The Diels–Alder Approach towards Cannabinoids

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Received 23 December 2004; revised 23 May 2005

Dedicated to Albert Eschenmoser on the occasion of his 80th birthday

Abstract: Starting from the efficient synthesis of benzopyrans by base-catalyzed condensation reactions between substituted 2-hydroxybenzaldehydes and α,β-unsaturated aldehydes, thermal, Lewis acid catalyzed and enantioselective organo-promoted Diels–Alder reactions towards the tricyclic cannabinoid system are presented. The procedures are exemplified by the synthesis of a pentacycle and various tricycles respectively, in up to 95% enantiomeric excess and provide a versatile entry to this group of natural products with tetrahydrocannabinol (THC) being the most prominent one. Most published strategies are based on the formation of the tricyclic system by condensation between readily available phenols and monoterpenes, whereas we present a novel approach to cannabinoid derivatives based on a modular synthesis.

Key words: natural product synthesis, cannabinoids, asymmetric synthesis

Nature has always been an important source for pharmaceutically interesting compounds. Many of the active components of modern medicines are obtained by extraction from their natural sources (e. g. vancomycin) or partial synthesis (e. g. Taxol). One of these compounds with the longest history in pharmacology is morphine, the first drug that was obtained as a pure substance in 1803 by F. W. A. Sertürner from opium poppy (*Papaver somniferum*).[1] Its application can be traced back to at least the ancient Greeks, and today it is used as a final form of analgesic for patients suffering from extreme pain. Despite morphine's usefulness as a drug, it is also a potent poison causing respiratory paralysis, thus limiting its therapeutic value. There is another well-known group of psychotropic compounds, isolated from Indian hemp (*Cannabis sativa* var. *indica*). These compounds, about 60 in number, are categorized as 'cannabinoids', with (–)-Δ^9-tetrahydrocannabinol (Δ^9-THC) (**1a**) being the most prominent.[2] It consists of a tricyclic 6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene core structure. Other naturally occurring cannabinoids are the Δ^8-isomer **1b**, (–)-cannabidiol (**1c**), or cannabinol (**1d**, Figure 1). Two cannabinoid receptors, CB_1 and CB_2 receptors, have been reported, and the existence of a third receptor has been proposed.[3] While expression of the CB_2 receptor is restricted to the cells of the immune system, the CB_1 receptor can be found throughout the body. The highest CB_1 concentrations have been reported in the cerebral cortex, hippocampus, basal ganglia, and cerebellum. Conversely it is almost absent in the respiratory centers, Δ^9-THC overdoses show low mortalities, a possible advantage against classical analgesics like morphine.

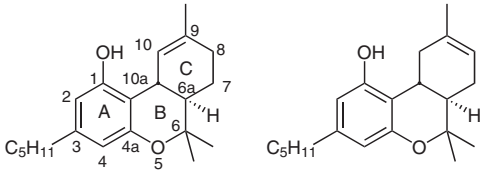


Figure 1 Four naturally occurring cannabinoids

Besides the classical cannabinoids exhibiting the tricyclic core, other exo- and endogenous ligands have been described. The most important exogenous ligands are aminoalkylindoles, such as (*R*)-(–)-WIN55212 (**2**). The endogenous ligands consist of ethanol amides of polyunsaturated carboxylic acids, such as anandamide (**3**)[4] (Figure 2).

Extensive *S*tructure *A*ctivity *R*elationship (SAR) studies for the classical cannabinoids have been reported. The dihydropyran moiety is unnecessary for active compounds.

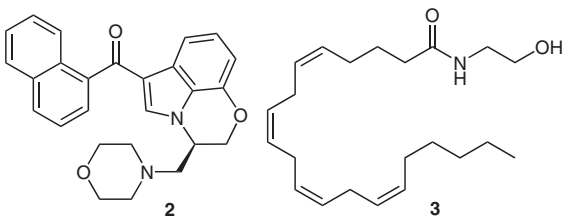


Figure 2 The exogenous ligand (*R*)-(–)-WIN55212 (**2**) and the endogenous ligand anandamide (**3**)

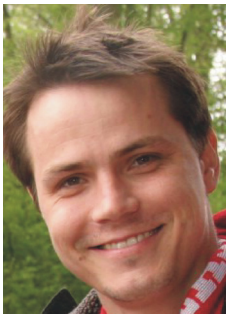
SYNTHESIS 2005, No. 11, pp 1888–1900
Advanced online publication: 29.06.2005
DOI: 10.1055/s-2005-870008; Art ID: T16104SS

Several open-ring derivatives show significant affinity towards the CB_1 and CB_2 receptors.[5] On the other hand, cannabinoids, being protected at or missing the hydroxy group on C-1 lack affinity towards the CB_1 receptor, but retain some of their activity on the CB_2 receptor.[6] The loss of CB_1 affinity leads to CB_2 selective ligands. The only exceptions are esters, which are probably hydrolyzed in vivo to form the active phenols.

The presence of a lipophilic side chain on C-3 is a prerequisite for cannabinoid activity. The minimum length is a propyl chain. It can be longer than a pentyl chain and branching on C-1′ has been shown to improve the activity. An all-carbon chain is not a must, ethers are also accepted. While alkylation on C-2 is accepted, alkylation on C-4 and acylation or carboxylation on C-2 and C-4 abolishes activity. The substitution of the terpene moiety (ring C, Figure 1) is more flexible. Monohydroxylation is tolerated and neither the double bond nor the methyl group is essential for binding to the receptors. Although various syntheses of THC have been reported,[7] almost all strategies are based on condensation of the aromatic ring sys-

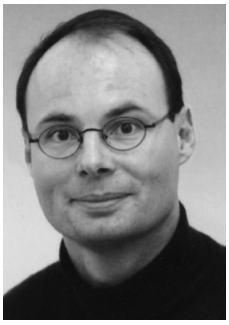
Biographical Sketches

Bernhard Lesch was born in Siegburg, Germany, in 1977. He studied chemistry at the University of Bonn and received his Diploma in 2002. He is a member of the Graduiertenkolleg 804 and is a scholarship holder of the Graduiertenförderung des Landes Nordrhein-Westfalen.



Jakob Toräng was born in Grindsted, Denmark, in 1975. In 2003, he obtained a master of science degree in molecular biology and chemistry from Roskilde University Center. Since 2003, he has been a graduate student at the University of Bonn and is a scholarship holder of Graduiertenkolleg 804.

Martin Nieger was born in Northeim, Germany, in 1959. He studied Biology and Chemistry at the Universities of Göttingen and Bonn and received his Ph.D. in 1989, after working with Edgar Niecke in Bonn. Since 1990, he has been responsible for the common X-ray laboratory of the Department of Organic Chemistry and the Department of Inorganic Chemistry, University of Bonn. In 1995 he was appointed as Docent for Chemistry (Crystallography) at the University of Joensuu, Finland.



Stefan Bräse was born in Kiel, Germany, in 1967. He studied at the Universities of Göttingen, Bangor (UK) and Marseille and received his Ph.D. in 1995, after working with Armin de Meijere in Göttingen. After post-doctoral appointments at Uppsala University (Jan E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou) as DAAD fellow, he began his independent research career at the RWTH Aachen in 1997. In June 2001, he completed his Habilitation and moved to the University of Bonn as a Professor of Chemistry. In 2003, he moved to the University of Karlsruhe as a full professor. He is recipient of the Orchem prize of the Gesellschaft Deutscher Chemiker (2000) and the Lilly Lecture Award (2001). His research interests include asymmetric metal-catalyzed processes and combinatorial chemistry towards the synthesis of biologically active compounds.

tem A, with preformed C systems readily available from chiral pool-based monoterpenes (i.e. verbenol,[8] *p*-menth-2-ene-1,8-diol[9], *p*-mentha-2,8-diene-1-ol[10], or phellandrene[11]), or by enantioselective Diels–Alder reactions,[12] while other strategies form the ring C by a Claisen rearrangement,[13] or a Claisen condensation.[14] In this article, we present a novel approach to cannabinoids based on a modular synthesis.

The retrosynthetic analysis of the THC-tricycle is shown in Figure 3. According to the SAR studies discussed above, the retro-synthetic approach was designed to be flexible in the terpene part of the molecule, while giving an easy entrance towards the arene, and still allowing variations in the aliphatic side chain. The envisaged synthesis allows a combinatorial approach because many organolithium and magnesium reagents (1,2-addition), α,β-unsaturated aldehydes and ketones (condensation, Diels–Alder reaction), and triphenylphosphonium salts (Wittig reaction) are commercially available.

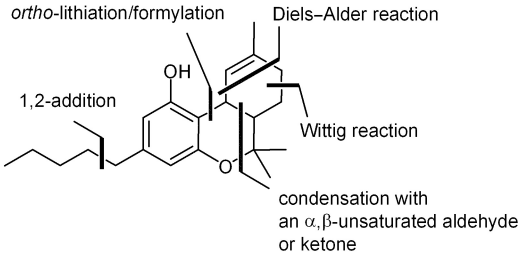
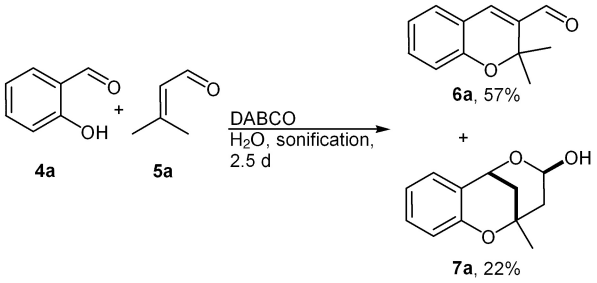


Figure 3 Retrosynthetic analysis of the THC-tricycle

The condensation of Michael acceptors with salicylic aldehyde (**4a**) to yield benzo[*b*]pyrans has proven to be a versatile and flexible entrance to these compounds.[15] The application of this concept on cyclohexenones to yield xanthenones has been reported recently.[16]

Extending this procedure to senecialdehyde (**5a**) gave rise to the chromene **6a** (Scheme 1).[17]



Scheme 1 Synthesis benzopyrans **6a** and **7a**[17]

Surprisingly, a byproduct could be isolated from the reaction mixture. Using ^{1}H and ^{13}C NMR spectroscopy, the structure **7a** was assigned to this compound. An X-ray analysis of a single crystal revealed the relative configuration of **7a**. Both the methyl and the hydroxy group take up equatorial positions (Figure 4). Within the crystal, the

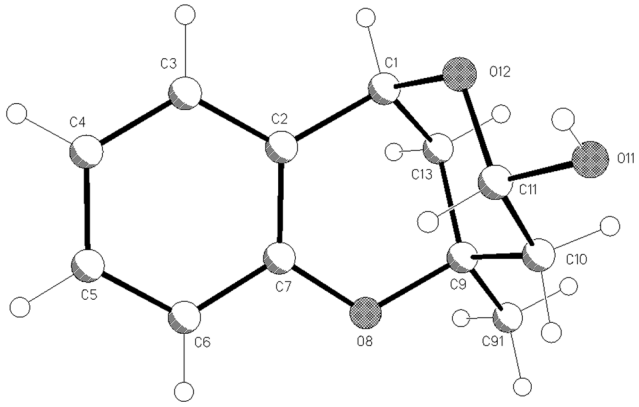
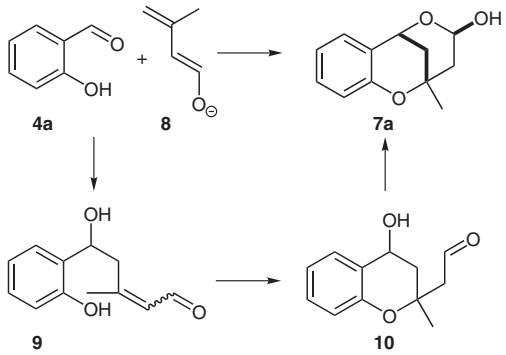


Figure 4 X-ray structure of **7a**

compound forms dimers, which are stabilized by two intramolecular hydrogen bonds.

