EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202200392

Chemistry Europe
European Chemical Societies Publishing

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Total Synthesis of (−)-Cannabidiol-C_4

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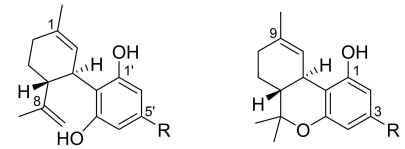
Dedicated to Professor Cesare Gennari on the occasion of his 70th birthday.

Cannabidiol-C_4 **1** (CBD-C_4, cannabidibutol) is a natural product that is present in the extracts of *Cannabis*. Its isolation has not been reported to date. The aim of the proposed synthesis is to secure the availability of the pure compound, its spectroscopic characterization, and to confirm its presence in low amounts in the extracts. The enantioselective total synthesis is based on *a*) the use 3,5-dimetoxybenzaldehyde as starting material, *b*) Corey-Bakshi-Shibata reduction, *c*) Claisen-Ireland rearrangement, *d*) ring-closing metathesis, and *e*) completely not-trivial demethylation induced by sodium ethanethiolate.

Introduction

Cannabis is an angiosperm of the Cannabaceae family and can be found in three species: *Cannabis Sativa*, *Cannabis Indica* and *Cannabis Ruderalis*.[1] This plant contains more than 500 compounds, 120 of which have been identified as cannabinoids.[2] The main and most potent psychoactive compound in cannabis is Δ^9-Tetrahydrocannabidiol (THC), but cannabidiol (CBD) is also present in large quantities (Figure 1). Cannabinoids have demonstrated effects through weak agonist activity on Cannabinoid-1 (CB1) and Cannabinoid-2 (CB2) receptors, which leads to the known effects of smoking cannabis such as increased appetite, pain reduction, and changes in emotional and cognitive processes.[3–6] For these reasons, the therapeutic properties of cannabis are increasingly exploited in the medical field. There is evidence of therapeutic effects of cannabis on some symptoms associated with neurological disorders,[7] like multiple sclerosis characterized by discomforts such as cramps, tremors, and spasticity. Due to the evidence as an appetite stimulant and anti-nauseant, THC has been approved against the weight-loss-related anorexia often observed in AIDS patients and to relieve nausea and vomiting induced by chemotherapy treatments.[8–11] There are other less confirmed effects still being studied against inflammation, anxiety, epilepsy, and cancer.[12–14]



R = C_4H_9: CBD-C_4 (**1**)
R = C_5H_{11}: CBD (**2**)

R = C_5H_{11}: THC

Figure 1. Structure of CBD **1** and **2** and THC.

Although many other cannabinoids demonstrate biological activity, they have not been well studied due to their limited quantities and the difficulty of isolation. The total synthesis of the natural cannabinoids, chemical modifications and the synthesis of analogues would allow a greater understanding of these slight effects.

CBD (**2**) is the main cannabinoid of *Cannabis* extracts, but CBD-C_4 (**1**) can also be detected in low concentrations. This compound differs from CBD by having a butyl side chain at 5′-aryl position in place of the conventional pentyl chain.

Since CBD-C_4 has always been extracted in complex mixtures with other natural products present in *Cannabis*, the isolation as a pure compound in acceptable amounts is impossible. Therefore, obtaining this molecule through an enantioselective synthetic route becomes of particular interest. In this way, CBD-C_4 can be used as a reference in analysis and the biological and pharmacological properties can be better studied.

Results and Discussion

After a careful assessment of the enantioselective syntheses of CBD,[15] we considered as particularly noteworthy the one recently reported by Leahy *et al.*[16] and we decided to plan the asymmetric total synthesis of CBD-C_4 (**1**) based on the same general strategy. The adaptation of the experimental procedures revealed some critical issues that we have specifically overcome for the CBD-C_4 synthesis. To underline the existing

