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

Thomas Hurrle,[a, b] Franziska Gläser,[a] Manuel C. Bröhmer,[a] Martin Nieger,[c] and Stefan Bräse*[a, b]

Based on the Diels-Alder reaction of vinylchromenes with electron-poor dienophiles, we developed a strategy for the synthesis of tetrahydrocannabinol derivatives. Substituted vinyl chromenes 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 Δ^9-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, Δ^9-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.[5] 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)
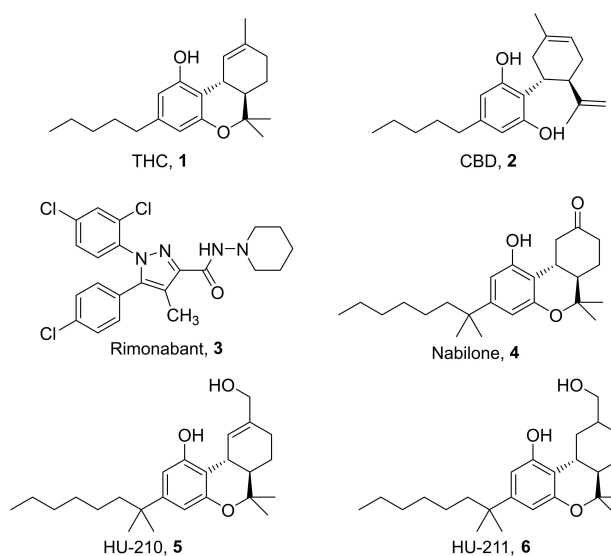

Figure 1. The phytocannabinoids THC (**1**) and CBD (**2**), non-classical cannabinoid Rimonabant (**3**), and the classical cannabinoids Nabilone (**4**), HU-210 (**5**), and HU-211 (**6**).

[a] Dr. T. Hurrle, Dr. F. Gläser, Dr. M. C. Bröhmer, Prof. Dr. S. Bräse
Institute of Organic Chemistry
Karlsruhe Institute of Technology (KIT) Campus South
Fritz-Haber-Weg 6
76131 Karlsruhe (Germany)
E-mail: braese@kit.edu
[b] Dr. T. Hurrle, Prof. Dr. S. Bräse
Institute of Biological and Chemical Systems (IBCS-FMS)
Karlsruhe Institute of Technology (KIT) Campus North
Hermann-von-Helmholtz-Platz 1
76344 Eggenstein-Leopoldshafen (Germany)
[c] Dr. M. Nieger
Department of Chemistry
University of Helsinki
P.O. Box 55, A.I.Virtasen aukio 1
00014 Helsinki (Finland)

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

ChemistryOpen

Full Papers
doi.org/10.1002/open.202000343

Chemistry Europe
European Chemical
Societies Publishing

showed severe psychiatric side effects and was consequently suspended.[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® 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.[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.[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.[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.[17]

Strategies to synthesize classical cannabinoids cover a broad range of approaches.[8] Minami and Coworkers have shown that vinyl chromenes **7** (Scheme 1A) can undergo Diels-Alder reactions.[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).[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.[19] 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).[19] 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**.
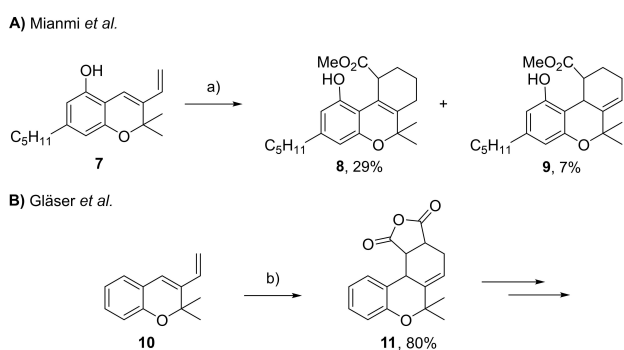
At first, the dimethylchromenes **16a** and **16b** were synthesized (Scheme 3). One feasible pathway is a two-step protocol in which a Friedel-Crafts acylation towards acylbenzenes **15a** and **15b** is followed by an aldol reaction that has been employed by Ko *et al.* for other derivatives.[20] The 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.[21] 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**.
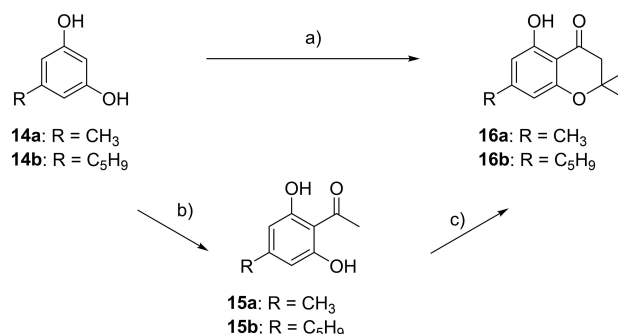
The dimethylchromenes **16a** and **16b**, were then transferred to vinyl chromenes **13a** and **13b** in five synthetic steps (Scheme 4). First, the phenolic hydroxyl groups of **16** are protected as methoxy groups with methyl iodide in good to excellent yields. For larger quantities, dimethyl sulfate in acetone led to similar good results. The hydroxymethylation of methoxy ethers **17** is achieved via lithiation at C-3 and the
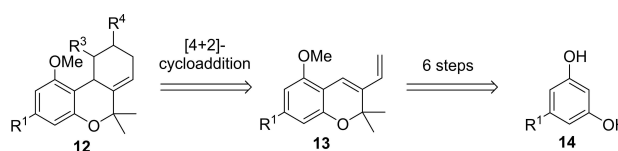
Scheme 2. Vinyl chromenes 13 as synthetic hub towards cannabinoids.[19]