In a hypothesis, the formation of **7a** involves the conjugated addition of the dienolate **8** to the benzaldehyde **4a**. The phenolic hydroxy group undergoes 1,4-addition to the α,β-unsaturated aldehyde **9** and the addition product **10** forms the lactol **7a** (Scheme 2).

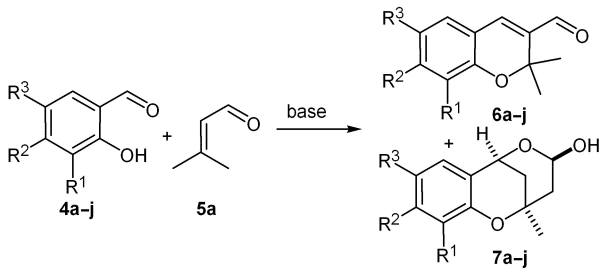


Scheme 2 Proposed mechanism for the formation of **7a**

Optimization of the reaction revealed that sodium carbonate favors the formation of **6**, while triethylamine favors the formation of **7**. With respect to the hydroxylated arene in THC, several salicylic aldehydes were tested in this reaction. All products, **6a–j** and **7a–j**, were isolated in acceptable yields. This issue was discussed in detail in a previous communication.[17] The results are summarized in Table 1.[17]

A synthetic route to cannabinoids was established, using chromene **6a** as a model system. Thus, **6a** was reacted with the dienolate of methyl acetoacetate (**11**) to give the aldol product **12**, which was obtained as an orange oil after aqueous work-up. Purification of the oil was difficult, due to dehydration of the product on silica gel. Therefore, the crude product was refluxed in toluene with aqueous formic acid, causing elimination, saponification, and decarboxylation in a one-pot procedure. The resulting diene **13** was reacted with norbornene to give the Diels–Alder adduct **14** (Scheme 3).

Table 1 Synthesis of Chromenes **6a–j** and **7a–j**[17]

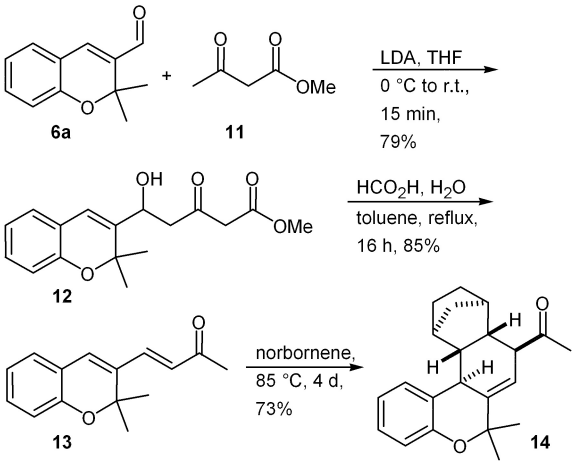


Benz-aldehyde	R^1	R^2	R^3	Conditions[a]	Yield **6** (%)[b]	Yield **7** (%)[b]
4a	H	H	H	A	65	19
4a	H	H	H	B	19	46
4b	OMe	H	H	A	58	23
4b	OMe	H	H	B	13	36
4c	H	OMe	H	A	36	15
4c	H	OMe	H	B	4	44
4d	H	H	OMe	A	81	10
4d	H	H	OMe	B	36	46
4e	H	NEt_2	H	A	0	6
4e	H	NEt_2	H	B	0	4
4f	OMe	H	Br	A	44	27
4f	OMe	H	Br	B	10	57
4g	Br	H	Cl	A	58	17
4g	Br	H	Cl	B	17	51
4h	H	H	NO_2	A	0	9
4h	H	H	NO_2	B	0	47
4h	H	H	NO_2	C	27	37
4i	allyl	H	H	A	52	23
4i	allyl	H	H	B	19	61
4j	Ph	H	H	A	65	24[c]
4j	Ph	H	H	B	23	44[c]

[a] Conditions: A: Na_2CO_3 (0.5 equiv), stirring, 55 °C, 2.5 d. B: Et_3N (0.5 equiv), stirring, 55 °C, 2.5 d. C: DABCO (0.5 equiv), stirring, 55 °C, 2.5 d.
[b] Isolated yields.
[c] While all other compounds were single diastereomers, **7j** was obtained as a 1:1 mixture, probably differing in the relative stereochemistry of the lactol hydroxy group.

The relative configuration of **14** was determined by X-ray analysis of a single crystal (Figure 5). Although this result seemed promising, none of the other tested dienophiles (2-methoxyprop-1-ene, *n*-butyl vinyl ether and cyclohexene) reacted with **13**.

Therefore, we turned our attention on a vinyl precursor having the correct substitution pattern of THC. A benzaldehyde with an appropriate alkyl substitution was obtained by formylation of 3,5-dimethoxypentylbenzene, which was prepared by procedures described in literature.[18] Accordingly, 3,5-dimethoxybenzoic acid (**15**) was reduced with lithium aluminum hydride to the corresponding benzylic alcohol **16**. The product **16** was then oxidized using pyridinium dichromate to give 3,5-dimethoxybenzaldehyde (**17**). The aldehyde was reacted



Scheme 3 Synthesis of pentacycle **14** by a Diels–Alder strategy

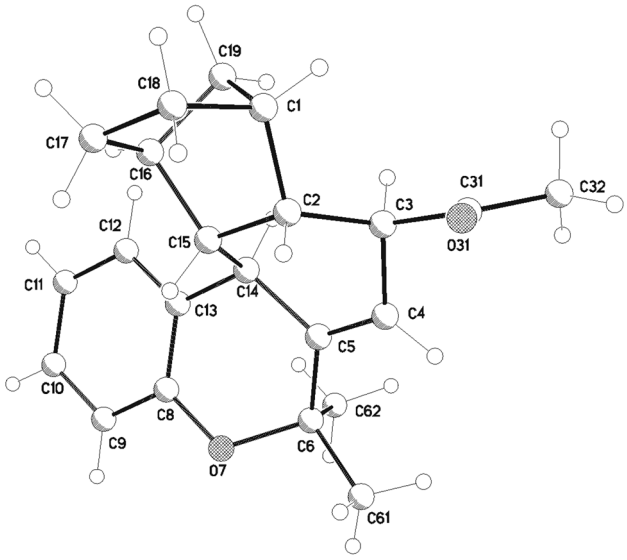
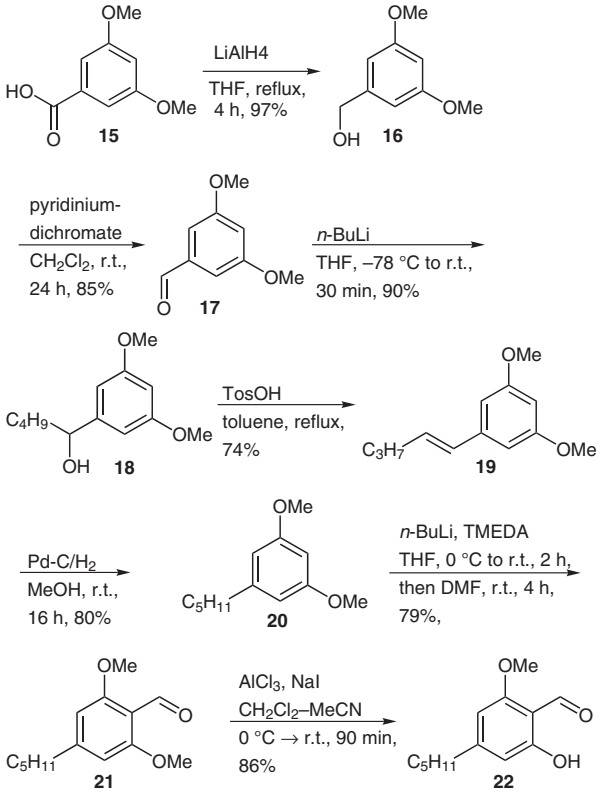


Figure 5 X-ray structure of **14**

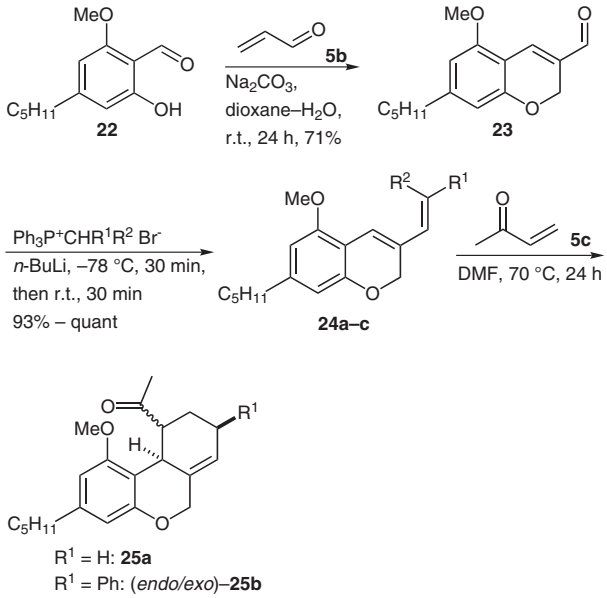
with *n*-BuLi to give the benzylic alcohol **18**. An acidic dehydration yielded the styrene **19**, which was hydrogenated to 3,5-dimethoxypentylbenzene (**20**). *Ortho*-directed metalation and trapping of the aryllithium compound with DMF resulted in the aldehyde **21** after aqueous workup. This aldehyde was finally mono-deprotected using $AlCl_3$/NaI, to provide benzaldehyde **22** (Scheme 4).