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202200392

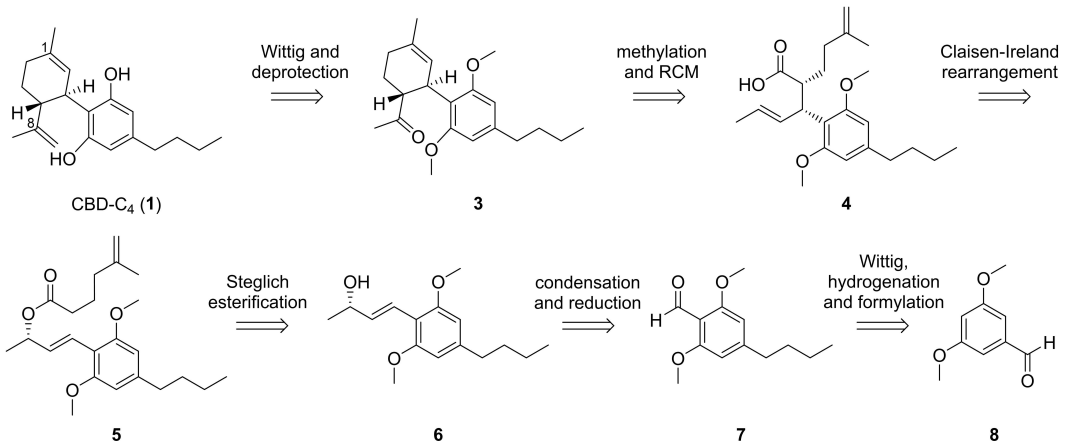
Part of the "Cesare Gennari's 70th Birthday" Special Collection.

Research Article
doi.org/10.1002/ejoc.202200392

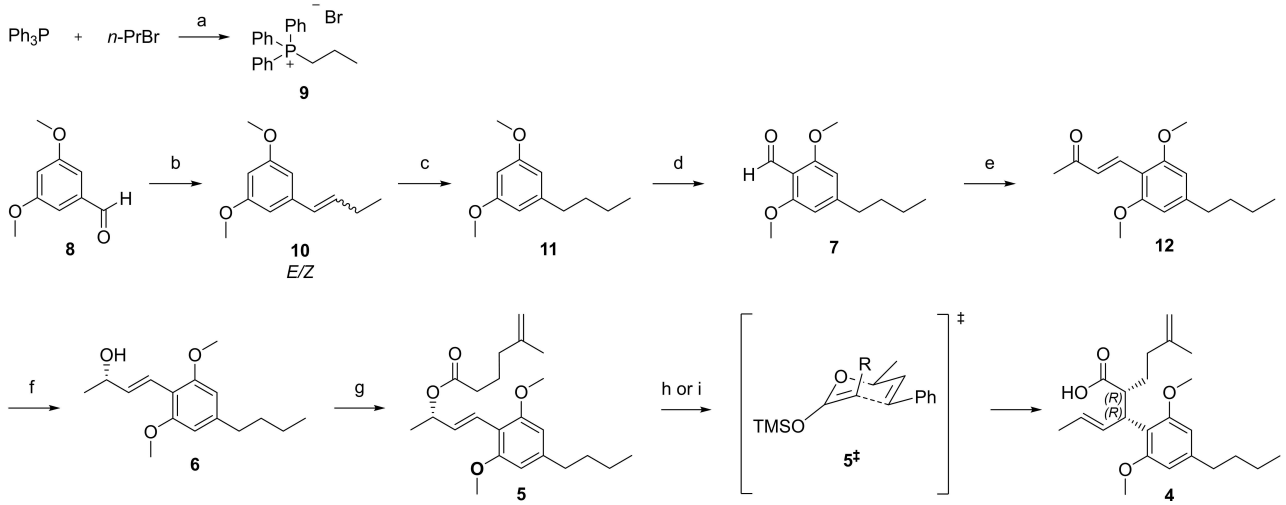
interest in cannabinoids, two alternative syntheses of CBD-C_4 have been published at the same time as our planned synthesis.[17,18]

The general retrosynthetic approach for our synthesis of CBD-C_4 is shown in Scheme 1. Namely, **1** should be achieved through the demethylation and olefination of the corresponding ketone **3**, which should result from the ring-closing metathesis (RCM) reaction carried out on the methyl ketone derivative obtained from the corresponding carboxylic acid intermediate **4**. The latter should stem from the stereocontrolled Claisen-Ireland rearrangement of the stabilized enolate of ester **5**, which would be prepared from alcohol **6** by condensation with a carboxylic acid. Alcohol **6** should be obtained from condensation under basic conditions of **7** with acetone, followed by enantioselective reduction of the carbonyl group. Furthermore, **7** should arise starting from the commercially available aldehyde **8**, exploiting the Wittig olefination and the subsequent hydrogenation of the resulting double bond.