Scheme 1. A): Diels-Alder-concept by Minami et al.: a) 10 equiv. acrylic acid methyl ester, 1 equiv. DBU, DMF, 100 °C.[18] **B**): Diels-Alder-concept by Gläser et al. b) maleic anhydride, CH3CN, r.t., 12 h.[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, C₆H₅Cl, AcCl, 30 min, 40 °C, then 45 min, 75 °C, **15a** 77 %, **15b** 79 %; c) acetone, pyrrolidine, toluene, 110 °C, 14 h, Dean-Stark conditions, **16a** 62 %, **16b** 38 %.
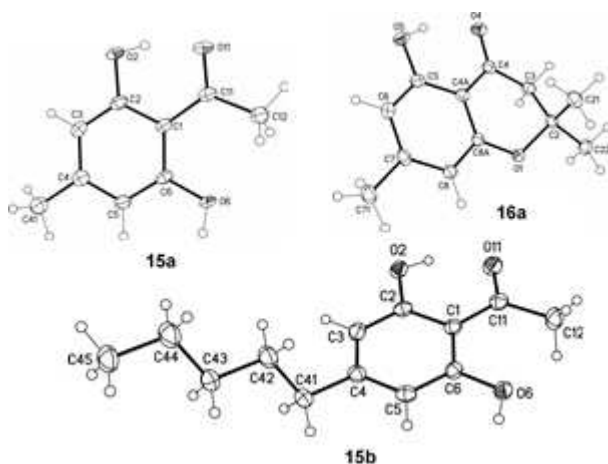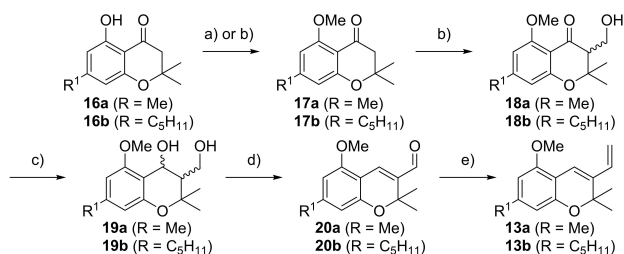
ChemistryOpen

Full Papers
doi.org/10.1002/open.202000343

Chemistry
Europe
European Chemical
Societies Publishing

Figure 2. Molecular crystal structures of **15 a** (one of the two crystallographic independent molecules), **16 a**, and **15 b** (displacements are drawn at 50 % probability levels).

Scheme 4. Synthesis of vinyl chromenes **13 a** and **13 b**: a) MeI, K₂CO₃, DMF, *reflux*, 12 h, 82 % **17 a**, 95 % **17 b**; b) Me₂S₂O₄, Acetone, reflux, 4 h, 97 % **17 b**; c) LiTMP, N-(hydroxymethyl)phthamimide, THF, −78 °C, 2 h, 82 % **18 a**, 82 % **18 b**; d) LiAlH₄, THF, 0 °C bis r. t., 2 h, 77 % **19 a**, >98 % **19 b**; e) Oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, −55 °C, 3 h, 80 % **20 a**, 89 % **20 b**; f) MePPh₃Br, t-BuOK, THF, −78 °C to r. t., 30 min, 81 % **13 a**, 95 % **13 b**.