Condensation of **22** with senecialdehyde (**5a**) failed. This was probably due to the lowered electrophilicity of the benzaldehyde. This result is consistent with the observation that the *p*-methoxybenzaldehyde **4c** gave lower yields than the two *meta*-methoxy derivatives **4b**,**d** upon reaction with senecialdehyde. When the more reactive acrolein (**5b**) was used instead of senecialdehyde, the desired chromene **23** was obtained. This was converted into electron rich dienes **24a–c** through a Wittig reaction with methyltriphenylphosphonium bromide and benzyl-



Scheme 4 Synthesis of 2-hydroxy-6-methoxy-4-pentylbenzaldehyde (**22**)

triphenylphosphonium bromide, respectively. The benzyl Wittig reagent gave a 1:1 mixture of the diastereomers **24b**,**c**, which were separated by column chromatography (Scheme 5, Table 2).



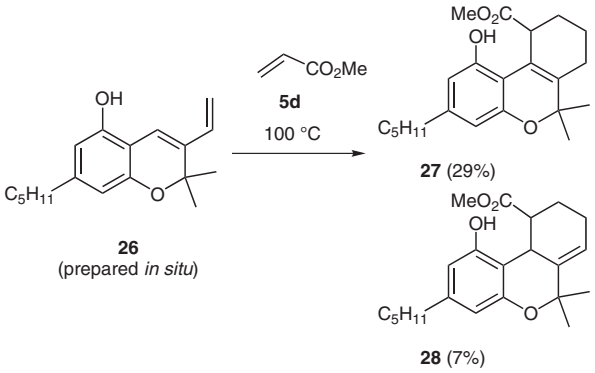
Scheme 5 Preparation and Thermal Diels–Alder Reactions of Dienes **24a–c**

Table 2 Yields of Compounds **24a** and **25** Prepared

Entry	R^1	R^2	Yield of **24** (%)	Yield of **25** (%)
a	H	H	quant	62
b	Ph	H	47[a]	50[b]
c	H	Ph	46[a]	0

[a] Both **24b**,**c** were obtained from the Wittig reaction and separated by column chromatography.
[b] Combined yield of 2.1:1 *endo*/*exo* mixture.

A similar diene **26a** has been previously synthesized, but not isolated, and its Diels–Alder reaction with methyl acrylate **5d** has been reported (Scheme 6).[19] In this case, a free phenol **26** was reacted with methyl acrylate (**5d**) to give tricycles **27** and **28** in mediocre yields with the isomerized **27** as the major product.

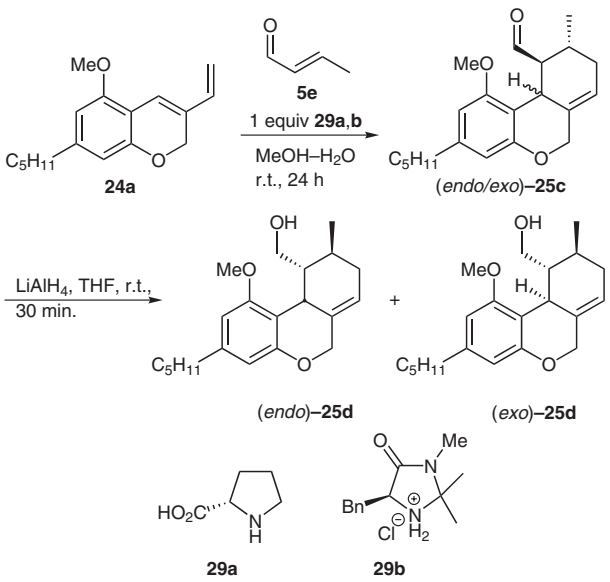


Scheme 6 Cannabinoid synthesis according to Minami et al.[19]

In contrast, dienes **24a**,**b** gave in both thermal and Lewis acid catalyzed Diels–Alder reactions, using but-3-en-2-one (**5c**) as the dienophile, the tricycles **25a**,**b**, and no isomerization of the double bond could be observed (Scheme 5). This gives the opportunity to build up the stereogenic center on C-10a by an enantioselective Diels–Alder reaction. Comparing the Lewis acid catalyzed reaction of **24a** (28% yield) with the thermal Diels–Alder reaction of **24a** (62% yield), the thermal reaction proved to be superior over the Lewis acid-catalyzed reaction. This points out to an acid lability of the starting material and/or the product. Therefore, **24b**,**c** were only used in a thermal Diels–Alder reaction. While the Diels–Alder adduct **25a** was isolated as a single diastereomer, the *E*-isomer **24b** gave a mixture of two isomers *endo*/*exo*-**25b** in a ~2:1 ratio. In contrast to this, the *Z*-isomer **24c** showed no turnover under the conditions used for **24a**,**b**.

Neither the regio- nor the stereochemistry of **25a** could be deduced from the NMR spectra (^{1}H, ^{13}C, DEPT, HH-COSY, HMQC, NOESY). The signals at C-10 and C-10a are useful for assigning the stereo- and regiochemistry. Unfortunately, they occur at 3.72–3.79 ppm, which obstructed the deduction from the NMR spectra. These protons could be identified by a coupling of the proton multiplet in the HMQC spectra with two carbons at δ = 47.6 and 34.7. Those carbons have a positive signal in the DEPT spectra, identifying them as the aliphatic CH groups. Likewise, the CH_2 groups form complex multiplet structures, which generated even more difficulty as they superpose between 1.82 and 2.22 ppm. Therefore, the regiochemistry of the published compound is adopted. In the case of **25b**, it was possible to identify the *endo*-**25b** and the *exo*-**25b** adducts on the basis of ^{1}H NMR and HH-COSY spectra. This was due to the fact that C-8 is a CH group in *endo*/*exo*-**25b**, which shows a significant different shift than the CH_2 group in **25a**, giving separated signals for the protons on C-8 and C-9.

To introduce the 9-methyl group, the reaction with crotonaldehyde (**5e**) as substrate was attempted. No reaction was observed at room temperature. As a Lewis acid catalyzed reaction is not applicable (see above), we turned our focus on the organocatalysis of Diels–Alder reactions. Several groups have reported the effective use of secondary amines as catalysts for the activation of α,β-unsaturated ketones and aldehydes in Diels–Alder reactions via the corresponding iminium ions,[20] and recently this method has found its application in the total synthesis of (+)-hapalindole Q.[21] To test the validity of this concept on our substrates, we tested L-proline (**29a**) as a readily available chiral secondary amine with crotonaldehyde as dienophile to introduce the 9-methyl group. The desired products *endo*/*exo*-**25c** were obtained in 39% yield based on recovered starting material (Scheme 7, Table 3). The slow conversion in relation to the published examples[20] with organo-catalysts is due to the high substitution pattern of the diene. The product was formed as a 1:~2 mixture of *endo*-adducts, *endo*-**25c** and *exo*-adduct, *exo*-**25c**. The diastereomers could not be separated by column chromatography, but after reduction with lithium aluminum hydride the resulting alcohols *endo*/*exo*-**25d** are separable on silica gel. The enantiomeric excesses were only modest (20% ee for the *endo*- and 25% ee for the *exo*-isomer). The relative stereochemistry was assigned on the basis of ^{1}H NMR and HH-COSY experiments. When the catalyst **29b** introduced by MacMillan[20a] was applied, the yield was increased and both diastereomers were obtained in very good to excellent enantiomeric excesses (25% yield, 95% ee for *endo*-**25d**, 43% yield, 90% ee for *exo*-**25d**). The absolute configuration of the *endo*-product based on the model of MacMillan[20a] is 10a*R*, being the correct stereochemistry for the natural THC molecule. Both catalysts **29a** and **29b** favored the same enantiomers. Although this offers the first asymmetric Diels–Alder approach to the THC family, the diastereoselectivity as well as the chemical yields needs further improvement. A detailed investigation on the optimization of the chemical yield and the diastereoselectivity using different chiral secondary amines as well conversion to the natural product will be the subject of further studies.



Scheme 7 Organo-Promoted Diels–Alder Reactions

Table 3 Yields and Enantiomeric Excesses of **25d** Prepared

Catalyst	Yield (%)[a] (ee, %)[b] *endo*–**25d**	Yield (%)[a] (ee, %)[b] *exo*–**25d**	Conversion (%)
29a	11 (20)	28 (25)	53
29b	25 (95)	43 (90)	67

[a] Yield based on recovered starting material.
[b] Enantiomeric excess determined by HPLC with chiral stationary phase (Chiralpak AS) in comparison with racemic products.

A Diels–Alder approach described towards the cannabinoid tricycle, exemplified by the synthesis of tricycles **25a–d**, provides a versatile entry to this fascinating group of naturally occurring compounds. Most published strategies focus on the formation of the heterocycle, with the cyclohexane moiety preexisting in the starting material. However, the procedures presented in this article are especially flexible with respect to the substitution of the terpene unit, because there are many dienophiles available for Diels–Alder reactions. Moreover, the obtained products **25a–d** still allow further derivatization. Further improvement of enantioselective construction of the cyclohexane moiety by an organo-catalytic approach will be the focus of future investigations.

^{1}H NMR: Bruker DP 300 (300 MHz), Bruker DP 400 (400 MHz); δ = 7.26 for $CHCl_3$, 7.27 for benzene-d_5. Description of signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, mc = centered multiplet, dd = doublet of doublet, ddd = doublet of dd, dddd = dd of dd, dt = doublet of triplets, dq = doublet of quartets, and tt = triplet of triplets. The spectra were analyzed according to first order. All coupling constants are absolute values. Abbreviations for signals: C_{arom} or H_{arom} = aromatic C or H, C_{aliph} or H_{aliph} = aliphatic C or H, naph = naphthyl, Tol = tolyl. ^{13}C NMR: Bruker DP 300 (75 MHz), Bruker DP 400 (100 MHz); δ = 77.16 for $CDCl_3$, 128.5 for benzene-d_5. The signal structure was analyzed by DEPT and described as follows: + = primary or tertiary C-atom (positive signal), – = secondary C-atom (negative signal), q = quaternary C-atom (no signal). IR: Perkin-Elmer FT-IR 1750. The substances were measured in KBr pellets. MS, EI-HRMS: (EI, 70 eV, I) Kratos MS 50 (70 eV) and (EI, 70 eV, II) Thermo Quest Finnigan MAT 95 XL (70 eV). GC analytical: Hewlett-Packard HP 5890 Serie II 12 m × 0.25 mm capillary column HP I (carrier gas N_2). X-ray analysis: Nonius Kappa CCD. TLC: Silica gel coated aluminum plates (Merck, silica gel 60, F_{254}). Detection under UV light at 254 nm, displayed with molybdato phosphate (5% phosphomolybdic acid in EtOH, dipping solution), or $KMnO_4$ (0.45 g $KMnO_4$ and 2.35 g of Na_2CO_3 in 90 mL of H_2O, dipping solution). Elemental analysis: elementar vario EL at the Mikroanalytisches Labor des Instituts für Organische Chemie der Universität Bonn. Melting points were determined on a hot plate apparatus and are corrected. Descriptions without nominated temperature were done at r.t. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Janssen, and Merck. Solid materials were powdered. EtOAc, light petroleum ether and CH_2Cl_2 were distilled prior to use. Solvents for reactions for organometallic and other sensitive materials (Et_2O, THF, CH_2Cl_2, MeCN) were dried according to standard procedures and distilled under argon. Anhyd DMF was purchased from Acros. All other solvents, reagents and chemicals were used as purchased. Abbreviations: Light petroleum ether (bp 40–60 °C): PE. Pentane: pen.