The synthesis of **1** began with the commercial 3,5-dimetoxybenzaldehyde **8** (Scheme 2). The first step of Wittig olefination required the *in situ* preparation of the active ylide with *n*-butyllithium (*n*-BuLi), starting from the prepared triphenyl(propyl)phosphonium bromide **9**. The outcome was a mixture of *E*/*Z* alkene **10** achieved with a 94% yield. Both isomers were hydrogenated in the presence of catalytic amounts of Pd/C and the conversion was monitored by ^{1}H-NMR analysis. This allowed to optimize the reaction conditions by reducing the amount of catalyst; when a greater amount of Pd/C was used[19–21], the formation of several by-products in a short time was detected. The use of 10% w/w of catalyst gave a 12% yield, while we achieved a satisfactory yield of 83% by reducing the amount of catalyst to 0.5% w/w.



Scheme 1. Retrosynthetic strategy for the synthesis of CBD-C_4.



Scheme 2. *Reaction conditions*: a) dry toluene, reflux 95 °C, 20 h, 77%; b) *i*) **9** 1 eq, *n*-BuLi 1 eq, dry THF, 0 °C, 2 h, *ii*) **8** 1 eq, −78 °C to 65 °C, 8 h, 94%; c) H_2, Pd/C 0.5%, MeOH, rt, 3 h, 83%; d) *i*) *n*-BuLi 1.5 eq, TMEDA 1.5 eq, dry THF, −78 to −20 °C, 30 min; *ii*) dry DMF 1.5 eq, −20 °C, 40 min, 94%; e) 2.5 M NaOH 3.5 eq, acetone 5 eq, H_2O, 60 °C, 15 h, 80%; f) (*R*)-(+)-2-Methyl-CBS-oxazaborolidine 0.2 eq, BH_3 1.4 eq, dry THF, −78 °C, 18 h, 87%, 74 ee; g) 5-methyl-5-hexenoic acid 1.5 eq, EDC-HCl 1.8 eq, TEA 1.8 eq, DMAP 0.5 eq, DCM, 0 °C to rt, 15 h, 80%; h) *i*) TMSCl 4.9 eq, TEA 4.4 eq, dry THF, −78 °C, *ii*) **5** 1 eq, LDA 1.5 eq, dry THF, −78 °C 1.5 h to rt 1 h, then reflux 5 h, 85%; i) *i*) KHMDS 3 eq, **5** 1 eq Tol, −78 °C, 1 h, *ii*) [Py 4.5 eq + TMSCl 6 eq, Tol, 0 °C], −78 °C 10 min then rt 4 h, 73%.

The regioselectivity of the formylation reaction is based on *ortho*-lithiation that exploits the presence of the methoxy directing groups on the phenyl. This reaction required many efforts to obtain satisfactory yields due to the rapid formation and high reactivity of the Li-intermediate, even using N,N,N′,N′-tetramethylethylenediamine (TMEDA) as a stabilizing additive. ^{1}H-NMR analysis of quenched reaction aliquots with deuterated water allowed to check the complete formation of the aryl-lithium specie within 30 min of stirring after the addition of *n*-BuLi at −78 °C.

Then, the addition of dimethylformamide (DMF) provided **7** with 94% yield in 40 min at −20 °C. This reaction was particularly sensitive to temperature and reaction time, and an increase in these parameters caused a drastic decrease in yield or failure of aryl functionalization. Condensation of **7** and acetone in the basic aqueous condition provided **12** in 80% yield.

Subsequently, alcohol **6** was obtained from ketone **12** in 87% yield through the enantioselective reduction of Corey-Bakshi-Shibata, which involved the use of (*R*)-2-methyl-CBS-oxazaborolidine catalyst and BH_3 at −78 °C. Compound **6** was obtained with an enantiomeric excess of 74% determined by HPLC analysis. Next, a Steglich condensation was performed between **6** and 5-methyl-5-hexenoic acid in the presence of EDC/DMAP, providing the ester intermediate **5** in 80% yield.

Claisen-Ireland rearrangement,[22] a [3,3]-sigmatropic transposition reaction, was exploited to obtain the key intermediate **4**. An allyl silyl ketene acetal was generated *in situ* under kinetic control starting from the ester **5**. The use of lithium diisopropylamide (LDA) at −78 °C in the presence of trimethylsilyl chloride (TMS–Cl) provided the formation of the *E* enolate,[23,24] which can evolve stereoselectively into the $\mathbf{5}^{\neq}$ chair transition state (TS). By heating, the desired product was obtained in 85% yield as a single (*R*,*R*)-diastereoisomer because the *E*/*E* configuration in the chair-like TS guarantees the *cis* outcome. The use of potassium hexamethyldisilazide (KHDMS) (according to the procedure described by Leahy *et al.*[16]) provided the same diastereoisomer in 73% yield, although the type of base used should have generated the enolate in the *Z* configuration that would lead to the formation of the (*S*,*R*)-diastereoisomer. We confirmed the structure of compound **4** by X-ray diffraction analysis of crystals obtained in methanol (Figure 2).