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 **13 a** and **13 b**. The structures of **17 a** and **18 a** 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 **13 b** 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 **13 a** (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.
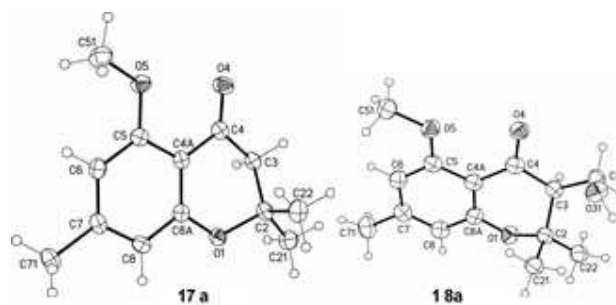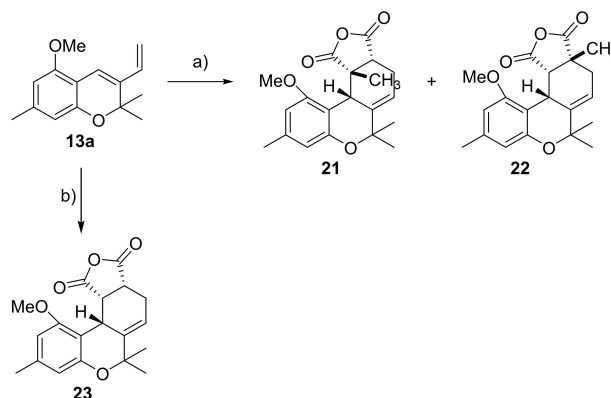

Figure 3. Molecular structures of **17 a** and **18 a** (displacements are drawn at 50 % probability levels).

Scheme 5. Diels-Alder modification of **13 a**: a) methyl maleic anhydride, CH₂Cl₂, RT, 16 h, 34 % **21**, 1 % **22**; b) maleic anhydride, CH₃CN, RT, 13 h, 73 %.

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 **13 b**, 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-enoate, 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
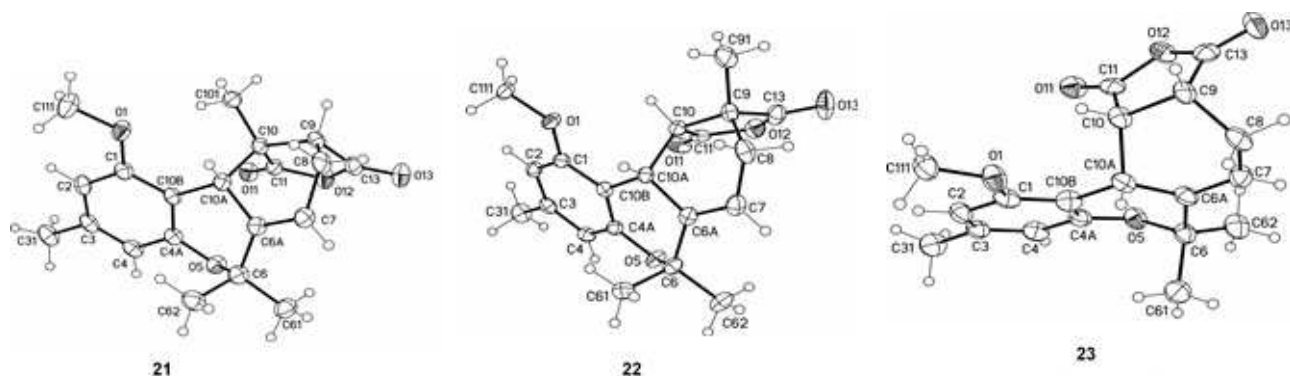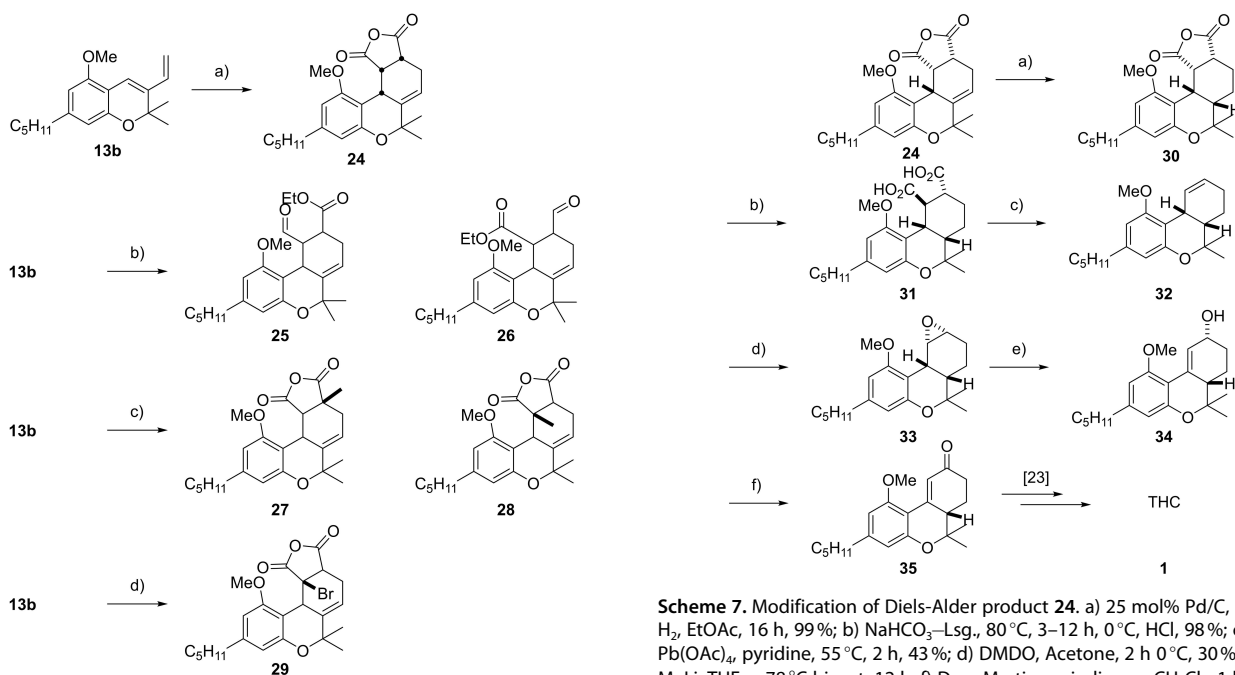
ChemistryOpen