5-(2,2-Dimethyl-2*H*-chromen-3-yl)-5-hydroxy-3-oxopentanoic Acid Methyl Ester (12)

Diisopropylamine (4.55 g, 6.32 mL, 45.0 mmol) was dissolved in anhyd THF (10 mL) under argon. The solution was cooled to –78 °C and *n*-BuLi (24 mL, 1.6 M solution in hexane, 38 mmol) was added. The flask was immersed in an ice bath and the mixture was stirred for 30 min. At 0 °C, methyl acetoacetate (1.92 g, 1.78 mL, 16.5 mmol) was added slowly, whence the color of the solution turned orange. After stirring for 15 min at 0 °C, 2,2-dimethyl-2*H*-chromene-3-carbaldehyde (**6a**; 2.82 g, 15 mmol) dissolved in anhyd THF (10 mL) was added. The cooling was removed and the mixture was stirred for 15 min at r.t. After completion of the reaction, brine (30 mL) and dil. H_2SO_4 (c = 2 mol/L) was added, the phases were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated, and the crude product was purified by flash column chromatography (EtOAc–PE, 1:5 to remove the starting material, then EtOAc–PE, 1:1 to isolate the product) yielding 3.61 g (79%) of the title compound as a yellow oil. The NMR in $CDCl_3$ showed about 10% of the enol form.

^{1}H NMR (300 MHz, $CDCl_3$): δ (keto form) = 1.44 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 2.90 (d, ^3J = 3.6 Hz, 1 H, CH_aH$_b$CHOH), 2.91 (d, ^3J = 8.1 Hz, 1 H, CH$_a$$H_b$CHOH), 3.02 (br s, 1 H, OH), 3.50 (s, 2 H, COCH_2CO$_2$CH$_3$), 3.70 (s, 3 H, CO$_2$CH$_3$), 4.69 (dd, ^3J = 8.1, 3.6 Hz, 1 H, CH$_a$H$_b$C*H*OH), 6.37 (s, 1 H, H-4′), 6.77 (d, ^3J = 8.1 Hz, 1 H$_{arom}$), 6.83 (ddd, ^3J = 7.3, 7.3 Hz, ^4J = 1.1 Hz, 1 H$_{arom}$), 6.99 (dd, ^3J = 7.3 Hz, ^4J = 1.4 Hz, 1 H$_{arom}$), 7.09, (ddd, ^3J = 7.8, 7.7 Hz, ^4J = 1.6 Hz, 1 H$_{arom}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (keto form) = 26.0, 26.3 (+, 2 CH_3), 48.8, 49.5 (–, 2 CH_2), 52.4 (+, OCH_3), 66.0 (+, CHOH), 77.9 [q, O*C*(CH$_3$)$_2$], 116.1, 119.7, 120.9, 126.5, 129.2 (+, CH_{arom}, C-4′), 121.8, 140.9. 152.2 (q, C_{arom}, C-3′), 167.2 (C-1), 202.5 (C-3).

MS (EI, 70 eV, I): *m*/*z* (%) = 304 (17, [M$^+$]), 289 (81, [M$^+$ – CH_3]), 173 (100, [M$^+$ – $C_5H_7O_4$]).

HR-EIMS (EI, 70 eV, I): *m*/*z* calcd for $C_{17}H_{20}O_5$: 304.1311; found: 304.1314.

(*E*)-4-(2,2-Dimethyl-2*H*-chromen-3-yl)but-3-en-2-one (13)

To a solution of **12** (1.81 g, 5.95 mmol) in toluene (25 mL), were added formic acid (1 mL) and H_2O (0.5 mL) and the mixture was refluxed for 16 h. After cooling to r.t., the mixture was dried

(Na_2CO_3), the solvent was evaporated and the crude product was purified by flash column chromatography (EtOAc–PE, 1:5) to give 1.15 g (85%) of the title compound as a yellow oil; R_f 0.49 (EtOAc–PE, 1:5).

IR (KBr): 2979, (C–H_{aliph}), 1711 (C=O), 1586 (C=C_{arom}) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 [s, 6 H, C(CH_3)$_2$], 2.31 (s, 3 H, H-1), 6.49 (d, ^3J = 16.1 Hz, 1 H, H-3), 6.75, (s, 1 H, H-4′), 6.79 (d, ^3J = 8.1, 1 H_{arom}), 6.86 (ddd, ^3J = 7.4, 7.4 Hz, ^4J = 1.1 Hz, 1 H_{arom}), 7.04 (dd, ^3J = 7.4 Hz, ^4J = 1.7 Hz, 1 H_{arom}), 7.10 (dd, ^3J = 16.1 Hz, ^4J = 0.85 Hz, 1 H, H-4), 7.09, (ddd, ^3J = 7.8, 7.8 Hz, ^4J = 1.4 Hz, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8 [+, C(*C*H_3)$_2$], 27.9 (+, *C*H_3CO), 78.5 [q, O*C*(CH_3)$_2$], 116.3, 121.2, 125.7, 127.3, 130.7, 139.7 (+, C-3, C-4, C-4′, CH_{arom}), 121.3, 126.4 (q, C-3′, C_{arom}), 153.1 (q, C_{arom}–O), 197.6 (C-2).

MS (EI, 70 eV, II): *m*/*z* (%) = 228 (27, [M^+]), 213 (100, [M^+ – CH_3]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{15}H_{16}O_2$: 228.1150; found: 228.1151.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.91; H, 7.14.

3-Acetyl-6,6-dimethyl-7-oxapentacyclo[14.2.1.0^{2,15}.0^{5,14}.0^{8,13}]nonadeca-4,8,10,12-tetraene (14)

A neat mixture of **13** (1.01 g, 4.43 mmol) and norbornene (834 mg, 8.86 mmol) was heated to 90 °C for 48 h and then to 60 °C for 48 h. After cooling to r.t., the crude product was purified by flash column chromatography, to afford 1.05 g (73%) of a mixture of the *exo/exo* adduct with another diastereomer in a 90.5:9.5 ratio (^{13}C NMR). The *exo/exo* product can be obtained by recrystallization from cyclohexene; mp 123–125 °C; R_f 0.79 (EtOAc–PE, 1:5).

IR (KBr): 3079 (C–H_{arom}), 2985, (C–H_{aliph}), 1716 (C=O), 1606 (C=C_{arom}) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.92–0.99 (m, 1 H_{aliph}), 1.05 (s, 3 H, CH_3), 1.07–1.14 (m, 2 H_{aliph}), 1.35 (t, ^3J = 9.6 Hz, 1 H_{aliph}), 1.40–1.45 (m, 1 H_{aliph}), 1.44 (s, 3 H, CH_3), 1.74, (dd, ^3J = 10.0, 9.8 Hz, 2 H, H-2, H-15), 1.99 (s, 1 H, H-1 or H-16), 2.18 (s, 3 H, CH_3C=O), 2.49 (s, 1 H, H-1 or H-16), 2.78 (ddd, ^3J = 10.8, 3.0 Hz, ^4J = 1.0 Hz, 1 H, H-3), 2.84 (d, ^3J = 10.4 Hz, 1 H, H-14), 5.60 (dd, ^3J = 3.2 Hz, ^4J = 3.2 Hz, 1 H, H-4), 6.78 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 1 H, H-9 or H-12), 6.85 (ddd, ^3J = 7.5, 7.5 Hz, ^4J = 1.3 Hz, 1 H, H-10 or H-11), 7.04 (ddd, ^3J = 7.7, 7.7 Hz, ^4J = 1.5 Hz, 1 H, H-10 or H-11), 7.19 (dd, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 1 H, H-9 or H-12).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.7, 26.8 [+, C(*C*H_3)$_2$], 29.3 (+, CH), 29.4, 29.5, 33.0 (–, C-17, C-18, C-19), 37.1, 39.9, 41.9, 47.2 (+, C-1, C-2, C-15, C-16), 52.1, 52.4 (+, C-3, C-14), 77.0 (q, C-6), 117.6, 118.7, 121.1, 127.3, 129.2 (+, C-4, C-9, C-10, C-11, C-12), 127.8, 146.4 (q, C-5, C-13), 153.7 (C-8), 210.8 (q, H_3C*C*=O).

MS (EI, 70 eV, II): *m*/*z* (%) = 322 (29, [M^+]), 307 (82, [M^+ – CH_3]), 279 (100, [M^+ – $COCH_3$]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{22}H_{26}O_2$: 322.1933; found: 322.1933.

Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.40; H, 8.04.

3,5-Dimethoxybenzylic Alcohol (16)

$LiAlH_4$ (25.0 g, 659 mmol) was suspended in anhyd THF (500 mL) under argon. To this suspension was added 3,5-dimethoxybenzoic acid (**15**; 80.0 g, 439 mmol) in anhyd THF (1 L) from a dropping funnel. During the addition, the mixture boiled slightly. After all the acid had been added, the mixture was refluxed for 4 h. The solution was cooled with an ice bath and the excess of $LiAlH_4$ was destroyed by the addition of H_2O (100 mL) (**caution!**). When no further H_2 was generated, the precipitate was dissolved by the addition of dil. H_2SO_4 (500 mL, conc. acid–H_2O, 1:3). Brine (300 mL) and CH_2Cl_2 (300 mL) were added, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL), and the combined organic layers were dried ($MgSO_4$). After evaporation of the solvent, 71.4 g (97%) of the title compound was obtained as a colorless solid, pure enough for synthetic purposes. To obtain analytically pure **16**, the crude product can be recrystallized from cyclohexene ; mp 42–43 °C; R_f 0.46 (EtOAc–PE, 1 :1).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.08 (br s, 1 H, OH), 3.78 (s, 6 H, OCH_3), 4.60 (s, 2 H, CH_2OH), 6.37 (t, ^4J = 2.3 Hz, 1 H, H-4), 6.51 (d, ^4J = 2.3 Hz, 2 H, H-2, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (+, OCH_3), 65.2 (–, CH_2OH), 99.6 (+, C-4), 104.5 (+, C-2, C-6), 143.3 (q, C-1), 160.9 (q, C-3, C-5).