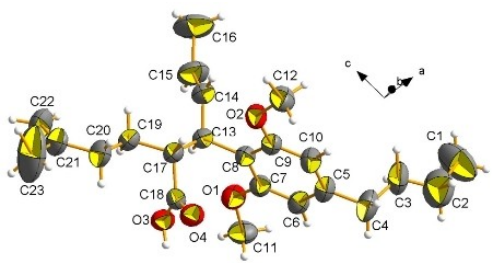
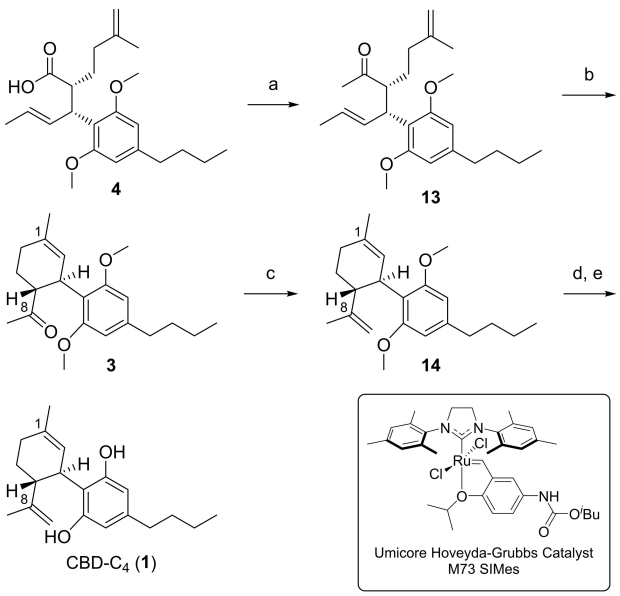


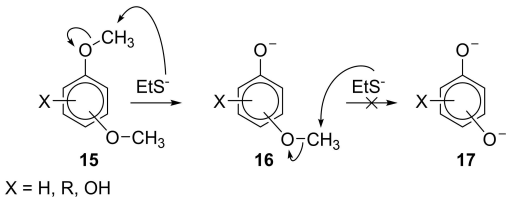
Figure 2. X-ray diffraction analysis of compound **4** crystal. CCDC 2161746 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Treating acid **4** with 2.5 equivalents of methyl lithium (MeLi) yielded the corresponding ketone **13** in 78% yield, which was subjected to the RCM (Scheme 3). Two types of catalysts were used to perform the reaction: Grubb's 2nd generation (79% yield) and Umicore M73 SIMes[25,26] (90% yield). The latter resulted to be more efficient in terms of yield and purification, therefore it was selected as the best catalyst to achieve the desired product **3**. Methylation by Wittig reaction required optimization of the method to obtain satisfactory yields. The main issue found in this protocol was the *in situ* formation of a highly unstable ylide. Therefore, the reaction time required for the formation of the active species at 0 °C with *n*-BuLi was reduced from 2 h, which gave a 40% yield for product isolation, to 45 min which led to a 56% yield in the isolation of **14**.

The deprotection reaction was another important goal to achieve. Although many procedures report the use of methylmagnesium iodide (MeMgI) as a successful protocol for the demethylation of CBD,[16,27–30] no acceptable results have been obtained with this method. Therefore, other possible reactions were considered, avoiding the use of acidic conditions, as cyclization of the substrate to THC-derivative isomers would be induced.[31] The use of a large excess of sodium ethanethiolate (EtSNa) in dry DMF at 140 °C in a sealed tube led to some encouraging results. By monitoring the reaction progression by HPLC, it was evident that the removal of the first methyl proceeded smoothly, but the second was more difficult. Increasing the amount of NaSEt the conversion did not progress, therefore the CBD-C_4 methyl ether intermediate was purified and isolated in 79% yield. Indeed, sequential demethylation of dimethoxybenzenes in a single step is difficult to achieve using nucleophilic reagents (Scheme 4).[32–37] The first demethylation involves the nucleophilic attack on a methyl