Full Papers
doi.org/10.1002/open.202000343

Chemistry Europe
European Chemical
Societies Publishing

Figure 4. Molecular structures of **21**, **22**, and **23** (displacements are drawn at 50 % probability levels).

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 H_2, EtOAc, 16 h, 99 %; b) $NaHCO_3$–Lsg., 80 °C, 3–12 h, 0 °C, HCl, 98 %; c) $Pb(OAc)_4$, pyridine, 55 °C, 2 h, 43 %; d) DMDO, Acetone, 2 h 0 °C, 30 %; e) MeLi, THF, −78 °C bis r. t. 12 h; f) Dess-Martin periodinane, CH_2Cl_2, 1 h, r. t., 49 %.

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, H_2O_2) resulted in over-oxidation and too mild conditions (e.g.H_2O_2/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

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, $CO(NH_2)_2 \cdot H_2O_2$, DCM, 0 °C, 2 h; D: 2.00 equiv. H_2O_2, 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	$CO(NH_2)_2 \cdot H_2O_2$	–[a]
4	D	H_2O_2	–[b]
5	E	DMDO	23
6	F	DMDO	28

[a] no product, starting material was lost, [b] no turnover, partial recovery of starting material.

ChemistryOpen

Full Papers
doi.org/10.1002/open.202000343

Chemistry Europe
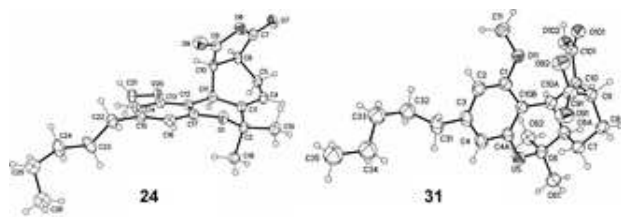European Chemical
Societies Publishing

Figure 5. Molecular structures of **24** (one of the two crystallographic independent molecules) and **31** (minor disordered parts omitted for clarity, displacements are drawn at 50% probability levels).

necessary conversions have been reported.[23] 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 tricycles. 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–Ka radiation ($\lambda = 0.71073$ Å) (**15a, 16a, 15b, 17a, 18a, 21, 22, 23**) or an Agilent SuperNova Dual diffractometer with Atlas detector at 123(2) K using Cu–Ka radiation ($\lambda = 1.54178$ Å) (**24, 31**). Direct Methods (SHELXS-97)[24] were used for structure solution and refinement was carried out using SHELXL-97[24] or SHELXL-2013[25] (full-matrix least-squares on F^2). 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, $C_9H_{10}O_3$, $M_r = 166.17$, crystal size $0.30 \times 0.10 \times 0.05$ mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 3.896(1)$ Å, $b = 27.004(3)$ Å, $c = 14.957(2)$ Å, $\beta = 91.90(1)°$, $V = 1572.7(5)$ Å^3, $Z = 8$, $\rho = 1.404$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.105$ mm^{-1}, $F(000) = 704$, $2\theta_{max} = 50.0°$, 10489 reflections, of which 2771 were independent ($R_{int} = 0.082$), 233 parameters, 4 restraints, $R_1 = 0.057$ (for 1761 I $> 2\sigma(I)$), $wR_2 = 0.149$ (all data), $S = 1.03$, largest diff. peak/hole $= 0.223/ -0.340$ e Å^{-3}.