MS (EI, 70 eV, I): *m*/*z* (%) = 168 (100) [M^+], 139, (68) [M^+ – CHO).

HR-EIMS (EI, 70 eV, I): *m*/*z* calcd for $C_9H_{12}O_3$: 168.0786; found: 168.0781.

3,5-Dimethoxybenzaldehyde (17)

To a solution of 3,5-dimethoxybenzylic alcohol (**16**; 52.6 g, 313 mmol) in CH_2Cl_2 (1 L) was added pyridinium dichromate (118 g, 313 mmol) via a wide-mouthed funnel and the mixture was stirred for 24 h. The solvent was evaporated and the residue was filtered over silica gel (eluent: EtOAc–PE, 1:1, +5% Et_3N). After evaporation of the solvent, the crude product was distilled under reduced pressure to yield 44.0 g (85%) of the title compound; bp 118–122 °C/1.9 mbar; mp 45–46 °C; R_f 0.76 (EtOAc–PE, 1:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 6 H, OCH_3), 6.59 (t, ^4J = 2.4 Hz, 1 H, H-4), 7.00 (d, ^4J = 2.4 Hz, 2 H, H-2, H-6), 9.89 (s, 1 H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6 (+, OCH_3), 107.1 (+, C-2, C-6), 107.1 (+, C-4), 138.4 (q, C-1), 161.2 (q, C-3, C-5), 191.8 (+, CHO).

MS (EI, 70 eV, I): *m*/*z* (%) = 166 (100, [M^+]), 137, (22, [M^+ – CHO]), 135 (26, [M^+ – OCH_3]).

HR-EIMS (EI, 70 eV, I): *m*/*z* calcd for $C_9H_{10}O_3$: 166.0630; found: 166.0629.

1-(3,5-Dimethoxyphenyl)pentan-1-ol (18)

3,5-Dimethoxybenzaldehyde (**17**; 8.31 g, 50.0 mmol) was dissolved in anhyd THF (70 mL) and cooled to –78 °C. *n*-BuLi (34 mL, 1.6 M solution in hexane, 55 mmol) was added slowly via a syringe. After the addition was complete, cooling was removed and the mixture was stirred for 1 h. The reaction was quenched with brine (100 mL) and the precipitate was dissolved in H_2O (50 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–PE, 1:5) to yield 10.1 g (90%) of the title compound as a colorless oil; R_f 0.27 (EtOAc–PE, 1:5).

IR (KBr): 3419 (br, O–H), 2999 (C–H_{arom}), 2934 (C–H_{aliph}), 1598 (C=C_{arom}) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, ^3J = 7.0 Hz, 3 H, CH_3), 1.17–1.39 (m, 4 H, 2 CH_2), 1.58–1.76 (m, 2 H, CH_2), 2.68 (br s, 1 H, OH), 3.70 (s, 6 H, OCH_3), 4.47 (dd, ^3J = 5.9, 7.3 Hz, 1 H, C*H*OH), 6.29 (t, ^4J = 2.3 Hz, 1 H, H-4′), 6.43 (d, ^4J = 2.3 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (+, CH_3), 22.4, 27.8, 38.5 (–, 3 CH_2), 55.0 (+, OCH_3), 99.0 (+, C-4′), 103.4 (+, C-2′, C-6′), 147.6 (q, C-1′), 160.6 (q, C-3′, C-5′).

MS (EI, 70 eV, II): *m/z* (%) = 224 (68, [M$^+$]), 168 (100, [M$^+$ – C_4H_8]), 167 (85, [M$^+$ – C_4H_9]), 139 (100, [M$^+$ – C_5H_9O]).

HR-EIMS (EI, 70 eV, II): *m/z* calcd for $C_{13}H_{20}O_3$: 224.1413; found: 224.1415.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.19; H, 8.79.

(*E*)-1-(3,5-Dimethoxyphenyl)pent-1-ene (19)

p-Toluenesulfonic acid (782 mg, 4.55 mmol) was suspended in toluene (150 mL) in a two-necked 500 mL flask equipped with a dropping funnel and a Dean–Stark trap and the mixture was heated to reflux. To this mixture was added slowly a solution of **18** (8.98 g, 45.5 mmol) in toluene (100 mL). After 60 min, no more H_2O was produced and the heating was removed. After cooling to r.t., Na_2CO_3 (2.5 g) was added, the mixture filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (EtOAc–PE, 1:5) to yield 6.89 g (74%) of the title compound as a colorless oil; R_f 0.72 (EtOAc–PE, 1:5).

IR (KBr): 2989 (C–H_{arom}), 2947 (C–H_{aliph}), 1592 (C=C_{arom}) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, ^3J = 7.4 Hz, 3 H, CH_3), 1.50 (tt, ^3J = 7.4, 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.19 (dt, ^3J = 7.1, 7.1 Hz, 2 H, $CHCH_2CH_2$), 3.81 (s, 6 H, OCH_3), 6.22 (dt, ^3J = 6.7, 16.2 Hz, 1 H, CH=C*H*CH_2), 6.33 (d, ^3J = 16.2 Hz, 1 H, C*H*=CH), 6.34 (t, ^4J = 2.2 Hz, 1 H, H-4′), 6.52 (d, ^4J = 2.2 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4 (+, CH_3), 22.4, 22.4, 35.0 (–, 3 CH_2), 55.2 (+, OCH_3), 99.1 (+, C-4′), 104.0 (+, C-2′, C-6′), 129.9, 131.4 (+, C-1, C-2), 140.0 (q, C-1′), 160.9 (q, C-3, C-5′).

MS (EI, 70 eV, II): *m/z* (%) = 206 (100, [M$^+$]), 191 (43, [M$^+$ – CH_3]), 177 (63, [M$^+$ – C_2H_5]).

HR-EIMS (EI, 70 eV, II): *m/z* calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1298.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.79; H, 8.60.

1-(3,5-Dimethoxyphenyl)pentane (20)

(*E*)-1-(3,5-Dimethoxyphenyl)pent-1-ene (**19**; 6.00 g, 29.1 mmol) and 5% Pd/C (308 mg, 1.46 mmol) were placed in a flask, the flask was sealed with a septum, evacuated and filled with H_2. MeOH (50 mL) was added via a syringe and the mixture was stirred for 20 h. Pd/C was recovered by filtration, the filtrate was dried ($MgSO_4$), and the solvent evaporated. The crude product was purified by flash column chromatography (EtOAc–PE, 1:5) to yield 4.84 g (80%) of the title compound as a colorless oil; R_f 0.86 (EtOAc–PE, 1:5).

IR (KBr): 2998 (C–H_{arom}), 2931 (C–H_{aliph}), 1596 (C=C_{arom}) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, ^3J = 7.5 Hz, 3 H, CH_3), 1.20–1.29 (m, 4 H, 2 CH_2), 1.52 (tt, ^3J = 7.5, 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 2.45 (t, ^3J = 7.9 Hz, 2 H, H-1), 3.68 (s, 6 H, 2 OCH_3), 6.21 (t, ^4J = 2.1 Hz, 1 H, H-4′), 6.26 (d, ^4J = 2.1 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (+, CH_3), 22.5, 30.9, 31.5, 36.2 (–, 4 CH_2), 55.1 (+, 2 OCH_3), 97.5 (+, C-4′), 106.4 (+, C-2′, C-6′), 129.9, 131.4 (+, C-1, C-2), 145.3 (q, C-1′), 160.7 (q, C-3′, C-5′).

MS (EI, 70 eV, II): *m/z* (%) = 208 (27, [M$^+$]), 152, (100, [M$^+$ – C_4H_{10}]).

HR-EIMS (EI, 70 eV, II): *m/z* calcd for $C_{13}H_{20}O_2$: 208.1463; found: 208.1456.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.77; H, 9.46.

2,6-Dimethoxy-4-pentylbenzaldehyde (21)

To a solution of **20** (4.66 g, 22.4 mmol) in anhyd Et_2O (150 mL) was added tetramethylethylenediamine (4.02 g, 5.18 mL, 34.6 mmol) under argon. The solution was cooled to 0 °C and *n*-BuLi (22 mL, 1.6 M solution in hexane, 35 mmol) was added. The mixture was warmed to r.t., and stirred for 2 h. To this mixture was added anhyd DMF (5.06 g, 5.38 mL, 69.2 mmol). After stirring for 4 h, brine (150 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 70 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by flash column chromatography (EtOAc–PE, 1:1) to yield 4.18 g (79%) of the title compound as a colorless oil; R_f 0.65 (EtOAc–PE, 1:1).

IR (KBr): 3004 (C–H_{arom}), 2933 (C–H_{aliph}), 1648 (C=O), 1607 (C=C_{arom}) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.9 Hz, 3 H, CH_3), 1.26–1.37 (m, 4 H, 2 CH_2), 1.57 (tt, ^3J = 7.4, 7.4 Hz, 2 H, $CH_2CH_2CH_2$), 2.55 (t, ^3J = 7.2 Hz, 2 H, H-1′), 3.83 (s, 6 H, OCH_3), 6.34 (s, 2 H, H-3, H-5), 10.40 (s, 1 H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (+, CH_3), 22.3, 30.4, 31.3, 37.0 (–, 4 CH_2), 55.8 (+, OCH_3), 103.9 (+, C-3, C-5), 112.2 (q, C-4), 152.4 (q, C-1), 162.1 (q, C-2, C-6), 188.7 (+, CHO).

MS (EI, 70 eV, I): *m/z* (%) = 236 (54, [M$^+$]), 180, (100, [M$^+$ – C_4H_{10}]).

HR-EIMS (EI, 70 eV, I): *m/z* calcd for $C_{14}H_{20}O_3$: 236.1413; found: 236.1414.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.85; H, 8.52.

2-Hydroxy-6-methoxy-4-pentylbenzaldehyde (22)

2,6-Dimethoxy-4-pentylbenzaldehyde (**21**; 3.63 g, 15.4 mmol) and NaI (5.76 g, 38.5 mmol) were dissolved in anhyd CH_2Cl_2–MeCN (1:2, 150 mL) under argon. The solution was cooled to 0 °C and $AlCl_3$ (5.13 g, 38.5 mmol) was added. During the addition, the color of the solution turned to dark red. Cooling was removed and the mixture was stirred for 90 min. Brine (100 mL) and H_2O (30 mL) were added, and the pH of the mixture was adjusted to 1–2 with H_2SO_4 (*c* = 2 mol/L). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), the solvent was evaporated and the crude product was purified by flash column chromatography (EtOAc–PE, 1:5 + 1% AcOH) to yield 2.94 g (86%) of the title compound as a colorless oil; R_f 0.62 (EtOAc–PE, 1:5).

