**Experimental Section**

**X-ray Crystal Structure Determination**

The single-crystal X-ray diffraction studies were carried out on a BrukerNonius KappaCCD diffractometer at 123(2) K using Mo–Kα radiation (λ=0.71073 Å) (15a, 16a, 15b, 17a, 18a, 21, 22, 23) or an Agilent SuperNova Dual diffractometer with Atlas detector at 123(2) K using Cu–Kα radiation (λ=1.5418 Å) (24, 31). Direct Methods (SHELXS-97) were used for structure solution and refinement was carried out using SHELXL-97 or SHELXL-2013 (full-matrix least-squares on F²). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(O)) free. Semi-empirical absorption corrections were applied for 24 and 31.

15a: colorless crystals, C₁₅H₂₂O₃, Mᵣ = 266.37, crystal size 0.10×0.05 mm, monoclinic, space group P2₁/c (No. 14), a = 3.896(1) Å, b = 27.004(3) Å, c = 14.957(2) Å, α = 91.90(1)°, V = 1572.75(5) Å³, Z = 8, ρ = 1.404 Mg/m³, μ(Mo-Kα) = 0.105 mm⁻¹, F(000) = 704, 2θmax = 50.0°, 10498 reflections, of which 2771 were independent (Rint = 0.082), 233 parameters, 4 restraints, R(1) = 0.057 (for 1761 I > 2σ(I)), wR2 = 0.149 (all data), S = 1.03, largest diff. peak/hole = 0.223/−0.340 e Å⁻³.

15b: colorless crystals, C₁₆H₁₇O₅, Mᵣ = 260.23, crystal size 0.50×0.30×0.02 mm, orthorhombic, space group Pbcn (No. 61), a = 6.452(1) Å, b = 16.056(2) Å, c = 19.933(2) Å, V = 2067.05(1) Å³, Z = 8, ρ = 1.325 Mg/m³, μ(Mo-Kα) = 0.095 mm⁻¹, F(000) = 880, 2θmax = 55.0°, 14289 reflections, of which 2374 were independent (R(1) = 0.024), 142 parameters, 1 restraint, R(int) = 0.037 (for 2057 I > 2σ(I)), wR2 = 0.103 (all data), S = 1.03, largest diff. peak/hole = 0.310/−0.181 e Å⁻³.

16a: yellow crystals, C₁₆H₁₉O₅, Mᵣ = 222.26, crystal size 0.24×0.12×0.08 mm, monoclinic, space group P2₁/n (No. 14), a = 8.156(1) Å, b = 12.127(1) Å, c = 12.250(1) Å, β = 91.821(1)°, V = 1211.02(2) Å³, Z = 4, ρ = 1.219 Mg/m³, μ(Mo-Kα) = 0.085 mm⁻¹, F(000) = 480, 2θmax = 55.0°, 16004 reflections, of which 2766 were independent (R(1) = 0.046), 152 parameters, 2 restraints, R(int) = 0.047 (for 1949 I > 2σ(I)), wR2 = 0.116 (all data), S = 1.03, largest diff. peak/hole = 0.261/−0.181 e Å⁻³.

17a: colorless crystals, C₁₅H₂₁O₅, Mᵣ = 250.28, crystal size 0.36×0.30×0.03 mm, triclinic, space group P-1 (No. 2), a = 5.600(1) Å, b = 8.754(1) Å, c = 11.880(1) Å, α = 74.741(1)°, β = 86.021(1)°, γ = 83.741(1)°, V = 558.00(13) Å³, Z = 2, ρ = 1.311 Mg/m³, μ(Mo-Kα) = 0.092 mm⁻¹, F(000) = 536, 2θmax = 50.0°, 6143 reflections, of which 2185 were independent (R(1) = 0.046), 168 parameters, 1 restraint, R(int) = 0.037 (for 1580 I > 2σ(I)), wR2 = 0.123 (all data), S = 1.04, largest diff. peak/hole = 0.321/−0.248 e Å⁻³.

18a: colorless crystals, C₁₅H₂₂O₅, Mᵣ = 342.38, crystal size 0.30×0.12×0.06 mm, monoclinic, space group P2₁/c (No. 14), a = 9.726(1) Å, b = 11.069(1) Å, c = 16.369(2) Å, α = 105.284(1)°, V = 1736.0(3) Å³, Z = 4, ρ = 1.310 Mg/m³, μ(Mo-Kα) = 0.094 mm⁻¹, F(000) = 728, 2θmax = 55.0°, 19159 reflections, of which 3975 were independent (R(1) = 0.060), 228 parameters, R(int) = 0.056 (for 2942 I > 2σ(I)), wR2 = 0.149 (all data), S = 1.02, largest diff. peak/hole = 0.363/−0.330 e Å⁻³.

21: colorless crystals, C₁₅H₂₂O₅, Mᵣ = 342.38, crystal size 0.30×0.12×0.06 mm, monoclinic, space group P2₁/c (No. 14), a = 11.055(1) Å, b = 12.230(1) Å, c = 16.692(1) Å, α = 94.155(1)°, V = 17115.5(2) Å³, Z = 4, ρ = 1.329 Mg/m³, μ(Mo-Kα) = 0.095 mm⁻¹, F(000) = 779, 2θmax = 55.0°, 16881 reflections, of which 3291 were independent (R(1) = 0.035), 228 parameters, R(int) = 0.046 (for 2965 I > 2σ(I)), wR2 = 0.119 (all data), S = 1.03, largest diff. peak/hole = 0.288/−0.257 e Å⁻³.

23: colorless crystals, C₁₅H₂₂O₅, Mᵣ = 328.35, crystal size 0.28×0.08×0.03 mm, triclinic, space group P-1 (No. 2), a = 5.5653(5) Å, b = 10.3182(15) Å, c = 14.6468(7) Å, α = 107.767(7)°, β = 94.964(6)°, γ = 96.607(9)°, V = 789.02(14) Å³, Z = 2, ρ = 1.382 Mg/m³, μ(Mo-Kα) = 0.100 mm⁻¹, F(000) = 348, 2θmax = 50.0°, 9012 reflections, of which 2763 were independent (R(1) = 0.108), 219 parameters, R(int) = 0.107 (for 1539 I > 2σ(I)), wR2 = 0.304 (all data), S = 1.09, largest diff. peak/hole = 0.534/−0.457 e Å⁻³.

24: colorless crystals, C₁₅H₂₂O₅, Mᵣ = 384.45, crystal size 0.20×0.08×0.02 mm, triclinic, space group P-1 (No. 2), a = 11.5457(3) Å, b = 11.5996(6) Å, c = 16.0800(7) Å, α = 72.497(4)°, β = 88.706(3)°, γ = 87.052(3)°, V = 2051.04(15) Å³, Z = 4, ρ = 1.245 Mg/m³, μ(Cu-Kα) = 14.08 (all data), S = 1.03, largest diff. peak/hole = 0.223/−0.340 e Å⁻³.
Conflict of Interest

The authors declare no conflict of interest.

Keywords: natural products - medicinal chemistry - fused-ring systems - cycloaddition reactions - Diels-Alder reactions

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