15a is a redetermination of (2,6-dihydroxy-4-methylphenyl) ethanone at 123 K [CCDC-732688, S. K.Seth, D.K. Hazra, M. Mukherjee, T.Kar, *Journal of Molecular Structure*, 2009, **936**, 277–282, DOI: 10.1016/j.molstruc.2009.08.013].

15b: colorless crystals, $C_{12}H_{14}O_3$, $M_r = 206.23$, crystal size $0.50 \times 0.30 \times 0.20$ mm, orthorhombic, space group $Pbca$ (No. 61), $a = 6.452(1)$ Å, $b = 16.056(2)$ Å, $c = 19.953(2)$ Å, $V = 2067.0(5)$ Å^3, $Z = 8$, $\rho = 1.325$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.095$ mm^{-1}, $F(000) = 880$, $2\theta_{max} = 55.0°$, 14289 reflections, of which 2374 were independent ($R_{int} = 0.024$), 142 parameters, 1 restraint, $R_1 = 0.037$ (for 2057 I $> 2\sigma(I)$), $wR_2 = 0.103$ (all data), $S = 1.03$, largest diff. peak/hole $= 0.310/ -0.181$ e Å^{-3}.

16a: yellow crystals, $C_{13}H_{18}O_3$, $M_r = 222.27$, crystal size $0.24 \times 0.12 \times 0.08$ mm, monoclinic, space group $P2_1/n$ (No. 14), $a = 8.156(1)$ Å, $b = 12.127(1)$ Å, $c = 12.250(1)$ Å, $\beta = 91.82(1)°$, $V = 1211.0(2)$ Å^3, $Z = 4$, $\rho = 1.219$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.085$ mm^{-1}, $F(000) = 480$, $2\theta_{max} = 55.0°$, 16004 reflections, of which 2766 were independent ($R_{int} = 0.046$), 152 parameters, 2 restraints, $R_1 = 0.047$ (for 1949 I $> 2\sigma(I)$), $wR_2 = 0.116$ (all data), $S = 1.03$, largest diff. peak/hole $= 0.261/ -0.181$ e Å^{-3}.

17a: colorless crystals, $C_{13}H_{16}O_3$, $M_r = 220.26$, crystal size $0.36 \times 0.30 \times 0.03$ mm, triclinic, space group $P\text{-}1$ (No. 2), $a = 5.600(1)$ Å, $b = 8.754(1)$ Å, $c = 11.880(1)$ Å, $\alpha = 74.74(1)°$, $\beta = 86.02(1)°$, $\gamma = 83.74(1)°$, $V = 558.00(13)$ Å^3, $Z = 2$, $\rho = 1.311$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.092$ mm^{-1}, $F(000) = 236$, $2\theta_{max} = 55.0°$, 8935 reflections, of which 2559 were independent ($R_{int} = 0.053$), 149 parameters, $R_1 = 0.054$ (for 1936 I $> 2\sigma(I)$), $wR_2 = 0.142$ (all data), $S = 1.04$, largest diff. peak/hole $= 0.321/ -0.248$ e Å^{-3}.

18a: colorless crystals, $C_{14}H_{18}O_4$, $M_r = 250.28$, crystal size $0.30 \times 0.20 \times 0.15$ mm, monoclinic, space group $P2_1/n$ (No. 14), $a = 6.0039(4)$ Å, $b = 21.0202(13)$ Å, $c = 10.3763(8)$ Å, $\beta = 106.281(4)°$, $V = 1257.01(15)$ Å^3, $Z = 4$, $\rho = 1.323$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.096$ mm^{-1}, $F(000) = 536$, $2\theta_{max} = 50.0°$, 6143 reflections, of which 2185 were independent ($R_{int} = 0.046$), 168 parameters, 1 restraint, $R_1 = 0.049$ (for 1580 I $> 2\sigma(I)$), $wR_2 = 0.123$ (all data), $S = 1.04$, largest diff. peak/hole $= 0.225/ -0.229$ e Å^{-3}.