IR (KBr): 2956 (C–H_{arom}), 2932 (C–H_{aliph}), 1646 (C=O), 1574 (C=C_{arom}) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.0 Hz, 3 H, CH_3), 1.27–1.38 (m, 4 H, 2 CH_2), 1.61 (tt, ^3J = 7.5, 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 2.54 (t, ^3J = 7.8 Hz, 2 H, H-1′), 3.86 (s, 6 H, 2 OCH_3), 6.18 (d, ^4J = 0.8 Hz, 1 H_{arom}), 6.34 (d, ^4J = 0.8 Hz, 1 H_{arom}), 10.23 (s, 1 H, CHO), 11.97 (s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (+, CH_3), 22.4, 30.1, 31.4, 37.6 (–, 4 CH_2), 55.6 (+, 2 OCH_3), 101.5, 109.4 (+, C-3, C-5), 109.1 (q, C-4), 155.4 (q, C-1), 162.3, 163.6 (q, C-2, C-6), 193.4 (+, CHO).

MS (EI, 70 eV, II): *m/z* (%) = 222 (21, [M$^+$]), 166, (100, [M$^+$ – C_4H_{10}]).

HR-EIMS (EI, 70 eV, II): *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1257.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.10; H, 8.20.

5-Methoxy-7-pentyl-2*H*-chromene-3-carbaldehyde (23)

2-Hydroxy-6-methoxy-4-pentylbenzaldehyde (**22**; 4.00 g, 18.0 mmol) and DABCO (1.01 g, 9.00 mmol) were dissolved in dioxane–H_2O (10:1, 9 mL). To this mixture was added acrolein (**5b**; 2.41 mL, 2.02 g, 36.0 mmol) via syringe over a period of 24 h. After stirring for further 24 h, dil. HCl (20 mL, *c* = 1 mol/L) and CH_2Cl_2 (20 mL) were added. The precipitate was dissolved in H_2O and the

phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by flash column chromatography (EtOAc–PE, 1:8) to yield 3.32 g (71%) of the title compound as a yellow oil, which crystallized upon standing ; mp 53–55 °C; R_f 0.50 (EtOAc–PE, 1:8).

IR (KBr): 3057 (C–H_{arom}), 2955, (C–H_{aliph}), 1666 (C=O), 1568 (C=C_{arom}) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 6.9 Hz, 3 H, H-5′), 2.38–1.38 (m, 4 H, 2 CH_2), 1.60 (tt, ^3J = 7.6, 7.6 Hz, 2 H, $CH_2CH_2CH_2$), 2.54 (t, ^3J = 7.8 Hz, 2 H, H-1′), 3.87 (s, 3 H, OCH_3), 4.95 (s, 2 H, H-2), 6.28 (s, 1 H_{arom}), 6.34 (s, 1 H_{arom}), 7.60 (s, 1 H, H-4), 9.52 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (+, C-5′), 22.5, 30.5, 31.4, 36.8 (–, C-1′ to C-4′), 55.7 (+, OCH_3), 62.9 (–, C-2), 104.0, 109.0 (+, CH_{arom}), 108.6, 128.7, 150.4 (q, C-3, C-4a, C-7), 137.2, (+, C-4), 156.8, 157.1 (q, C-5, C-9a), 189.6 (+, CHO).

MS (EI, 70 eV, II): *m*/*z* (%) = 260 (100, [M$^+$]), 231 (51, [M$^+$ – CHO]), 204 (49, [M$^+$ – C_4H_{10}]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{16}H_{20}O_3$: 260.1412; found: 258.1417.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: 73.34; H, 7.65.

5-Methoxy-7-pentyl-3-vinyl-2*H*-chromene (24a)

Methyltriphenylphosphonium bromide (1.47 g, 4.11 mmol) was suspended in anhyd THF (20 mL) under argon. The mixture was cooled to –78 °C and *n*-BuLi (1.93 mL, 1.6 M solution in hexane, 3.08 mmol) was added slowly. During the addition, the color of the solution turned to intense yellow. The mixture was stirred for 30 min, the cooling was removed and the mixture was again stirred for 30 min at r.t. The suspension of the Wittig reagent was cooled to –78 °C and a solution of **23** (534 mg, 2.05 mmol) in anhyd THF (20 mL) was added. After stirring for 30 min at –78 °C, cooling was removed and the mixture was stirred for 30 min at r.t. The reaction was quenched by the addition of silica gel , the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc–PE, 1:10). The title compound was obtained (530 mg, quant) as a colorless oil; R_f 0.77 (EtOAc–PE, 1:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 6.9 Hz, 3 H, H-5′), 1.28–1.42 (m, 4 H, 2 CH_2), 1.62 (tt, ^3J = 7.6, 7.6 Hz, 2 H, $CH_2CH_2CH_2$), 2.55 (t, ^3J = 7.7 Hz, 2 H, H-1′), 3.84 (s, 3 H, OCH_3), 4.92 (s, 2 H, H-2), 5.07 [d, ^3J = 17.6 Hz, 1 H, (*E*)-CH=CH*H*], 5.12 [d, ^3J = 10.8 Hz, 1 H, (*Z*)-CH = CH*H*], 6.29 (d, ^4J = 0.85 Hz, 1 H_{arom}), 6.36 (d, ^4J = 0.85 Hz, 1 H_{arom}), 6.49 (ddd, ^3J = 17.6, 10.8 Hz, ^4J = 0.57 Hz, 1 H, C*H*=CH_2), 6.74 (s, 1 H, H-4′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (+, C-5′), 22.5, 30.8, 31.5, 36.4 (–, C-1′ to C-4′), 55.5 (+, OCH_3), 64.8 (–, C-2), 103.8, 108.4, 118.7, 135.2 (+, CH_{arom}, CH_{olefin}), 109.6, 128.0, 144.9 (q, C-3, C-4a, C-7), 111.9, (+, CH=CH_2), 154.4, 155.4 (q, C-5, C-9a).

MS (EI, 70 eV, I): *m*/*z* (%) = 258 (100, [M$^+$]), 202 (76, [M$^+$ – C_4H_{10}]).

HR-EIMS (EI, 70 eV, I): *m*/*z* calcd for $C_{25}H_{22}O_2$: 258.1620; found: 258.1621.

(*E*/*Z*)-5-Methoxy-7-pentyl-3-styryl-2*H*-chromene (24b,c)

Benzyltriphenylphosphonium bromide (6.24 g, 14.4 mmol) was suspended in anhyd THF (150 mL) under argon. The mixture was cooled to –78 °C and *n*-BuLi (8.4 mL, 1.6 M solution in hexane, 14 mmol) was added slowly. During the addition, the color of the solution turned to intense yellow. The mixture was stirred for 30 min, the cooling was removed and the mixture was again stirred for 30 min at r.t. The suspension of the Wittig reagent was cooled to –78 °C and a solution of **23** (2.50 g, 9.62 mmol) in anhyd THF (40 mL) was added. After stirring for 30 min at –78 °C, the cooling was removed and the mixture was stirred for 30 min. at r.t. The reaction was quenched by the addition of silica gel, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (Et_2O–pen, 1:20) to obtain 1.28 g (40%) of **24b** as a slightly yellow solid and 1.69 g (53%) of **24c** as an oil.

24b

R_f 0.47 (Et_2O–pen, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, ^3J = 6.9 Hz, 3 H, H-5′), 1.22–1.31 (m, 4 H, 2 CH_2), 1.54 (tt, ^3J = 7.5, 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 2.46 (t, ^3J = 7.9 Hz, 2 H, H-1′), 3.76 (s, 3 H, OCH_3), 4.94 (s, 2 H, H-2), 6.20 (d, ^4J = 0.8 Hz, 1 H, H-4), 6.28 (d, ^4J = 0.5 Hz, 1 H_{arom}), 6.31 (d, ^3J = 16.3 Hz, 1 H, CH=C*H*Ph), 6.76 (d, ^4J = 0.5 Hz, 1 H_{arom}), 6.82 (dd, ^3J = 16.3, 0.8 Hz, 1 H, CH=CH), 7.14 (dddd, ^3J = 7.3, 7.3 Hz, ^4J = 1.1, 1.1 Hz, 1 H, *p*-HC_6H_4), 7.25 (dd, ^3J = 7.7 Hz, 2 H, 2 *m*-HC_6H_4), 7.34 (d, ^3J = 7.5 Hz, 2 *o*-HC_6H_4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, C-5′), 22.7, 31.0, 31.7, 36.7 (–, C-1′ to C-4′), 55.8 (+, OCH_3), 65.4 (–, C-2), 104.1, 108.6, 119.2, 126.4, 126.8, 127.5, 127.6, 128.2 (+, CH_{arom}, CH_{olefin}), 110.2, 137.5, 145.2 (q, C-3, C-4a, C-7), 154.5, 155.4 (q, C-5, C-9a).

MS (EI, 70 eV, II): *m*/*z* (%) = 334 (100, [M$^+$]), 277 (17, [M$^+$ – C_4H_9]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{25}H_{26}O_2$: 334.1933; found 334.1929.

24c

R_f 0.55 (Et_2O–pen, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, ^3J = 6.9 Hz, 3 H, H-5′), 1.20–1.29 (m, 4 H, 2 CH_2), 1.51 (tt, ^3J = 7.4, 7.4 Hz, 2 H, $CH_2CH_2CH_2$), 2.43 (t, ^3J = 7.5 Hz, 2 H, H-1′), 3.74 (s, 3 H, OCH_3), 4.27 (s, 2 H, H-2), 6.19 (m, 2 H, H-4, CH_{arom}), 6.21 (d, ^3J = 12.4 Hz, 1 H, CH=CH), 6.44 (d, ^3J = 12.4 Hz, 1 H, CH=CH), 6.75 (d, ^4J = 0.6 Hz, CH_{arom}), 7.11–7.27 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (+, C-5′), 22.7, 31.0, 31.6, 36.7 (–, C-1′ to C-4′), 55.7 (+, OCH_3), 66.8 (–, C-2), 104.1, 108.5, 121.3, 127.3, 128.2, 128.8, 129.1, 129.6 (+, CH_{arom}, CH_{olefin}), 110.7, 138.8, 145.1 (q, C-3, C-4a, C-7), 154.6, 155.5 (q, C-5, C-9a).

MS (EI, 70 eV, II): *m*/*z* (%) = 334 (100, [M$^+$]), 277 (17, [M$^+$ – C_4H_9]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{25}H_{26}O_2$: 334.1933; found 334.1928.