Scheme 3. *Reaction conditions*: a) MeLi 2.5 eq, Et_2O, 0 °C to rt, 4 h, 78%, b) Umicore M73 SIMes 0.1 eq, dry DCM, 40 °C, 15 h, 90%; c) $MePPh_3Br$ 1.2 eq, *n*-BuLi 1.2 eq, dry THF, 0 °C 45 min, to rt 18 h, 56%; d) NaSEt, 20 eq dry DMF, 140 °C, 24 h, 79%; e) NaSEt 30 eq, dry DMF, 145 °C, 20 h, 28%.



Scheme 4. Demethylation of dimethoxybenzenes using nucleophilic reagents.

group to provide methoxy phenolate **16**, which cannot be efficiently demethylated again by another nucleophile because the resulting species **17** would bring two negative charges. The same type of problem is treated in the literature on similar substrates, *i.e.*, benzene rings with dimethoxyl protecting groups and no electron-withdrawing groups.[34,38] Therefore, the monodemethylated compound was then again submitted to reaction with NaSEt to obtain the desired CBD-C_4 with a 28% yield in 20 h.

Once CBD-C_4 was synthetically obtained, it was used as a reference and internal standard in HPLC analyses to determine its presence within a CBD extract (Figure 3). The investigation provides positive results showing a perfect overlap of the reference peak with the traces of CBD-C_4 in the extract.

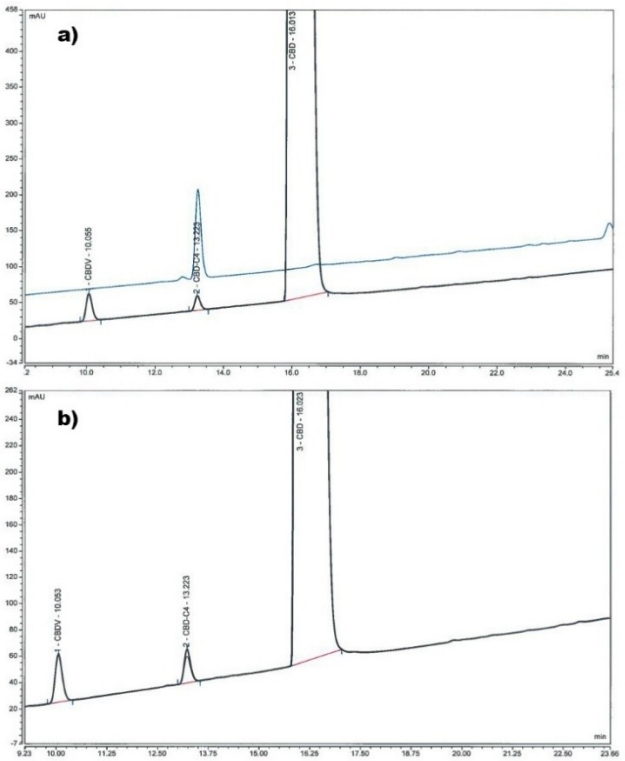


Figure 3. HPLC chromatogram of the *a*) CBD extract (black line) compared to CBD-C_4 used as reference (line blue) and *b*) CBD extract with CBD-C_4 used as internal standard to identify the impurity.

Conclusion

In conclusion, the asymmetric total synthesis of CBD-C_4 (**1**) was achieved in 12 steps by using common 3,5-dimetoxybenzaldehyde **8**. The introduction of a single stereocenter by the enantioselective reduction, the *E* configuration of the double bond of **5** and the correct *E* configuration of the enolate represent the bases for the stereochemistry in the Claisen-Ireland rearrangement. The last deprotection reaction presented a crucial problem that was overcome with the use of EtSNa.