21: colorless crystals, $C_{20}H_{22}O_5$, $M_r = 342.38$, crystal size $0.30 \times 0.12 \times 0.06$ mm, monoclinic, space group $P2_1/n$ (No. 14), $a = 9.726(1)$ Å, $b = 11.069(1)$ Å, $c = 16.369(2)$ Å, $\beta = 99.90(1)°$, $V = 1736.0(3)$ Å^3, $Z = 4$, $\rho = 1.310$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.094$ mm^{-1}, $F(000) = 728$, $2\theta_{max} = 55.0°$, 19159 reflections, of which 3975 were independent ($R_{int} = 0.060$), 228 parameters, $R_1 = 0.056$ (for 2942 I $> 2\sigma(I)$), $wR_2 = 0.149$ (all data), $S = 1.02$, largest diff. peak/hole $= 0.363/ -0.330$ e Å^{-3}.

22: colorless crystals, $C_{20}H_{22}O_5$, $M_r = 342.38$, crystal size $0.48 \times 0.16 \times 0.08$ mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 11.055(1)$ Å, $b = 12.230(1)$ Å, $c = 12.692(1)$ Å, $\beta = 94.15(1)°$, $V = 1711.5(2)$ Å^3, $Z = 4$, $\rho = 1.329$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.095$ mm^{-1}, $F(000) = 728$, $2\theta_{max} = 55.0°$, 16881 reflections, of which 3291 were independent ($R_{int} = 0.035$), 228 parameters, $R_1 = 0.046$ (for 2965 I $> 2\sigma(I)$), $wR_2 = 0.119$ (all data), $S = 1.03$, largest diff. peak/hole $= 0.288/ -0.257$ e Å^{-3}.

23: colorless crystals, $C_{19}H_{20}O_5$, $M_r = 328.35$, crystal size $0.28 \times 0.08 \times 0.03$ mm, triclinic, space group $P\text{-}1$ (No. 2), $a = 5.5653(5)$ Å, $b = 10.3182(15)$ Å, $c = 14.6468(7)$ Å, $\alpha = 107.767(7)°$, $\beta = 94.964(6)°$, $\gamma = 96.607(9)°$, $V = 789.02(14)$ Å^3, $Z = 2$, $\rho = 1.382$ Mg/m^{-3}, $\mu(\text{Mo–K}_\alpha) = 0.100$ mm^{-1}, $F(000) = 348$, $2\theta_{max} = 50.0°$, 9012 reflections, of which 2763 were independent ($R_{int} = 0.108$), 219 parameters, $R_1 = 0.107$ (for 1539 I $> 2\sigma(I)$), $wR_2 = 0.304$ (all data), $S = 1.09$, largest diff. peak/hole $= 0.534/ -0.457$ e Å^{-3}.

24: colorless crystals, $C_{23}H_{28}O_5$, $M_r = 384.45$, crystal size $0.20 \times 0.08 \times 0.02$ mm, triclinic, space group $P\text{-}1$ (No. 2), $a = 11.5457(3)$ Å, $b = 11.5996(6)$ Å, $c = 16.0800(7)$ Å, $\alpha = 72.497(4)°$, $\beta = 88.706(3)°$, $\gamma = 87.052(3)°$, $V = 2051.04(15)$ Å^3, $Z = 4$, $\rho = 1.245$ Mg/m^{-3}, $\mu(\text{Cu–K}_\alpha) =$

ChemistryOpen

Full Papers
doi.org/10.1002/open.202000343

Chemistry
Europe

European Chemical
Societies Publishing

0.703 mm^{-1}, $F(000) = 824$, $2\theta_{max} = 147.0°$, 13940 reflections, of which 7972 were independent ($R_{int} = 0.037$), 497 parameters, 177 restraint, $R_1 = 0.069$ (for 6940 I $> 2\sigma$(I)), w$R_2 = 0.205$ (all data), $S = 1.04$, largest diff. peak/hole $= 0.757/-0.511$ e Å^{-3}. In both crystallographic independent molecules the pentyl-substituents are disordered and disordered atoms were refined isotropically (see cif-file for details).