14-Acetyl-3-methoxy-5-pentyl-8-oxatricyclo[4.8.0^{1,10}.0^{2,7}]tetradeca-2,4,6,10-tetraene (25a)

Procedure A (Lewis Acid Catalyzed): 5-Methoxy-7-pentyl-3-vinyl-2*H*-chromene (**24a**; 247 mg, 956 μmol) and but-3-en-2-one (**5c**; 199 μL, 168 mg, 2.39 mmol)) were dissolved in anhyd CH_2Cl_2 (10 mL) and cooled to –78 °C. At this temperature, $BF_3{\cdot}OEt_2$ (12 μL, 14 mg, 96 μmol) was added to this mixture. The mixture was stirred for 5 h at –78 °C, cooling was removed and the stirring was continued for 15 min. During this period, the color of the mixture changed from orange to dark red. The mixture was poured into brine (15 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc–PE, 1:5) to yield 89.3 mg (28%) of the title compound as a colorless oil.

Procedure B (Thermal): A mixture of **24a** (1.58 g, 6.03 mmol) and **5c** (1.06 g, 1.25 mL, 15.1 mmol) in DMF (15 mL) was heated to 70 °C for 24 h. After cooling to r.t., the mixture was diluted with Et_2O (30 mL) and H_2O (40 mL), the layers were separated and the

aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc–PE, 1:5) to yield 1.22 g (62%) of the title compound as a colorless oil; R_f 0.55 (EtOAc–PE, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, ^3J = 6.9 Hz, 3 H, C-5′), 1.15–1.25 (m, 4 H, 2 CH_2), 1.48 (tt, ^3J = 7.5, 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 1.66 (s, 3 H, CH_3C=O), 1.79–2.19 (m, 4 H, H-12, H-13), 2.40 (t, ^3J = 7.9 Hz, 2 H, H-1′), 3.70 (s, 3 H, OCH_3), 3.72–3.79 (m, 2 H, H-1, H-14), 4.21 (dd, ^2J = 11.3 Hz, ^4J = 0.88 Hz, 1 H, H-9a), 4.31 (d, ^2J = 11.3 Hz, 1 H, H-9b), 5.61–5.64 (m, 1 H, H-11), 6.17 (d, ^4J = 1.4 Hz, 1 H, H-4 or H-6), 6.25 (d, ^4J = 1.4 Hz, 1 H, H-4 or H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (+, C-5′), 22.2, 22.4, 25.3, 30.7, 31.5, 35.9 (–, C-12, C-13, C-1′, C-2′, C-3′, C-4′), 29.1 (+, CH_3C=O), 34.7, 47.6 (+, C-1, C-14), 55.2 (+, OCH_3), 70.8 (–, C-9), 103.6, 110.0, 124.3 (+, C-4, C-6, C-11), 111.0, 131.5, 142.7 (q, C-2, C-5, C-10), 157.5, 158.0 (q, C-2, C-7), 210.0 (q, CH_3C=O).

MS (EI, 70 eV, II): *m*/*z* (%) = 328 (13, [M$^+$]), 258 (29, [M$^+$ – C_4H_6O]), 189 (100, [M$^+$ – $C_{10}H_{11}O_2$]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{21}H_{28}O_3$: 328.2038; found: 328.2031.

endo/*exo*-14-Acetyl-3-methoxy-5-pentyl-12-phenyl-8-oxatricyclo[4.8.0^{1,10}.0^{2,7}]tetradeca-2,4,6,10-tetraene (*endo*/*exo*-25b)

(*E*)-Methoxy-7-pentyl-3-styryl-2*H*-chromene (**24b**; 500 mg, 1.49 mmol) and but-3-en-2-one (**5c**; 262 mg, (311 μL, 3.74 mmol) were dissolved in DMF (2 mL) and heated to 70 °C under argon. After 24 h, another portion of **5c** (262 mg, 311 μL, 3.74 mmol) was added and the heating at 70 °C was continued for 24 h. The mixture was diluted with H_2O (10 mL) and Et_2O (10 mL), the phases were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by column chromatography to yield 204 mg (34%) of *endo*-**25b** as a colorless oil and 96.9 mg (16%) of *exo*-**25b** as a colorless solid.

endo-25b

R_f 0.44 (Et_2O–pen, 1:5) .

^{1}H NMR (400 MHz, C_6D_6): δ = 0.85 (t, ^3J = 7.0 Hz, 3 H, H-5′), 1.20–1.27 (m, 4 H, 2 CH_2), 1.35 (s, 3 H, CH_3C=O), 1.54 (tt, ^3J = 7.6, 7.6 Hz, 2 H, $CH_2CH_2CH_2$), 2.07 (ddd, ^2J = 14.0 Hz, ^3J = 4.4, 4.4 Hz, 1 H, H-13a), 2.24 (ddd, ^2J = 14.0 Hz, ^3J = 7.5, 6.5 Hz, H-13b), 2.45 (t, ^3J = 7.9 Hz, 2 H, H-1′), 3.17 (ddd, ^3J = 7.4, 7.4, 3.1 Hz, 1 H, H-14), 3.42 (s, 3 H, OCH_3), 3.71–3.79 (m, 2 H, H-1, H-12), 4.29 (d, ^2J = 12.1 Hz, 1 H, H-9a), 4.46 (d, ^2J = 12.1 Hz, 1 H, H-9b), 5.63 (d, ^3J = 3.1 Hz, 1 H, H-11), 6.22 (d, ^4J = 1.4 Hz, 1 H_{arom}), 6.73 (d, ^4J = 1.4 Hz, 1 H_{arom}), 7.10–7.15 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, C_6D_6): δ = 14.7 (+, C-5′), 23.4, 31.8, 32.4, 35.1, 36.9 (–, C-1′ to C-4′, C-13), 28.3, 34.5, 39.6, 49.0 (+, C-1, C-12, C-14, CH_3C=O), 55.5 (OCH_3), 71.0 (C-9), 104.6, 111.5, 126.2, 126.9, 128.5, 129.0, 129.2 (+, CH_{arom}, C-11), 112.3, 135.6, 143.2, 145.7, (q, C-2, C-5, C-10, C_q of C_6H_5), 158.7, 159.0 (q, C-3, C-7), 206.8 (q, CH_3C=O).

MS (EI, 70 eV, II): *m*/*z* (%) = 404 (44, [M$^+$]), 334 (100, [M$^+$ – C_4H_6O]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{27}H_{32}O_3$: 404.2351; found: 404.2351.

exo-25b

Mp 113–117 °C; R_f 0.23 (Et_2O–pen, 1:5).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.85 (t, ^3J = 7.0 Hz, H-5′), 1.33–1.40 (m, 4 H, 2 CH_2), 1.57 (s, CH_3C=O), 1.59 (tt, ^3J = 7.6, 7.6 Hz, 2 H, $CH_2CH_2CH_2$), 1.78 (ddd, ^2J = 13.1 Hz, ^3J = 13.0, 11.0 Hz, 1 H, H-13a), 2.50 (t, ^3J = 7.8 Hz, 2 H, H-1′), 2.85 (ddd, ^2J = 13.1 Hz, ^3J = 6.3, 2.4 Hz, 1 H, H-13b), 3.08 (ddd, ^3J = 13.0, 6.3, 2.4 Hz, 1 H, H-14), 3.48 (s, 3 H, OCH_3), 3.70–3.78 (m, 2 H, H-1, H-12), 4.17 (d, ^2J = 11.0 Hz, 1 H, H-9a), 4.24 (d, ^2J = 11.0 Hz, 1 H, H-9b), 5.52 (dd, ^3J = 2.7 Hz, ^4J = 2.7 Hz), 6.28 (d, ^4J = 1.3 Hz, 1 H_{arom}), 6.76 (d, ^4J = 1.3 Hz, 1 H_{arom}), 7.01–7.06 (m, 3 H, CH_{arom}, C_6H_5), 7.16–7.21 (m, 2 H, CH_{arom}, C_6H_5).

^{13}C NMR (100 MHz, C_6D_6): δ = 14.7 (+, C-5′), 23.4, 26.2, 31.9, 32.2, 36.9 (–, C-1′ to C-4′, C-13), 28.8, 34.7, 43.7, 54.0 (+, C-1, C-12, C-14, CH_3C=O), 55.4 (+, OCH_3), 71.2 (–, C-9), 104.7, 111.4, 127.7, 127.8, 129.0, 130.2 (CH_{arom}, C-11), 113.2, 135.7, 140.9, 143.4 (q, C-2, C-5, C-10, C_q of C_6H_5), 158.0, 160.0 (q, C-3, C-7), 208.4 (q, CH_3C=O).

MS (EI, 70 eV, II): *m*/*z* (%) = 404 (100, [M$^+$]), 361 (54, [M$^+$ – CH_3CO]), 334 (90, [M$^+$ – C_4H_6O]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{27}H_{32}O_3$: 404.2351; found: 404.2355.

(1*S*/*R*,13*S*,14*R*)-3-Methoxy-13-methyl-5-pentyl-8-oxatricyclo[4.8.0^{1,10}.0^{2,7}]tetradeca-2,4,6,10-tetraene-14-carbaldehyde (*endo*/*exo*-25c)

To a solution of **24a** (100 mg, 388 μmol) and L-proline (**29a**; 44.6 mg, 388 μmol) in MeOH (2 mL) were added H_2O (0.1 mL) and crotonaldehyde (**5e**; 54.4 mg, 63 μL, 776 μmol) and the mixture was stirred at r.t. for 24 h. A sat. aq solution of NH_4Cl (5 mL) and Et_2O (5 mL) were added, the phases were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by column chromatography to yield 54.8 mg (55%) of the diene **24a** and 22.5 mg (18%, 39% based on recovered starting material) of *endo*/*exo*-**25c** as a colorless oil; R_f 0.39 (Et_2O–pen, 1:10).

When **29b** was used as the catalyst, the catalyst was dissolved in MeOH (0.5 mL), and dil. HCl (0.35 mL, *c* = 1 mol/L, 350 μmol) and crotonaldehyde (**5e**, 54.4 mg, 63 μL, 776 μmol) were added and the mixture was stirred for 5 min. A solution of **24a** (100 mg, 388 μmol) in MeOH (1.5 mL) was added and the mixture was stirred for 24 h. After the work-up described above, the crude product was reduced without further purification according to the procedure described below.

To obtain a racemic mixture, D/L-proline [(*rac*)-**29a**] was used as a catalyst according to the procedure described for **29b**.