Experimental Section

General Experimental Procedures

Unless otherwise stated, reagents and solvents were purchased from Sigma Aldrich (Milan, Italy), Fluorochem (Hadfield, United Kingdom) or TCI (Zwijndrecht, Belgium) and used without further purification. All reactions were carried out in oven-dried glassware and dry solvents, under nitrogen atmosphere and were monitored by TLC on silica gel (Merck precoated 60F254 plates), with detection by UV light (254 nm) or by permanganate, or by HPLC. HPLC was performed on Agilent 1100 Series System. Products were purified by flash column chromatography, using silica gel Merk 60 (230–400 mesh) as stationary phase. ^{1}H-NMR spectra were recorded on a Bruker Avance Spectrometer 400 MHz and ^{13}C-NMR spectra were recorded on the same instrument 101 MHz, using commercially available deuterated (chloroform-*d*) solvent at room temperature. Chemical shifts are reported in parts per million (ppm), compared to TMS as an internal standard. Multiplicities in ^{1}H-NMR are reported as follow: s – singlet, d – doublet, t – triplet, m – multiplet, br – broad. Data for ^{13}C NMR are reported in chemical shift (δ/ppm). High resolution mass spectra (HRMS) were recorded using the Electrospray Ionization (ESI) technique on FT-ICR APEXII (Bruker Daltonics). Specific rotation values were measured on a Jasco P-1030 polarimeter at 20 °C, using a sodium D line wavelength λ 589 nm. The X-ray diffraction was carried out on Bruker Smart Apex II three-circle diffractometer

Synthesis of propyltriphenylphosphonium bromide 9: 1-bromopropane (2.66 g, 21.6 mmol) was added dropwise to a solution of triphenylphosphine (4.10 g, 16.0 mmol) in anhydrous toluene (3.48 mL). The mixture was heated at reflux for 22 hours and, once completed, the solid was filtered and washed with toluene. The product was dried in the oven at 100 °C for 12 hours to give **9** (4.76 g, 12.3 mmol, 77% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.93-7.89 (m, 3H), 7.84-7.76 (m, 12H), 3.60-3.52 (m, 2H), 1.61-1.53 (m, 2H), 1.08 (m, 3H).

Synthesis of 1-(but-1-en-1-yl)-3,5-dimethoxybenzene 10: *n*-BuLi (7.5 mL, 12 mmol, 1.6 M) was added to a solution of **9** (4.64 g, 12 mmol) in anhydrous THF (120 mL) at 0 °C, under nitrogen atmosphere. The reaction mixture was stirred for 2 hours at 0 °C, then cooled to −78 °C and 3,5-dimethoxybenzaldehyde (2.00 g, 12 mmol) was added. The reaction mixture was heated at reflux for 8 hours. The mixture was quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with AcOEt (3×60 mL). The combined organic layers were washed with water, then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 5:1) to provide **10** (2.16 g, 11.2 mmol, 94% yield) as pale-yellow oil. R_f 0.51; ^{1}H NMR (*E*+*Z*) (400 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 2H), 6.39–6.32 (m, 3H), 5.69-5.66 (m, 1H), 3.82 (s, 6H), 2.38 (qt, *J* = 7.5, 4.5 Hz, 2H), 2.25 (qt, *J* = 13.2, 6.5 Hz, 1H), 1.14-1.07 (m,

4.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.53, 139.68, 135.21, 133.22, 128.80, 128.25, 106.88, 104.05, 99.19, 98.75, 55.29, 25.97, 22.11, 14.43, 13.57. HRMS (ESI) *m/z* $[M+Na]^+$ 215.1055 (calcd for $C_{12}H_{16}O_2Na$, 215.1048).

Synthesis of 1-butyl-3,5-dimethoxybenzene 11: Pd/C (0.5% w/w) was added to a solution of **10** (1.92 g, 10.2 mmol) in MeOH (20.4 mL). The reaction mixture was stirred for 3 hours at room temperature under hydrogen. After filtration through a pad of celite, the residue was concentrated and the yellow crude oil was purified on silica gel (eluent: *n*-Hex/EtOAc 96:4) to give **11** (1.62 g, 8.33 mmol, 83% yield) as a pale-yellow oil. R_f 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, J = 1.83 Hz, 2H), 6.30 (s, 1H), 3.79 (s, 6H), 2.60–2.51 (m, 2H), 1.64–1.53 (m, 2H), 1.36 (h, J = 7.34 Hz, 2H), 0.93 (t, J = 7.33 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.86, 145.51, 106.67, 97.73, 55.36, 36.14, 33.56, 22.54, 14.09.