31: colorless crystals, $C_{23}H_{32}O_6$, $M_r = 404.48$, crystal size $0.30 \times 0.20 \times 0.03$ mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 14.109(3)$ Å, $b = 15.579(2)$ Å, $c = 10.487(1)$ Å, $\beta = 106.60(2)°$, $V = 2209.0(6)$ Å^3, $Z = 4$, $\rho = 1.216$ Mg/m^{-3}, μ(Cu–K$_\alpha$) $= 0.708$ mm^{-1}, $F(000) = 872$, $2\theta_{max} = 148.4°$, 6717 reflections, of which 4217 were independent ($R_{int} = 0.062$), 262 parameters, 79 restraints, $R_1 = 0.094$ (for 2773 I $> 2\sigma$(I)), w$R_2 = 0.254$ (all data), $S = 1.06$, largest diff. peak/hole $= 0.493/-0.362$ e Å^{-3}. The pentyl-substituent is disordered and disordered atoms were refined isotropically (see cif-file for details).

https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/open.2020000343 Deposition Numbers 1853371 (**15 a**), 1853373 (**15 b**), 1853372 (**16 a**), 1853374 (**17 a**), 1853375 (**18 a**), 1853378 (**21**), 1853377 (**22**), 1853376 (**23**), 1853379 (**24**), and 1853380 (**31**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures/?.

Supporting Information (see footnote on the first page of this article): Full experimental procedures and detailed spectroscopic data for all compounds.

Conflict of Interest

The authors declare no conflict of interest.

[1] R. Mechoulam, in *Cannabinoids*, John Wiley & Sons, Ltd, Chichester, UK, **2014**, pp. 1–15.

[2] Y. Gaoni, R. Mechoulam, *J. Am. Chem. Soc.* **1964**, *86*, 1646–1647.

[3] R. G. Pertwee, in *Endocannabinoids* (Ed.: R. G. Pertwee), Springer International Publishing, Heidelberg, **2015**, pp. 1–37.

[4] J. E. Beal, R. Olson, L. Lefkowitz, L. Laubenstein, P. Bellman, B. Yangco, J. O. Morales, R. Murphy, W. Powderly, T. F. Plasse, K. W. Mosdell, K. V. Shepard, *j. Pain Symp. Manag.* **1997**, *14*, 7–14.

[5] M. Lane, C. L. Vogel, J. Ferguson, S. Krasnow, J. L. Saiers, J. Hamm, K. Salva, P. H. Wiernik, C. P. Holroyde, S. Hammill, K. Shepard, T. Plasse, *j. Pain Symp. Manag.* **1991**, *6*, 352–359.

[6] a) K. Mackie, *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 101–122; b) J. Zajicek, P. Fox, H. Sanders, D. Wright, J. Vickery, A. Nunn, A. Thompson, U. M. r. group, *The lancet* **2003**, *362*, 1517–1526.

[7] K. Müller-Vahl, A. Koblenz, M. Jöbges, H. Kolbe, H. Emrich, U. Schneider, *Pharmapsych.* **2001**, *34*, 19–24.

[8] a) R. Mechoulam, Y. Gaoni, *J. Am. Chem. Soc.* **1965**, *87*, 3273–3275; b) K. E. Fahrenholtz, M. Lurie, R. W. Kierstead, *J. Am. Chem. Soc.* **1966**, *88*, 2079–2080; c) K. E. Fahrenholtz, M. Lurie, R. W. Kierstead, *J. Am. Chem. Soc.* **1967**, *89*, 5934–5941; d) R. Mechoulam, P. Braun, Y. Gaoni, *J. Am. Chem. Soc.* **1967**, *89*, 4552–4554; e) R. Mechoulam, P. Braun, Y. Gaoni, *J. Am. Chem. Soc.* **1972**, *94*, 6159–6165; f) R. K. Razdan, H. C. Dalzell, G. R. Handrick, *J. Am. Chem. Soc.* **1974**, *96*, 5860–5865; g) B. R. Martin, W. L. Dewey, L. S. Harris, J. Beckner, R. S. Wilson, E. L. May, *Pharmaco. Biochem. Behav.* **1975**, *3*, 849–853; h) T. H. Chan, T. Chaly, *Tetrahredron Lett.* **1982**, *23*, 2935–2938; i) W. E. Childers, H. W. Pinnick, *J. Org. Chem.* **1984**, *49*, 5276–5277; j) M. Moore, R. Rickards, H. Rönneberg, *Austral. J. Org.* **1984**, *37*, 2339–2348; k) M. Srebnik, N. Lander, A. Breuer, R. Mechoulam, *J. Chem. Soc., Perkin Transactions* **1984**, *1*, 2881–2886; l) L. Crombie, W. M. L. Crombie, S. V. Jamieson, C. J. Palmer, *J. Chem. Soc., Perkin Transactions* **1988**, *1*, 1243–1250; m) D. A. Evans, E. A. Shaughnessy, D. M. Barnes, *Tetrahredron Lett.* **1997**, *38*, 3193–3194; n) D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594; o) A. D. William, Y. Kobayashi, *Org. Lett.* **2001**, *3*, 2017–2020; p) A. D. William, Y. Kobayashi, *J. Org. Chem.* **2002**, *67*, 8771–8782; q) S. P. Nikas, G. A. Thakur, D. Parrish, S. O. Alapafuja, M. A. Huestis, A. Makriyannis, *Tetrahedron* **2007**, *63*, 8112–8123; r) B. M. Trost, K. Dogra, *Org. Lett.* **2007**, *9*, 861–863; s) E. L. Pearson, N. Kanizaj, A. C. Willis, M. N. Paddon-Row, M. S. Sherburn, *Chem. Eur. J.* **2010**, *16*, 8280–8284; t) L.-J. Cheng, J.-H. Xie, Y. Chen, L.-X. Wang, Q.-L. Zhou, *Org. Lett.* **2013**, *15*, 764–767; u) F. E. S. Souza, J. E. Field, M. Pan, N. J. Ramjit, T. Tharmanathan, T. Jende-Tindall, Alphora Research Inc., Can. **2006**, p. 8 pp; v) H. Gu, Mallinckrodt Inc., USA. **2004**, p. 14 pp; w) R. K. Razdan, H. C. Dalzell, G. R. Handrick, *J. Am. Chem. Soc.* **1974**, *96*, 5860–5865; x) H. H. Seltzman, M. K. Begum, C. D. Wyrick, *J. Labelled Compd. Radiopharm.* **1991**, *29*, 1009–1018.