^{1}H NMR (400 MHz, C_6D_6): δ = 0.97 (t, ^3J = 7.0 Hz, 3 H, H-5′), 1.07 (d, ^3J = 7.3 Hz, 3 H, $CHCH_3$), 1.33–1.40 (m, 4 H, 2 CH_2), 1.67 (tt, ^3J = 7.5 Hz, $CH_2CH_2CH_2$), 1.83–2.00 (m, 1 H, H-12a), 2.37 (dddd, ^2J = 19.0 Hz, ^3J = 8.9, 4.4 Hz, ^4J = 2.5 Hz, 1 H, H-12b), 2.58 (t, ^3J = 7.8 Hz, ^4J = 3.0 Hz, 2 H, H-1′), 2.64 (qdd, ^3J = 7.3, 6.8, 3.0 Hz, 1 H, H-13), 3.38–3.42 (m, 1 H, H-14), 3.43 (s, 3 H, OCH_3), 3.97–4.05 (m, 1 H, H-1), 4.21 (d, ^2J = 10.9 Hz, H-9a), 4.29 (d, ^2J = 10.9 Hz, 1 H, H-9b), 5.42 (dd, ^3J = 6.4, 3.1 Hz, 1 H, H-11), 6.31 (d, ^4J = 1.4 Hz, 1 H_{arom}), 6.80 (d, ^4J = 1.4 Hz, 1 H_{arom}), 9.67 (d, ^3J = 1.4 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, C_6D_6): δ = 14.7 (+, C-5′), 20.6, (+, C-13-CH_3), 23.4, 29.3, 31.8, 32.4, 36.9 (–, 5 peaks, C-1′ to C-4′, C-12), 28.2, 29.7, 52.7 (+, C-1, C-13, C-14), 55.4 (+, OCH_3), 71.2 (–, C-9), 104.6, 111.4, 126.0 (+, CH_{arom}, C-11), 111.2, 132.1, 143.9 (q, C-2, C-4, C-10), 158.9, 159.2 (C-3, C-7), 204 (CHO).

MS (EI, 70 eV, II): *m*/*z* (%) = 328 (34, [M$^+$]), 258 (29, [M$^+$ – C_4H_6O]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{21}H_{28}O_3$: 328.2038; found: 328.2033.

(1*R*/*S*,13*S*,14*R*)-14-Hydroxymethyl-3-methoxy-13-methyl-5-pentyl-8-oxatricyclo[4.8.0^{1,10}.0^{2,7}]tetradeca-2,4,6,10-tetraene (*endo*/*exo*-25d)

Endo/*exo*-**25c** (22.5 mg, 68.6 μmol) was dissolved in anhyd THF (2 mL) under argon. $LiAlH_4$ (approximately 100 mg) was added until no more H_2 was evolved. The mixture was stirred at r.t. for 30 min, diluted with aq HCl (10 mL, c = 1 mol/L) and Et_2O (10 mL), the phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by column chromatography to yield 8.4 mg (37%) of *endo*-**25d** and 13.8 mg (61%) of *exo*-**25d** as colorless oils.

When **29b** was used as a catalyst, the crude product of **25c** was treated as described to yield 31.9 mg of **24a**, 21.3 mg (17%, 25% based on recovered starting material) of *endo*-**25d** and 37.4 mg (29%, 43% based on recovered starting material) of *exo*-**25d**.

***endo*-25d**

R_f 0.66 (Et_2O–pen, 1:1).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.60 (t, ^3J = 7.1 Hz, 3 H, H-5′), 0.82 (d, ^3J = 6.9 Hz, 3 H, CHCH_3), 1.06–1.11 (m, 4 H, 2 CH_2), 1.31 (tt, ^3J = 7.6, 7.6 Hz, $CH_2CH_2CH_2$), 1.40 (qddd, ^3J = 13.4, 6.9, 5.3, 2.8 Hz, 1 H, H-13), 1.61 (ddd, ^2J = 18.4 Hz, ^3J = 5.3, 3.3 Hz, 1 H, H-12a), 1.75 (dddd, ^2J = 18.4 Hz, ^3J = 13.4, 6.3 Hz, ^4J = 3.0 Hz, 1 H, H-12b), 2.21 (t, ^3J = 7.9 Hz, 2 H, H-1′), 2.73 (dddd, ^3J = 5.8, 4.6, 4.6, 2.8 Hz, 1 H, H-14), 3.19, (5.8, ^4J = 3.3, 3.2 Hz, 1 H, H-1), 3.85 (d, ^2J = 11.1 Hz, 1 H, H-9a), 3.96 (d, ^2J = 11.1 Hz, H-9b), 5.12 (dd, ^3J = 5.3, 3.3 Hz, 1 H, H-11), 5.99 (d, ^4J = 1.4 Hz, 1 H_{arom}), 6.45 (d, ^4J = 1.84 Hz, 1 H_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 14.7 (+, C-5′), 20.8, (+, C-13-CH_3), 23.4, 31.8, 32.4, 33.1, 39.1 (–, 5 peaks, C-1′ to C-4′, C-12), 36.9, 43.8 (+, C-1, C-14), 55.5 (+, OCH_3), 60.3, 71.7 (–, C-9, CH_2OH), 104.6, 111.3, 128.6 (+, $CH_{arom.}$, C-11), 112.3, 133.0, 145.5 (q, C-2, C-4, C-10), 159.3, 159.8 (C-3, C-7).

MS (EI, 70 eV, II): *m*/*z* (%) = 330 (28, [M$^+$]), 258 (100, [M$^+$ – $CH_3CHOHCH{=}CH_2$]), 138 (46, [M$^+$ – $C_{12}H1_6O_2$]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{21}H_{30}O_3$: 330.2195; found: 328.2195.

***exo*-25d**

R_f 0.41 (Et_2O–pen, 1:1).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.85 (t, ^3J = 7.0 Hz, 3 H, H-5′), 1.10 (d, ^3J = 6.8 Hz, 3 H, $CHCH_3$), 1.34–1.41 (m, 4 H, 2 CH_2), 1.53 (ddd, ^2J = 17.2 Hz, ^3J = 6.1, 3.0 Hz, 1 H, H-12a), 1.58 (tt, ^3J = 7.5, 7.5 Hz, $CH_2CH_2CH_2$), 2.21 (ddd, ^2J = 17.2 Hz, ^3J = 5.4, 2.6 Hz, 1 H, H-12b), 2.28 (qddd, ^3J = 6.8, 5.4, 3.1, 3.0 Hz, 1 H, H-13), 2.48 (t, ^3J = 7.8 Hz, 2 H, H-1′), 2.90 (dddd, ^3J = 8.6, 6.0, 5.3, 3.1 Hz, 1 H, H-14), 3.22 (dd, ^2J = 10.6 Hz, ^3J = 8.6 Hz, 1 H, CH_aHOH), 3.32 (dd, ^2J = 10.6, ^3J = 5.3 Hz, 1 H, CHH_bOH), 3.42, (s, 3 H, OCH_3), 3.94 (ddd, ^3J = 6.0 Hz, ^4J = 4.0, 2.5 Hz, 1 H, H-1), 4.08 (dddd, ^2J = 11.9 Hz, ^4J = 2.0, 2.0, 0.8 Hz, 1 H, H-9a), 4.18 (d, ^2J = 11.9 Hz, 1 H, H-9b), 5.36 (dd, ^3J = 6.1, 2.6 Hz, 1 H, H-11), 6.23 (d, ^4J = 1.4 Hz, 1 H, H_{arom}), 6.68 (d, ^4J = 1.84 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 14.7 (+, C-5′), 20.8, (+, C-13-CH_3), 23.4, 31.8, 32.4, 33.1, 39.1 (–, 5 peaks, C-1′ to C-4′, C-12), 36.9, 43.8 (+, C-1, C-14), 55.5 (+, OCH_3), 60.3, 71.7 (–, C-9, CH_2OH), 104.6, 111.3, 128.6 (+, CH_{arom}, C-11), 112.3, 133.0, 145.5 (q, C-2, C-4, C-10), 159.3, 159.8 (C-3, C-7).

MS (EI, 70 eV, II): *m*/*z* (%) = 330 (30, [M$^+$]), 258 (100, [M$^+$ – C_4H_8O]).

HR-EIMS (EI, 70 eV, II): *m*/*z* calcd for $C_{21}H_{30}O_3$: 330.2195; found: 328.2193.

Crystal Structure Determinations of Compounds 7a and 14

The data were collected on a Nonius KappaCCD diffractometer at –150 °C using MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods (SHELXS-97).[22] The non-hydrogen atoms were refined anisotropically; H-atoms were refined using a riding model, H(O) free [full-matrix least-squares refinement on F^2 (SHELXL-97)].[23] Details of data collection and refinement are given in Table 4.[24]

Table 4 Crystallographic Data, Structure Solution and Refinement of **7a** and **14**

Compound	7a	14
formula	$C_{12}H_{14}O_3$	$C_{22}H_{26}O_2$
M_r	206.23	322.43
dimensions [mm]	0.60 × 0.50 × 0.30	0.50 × 0.30 × 0.10
crystal system	monoclinic	orthorhombic
space group	$P2_1/n$ (No. 14)	*Pbca* (No. 61)
a [Å]	7.0184(2)	9.7837(2)
b [Å]	6.0121(2)	17.6180(3)
c [Å]	23.7498)8)	20.3716(4)
α [°]	90	90
β [°]	93.235(2)	90
γ [°]	90	90
V [Å^3]	1000.53(6)	3511.44(12)
Z	4	8
ρ [g cm^{-3}]	1.369	1.220
μ [mm^{-1}]	0.098	0.076
F(000)	440	1392
2θmax. [°]	55	50
	$-5 \le h \le 9$	$-7 \le h \le 11$
	$-7 \le k \le 6$	$-19 \le k \le 20$
	$-30 \le l \le 30$	$-24 \le l \le 24$
no. of meas. data	4589	13890
no. of unique data	2196	3093
R_{int}	0.0520	0.0275
refinement on	F^2	F^2
no. of parameters/ restraints	139/1	218/0
$R1$ [for $I > 2\sigma$ (EI, 70 eV, I)]	0.0446	0.0364
$wR2$ (all data)	0.1275	0.0957
max/min difference peak [e Å^{-3}]	0.320/–0.283	0.222/–0.204

Acknowledgment

We would like to honor the fruitful cooperation and many stimulating discussions in the field of cannabinoid chemistry with Professor Andreas Zimmer and Professor Christa E. Müller. We acknowledge the help of Henning Vogt in determining the enantiomeric excesses. Furthermore, we would like to express our gratitude towards the DFG (Graduiertenkolleg 804 '*Analyse von Zellfunktionen durch kombinatorische Chemie und Biochemie*', fellowship to J.T., and the SPP 1133 '*Organocatalysis*') and the Graduiertenförderung Nordrhein Westphalen (fellowship to B.L.) for their financial support.

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(24) Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-258378 (**7a**) and CCDC-258379 (**14**), respectively. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge, UK.