[9] a) Biornica, **30. 10. 2017**; b) R. Mechoulam, L. Hanuš, *Chem. Phys. Lipids* **2002**, *121*, 35–43; c) R. Mechoulam, L. A. Parker, R. Gallily, *J. Clin. Pharmacol.* **2002**, *42*, 11S–19S; d) R. Kupper, Google Patents, **2006**.

[10] D. Piomelli, *Introduction to Cannabis and Cannabinoid Research*, Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA, **2016**.

[11] V. Di Marzo, L. D. Petrocellis, in *Cannabinoids*, John Wiley & Sons, Ltd, Chichester, UK, **2014**, pp. 261–289.

[12] R. S. Padwal, S. R. Majumdar, *The Lancet* **1974**, *369*, 71–77.

[13] a) C. B. Lee, *J. Korean Diabetes* **2013**, *14*, 58–62; b) P. Erkekoğlu, B. Giray, G. Şahin, *Fabad J. Pharm. Sci.* **2008**, *33*, 95–108.

[14] R. Q. Skrabek, L. Galimova, K. Ethans, D. Perry, *J. Pain* **2008**, *9*, 164–173.

[15] G. Bedi, Z. D. Cooper, M. Haney, *Addict. Biol.* **2013**, *18*, 872–881.

[16] W. A. Devane, A. Breuer, T. Sheskin, T. U. Jaerbe, M. S. Eisen, R. Mechoulam, *J. Med. Chem.* **1992**, *35*, 2065–2069.

[17] R. Kinden, X. Zhang, *Behav. Brain Res.* **2015**, *284*, 225–230.

[18] T. Minami, Y. Matsumoto, S. Nakamura, S. Koyanagi, M. Yamaguchi, *J. Org. Chem.* **1992**, *57*, 167–173.

[19] F. Gläser, M. C. Bröhmer, T. Hurrle, M. Nieger, S. Bräse, *Eur. J. Org. Chem.* **2015**, *2015*, 1516–1524.

[20] S. K. Ko, H. J. Jang, E. Kim, S. B. Park, *Chem. Commun.* (28) **2006**, 2962–2964.

[21] J. B. Press, G. H. Birnberg, *J. Heterocyclic Chem.* **1984**, *22*, 561.

[22] D. F. Taber, P. W. DeMatteo, R. A. Hassan, *Org. Synth.* **2013**, *90*, 350–357.

[23] a) J. W. Huffman, X. Zhang, M. J. Wu, H. H. Joyner, *J. Org. Chem.* **1989**, *54*, 4741–4743; b) J. W. Huffman, X. Zhang, M. J. Wu, H. H. Joyner, W. T. Pennington, *J. Org. Chem.* **1991**, *56*, 1481–1489; c) K. E. Fahrenholtz, M. Lurie, R. W. Kierstead, *J. Am. Chem. Soc.* **1967**, *89*, 5934–5941.

[24] G. Sheldrick, *Acta Cryst. A* **2008**, *64*, 112–122.

[25] G. Sheldrick, *Acta Cryst. C* **2015**, *71*, 3–8.