Synthesis of 4-butyl-2,6-dimethoxybenzaldehyde 7: A solution of **11** (843 mg, 4.34 mmol) in anhydrous THF (25.5 mL) was cooled at −78 °C under nitrogen atmosphere and freshly distilled TMEDA (0.976 mL, 6.51 mmol) was added to give a yellow solution. Then, *n*-BuLi (4.07 mL, 6.51 mmol, 1.6 M in hexane) was added dropwise. After 15 min, the reaction was warmed to −20 °C, and after additional 15 min anhydrous DMF (0.504 mL, 6.51 mmol) was added dropwise to the mixture. The reaction was stirred at −20 °C for 40 minutes before warming to room temperature and quenching with saturated aqueous NH_4Cl and water. The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under *vacuum*. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 8:2) to provide **7** (900 mg, 4.05 mmol, 94% yield) as a pale-yellow oil. R_f 0.17; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 6.38 (s, 2H), 3.87 (s, 6H), 2.60 (m, 2H), 1.56-1.57 (m, 2H), 1.36 (dq, J = 14.6, 7.4 Hz, 2H), 0.94 (t, J = 7.3, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.08, 162.39, 152.66, 112.44, 104.12, 56.07, 37.07, 33.14, 22.54, 14.00. HRMS (ESI) *m/z* $[M+Na]^+$ 245.1161 (calcd for $C_{13}H_{18}O_3Na$, 245.1154).

Synthesis of (*E*)-4-(4-butyl-2,6-dimethoxyphenyl)but-3-en-2-one 12: A solution of acetone (1.82 mL, 24.6 mmol) and NaOH (6.68 mL, 16.7 mmol, 2.5 M) was quickly added to a solution of **7** (1.09 g, 4.91 mmol) in water (24.6 mL). The reaction was heated at 60 °C for 7 hours, then cooled to room temperature, and diluted with Et_2O. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were washed with HCl (1 M) and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 75:25) to provide **12** (919 mg, 3.50 mmol, 80%) as a yellow oil that solidified into a light-yellow solid. R_f 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 16.5 Hz, 1H), 7.13 (d, J = 16.5 Hz, 1H), 6.39 (s, 2H), 3.88 (s, 6H), 2.60 (t, J = 7.8 Hz, 2H), 2.36 (s, 3H), 1.61 (tt, J = 7.1, 1.7 Hz, 2H), 1.38 (h, J = 7.4 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.72, 160.15, 147.80, 135.23, 129.53, 110.44, 104.12, 55.86, 36.81, 33.46, 27.07, 22.61, 14.10. HRMS (ESI) *m/z* $[M+Na]^+$ 285.1485 (calcd for $C_{16}H_{22}O_3Na$, 285.1467).

Synthesis of (*S*, *E*)-4-(4-butyl-2,6-dimethoxyphenyl)but-3-en-2-ol 6: A solution of (*R*)-(+)-2-Methyl-CBS-oxazaborolidine (1.13 mL, 1.13 mmol, 1 M in THF) in anhydrous THF (8.4 mL) was cooled at −78 °C under nitrogen atmosphere and BH_3·THF (7.92 mL, 7.92 mmol) was added. After 30 min, a solution of **12** in THF (1.48 g, 5.66 mmol) was added dropwise and the reaction was stirred at −78 °C for 4 hours. The reaction was warmed to room temperature and stirred for 12 hours. Then, the mixture was diluted with EtOAc, NaOH (1 M) was added, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under *vacuum*. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 7:3) to provide **6** (1.31 g, 4.96 mmol, 87%, ee 74%) as a pale-yellow oil. HPLC Analysis: Lux 3u amylose −2 column (petroleum ether/*i*-propylalcohol 85:15, 0.5 mL/min, 31.5 °C), λ = 254 nm, rt (−)**6** = 10.79, (+)**6** = 12.66. R_f 0.21; $[\alpha]^{20}_D = -11.9$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dd, J = 16.1, 1.1 Hz, 1H), 6.64 (dd, J = 16.1, 6.9 Hz, 1H), 6.38 (s, 2H), 4.46–4.42 (m, 1H), 3.84 (s, 6H), 2.58 (t, J = 7.8 Hz, 2H), 1.66-1.56 (m, 3H), 1.40-1.34 (m, 5H), 1.39 (d, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.47, 143.82, 136.65, 120.31, 111.34, 104.27, 71.00, 55.77, 36.49, 33.65, 23.56, 22.57, 14.10. HRMS (ESI) *m/z* $[M+Na]^+$ 287.1627 (calcd for $C_{16}H_{24}O_3Na$, 287.1623).

Synthesis of (*S*,*E*)-4-(4-butyl-2,6-dimethoxyphenyl)but-3-en-2-yl 5-methylhex-5-enoate 5: To a solution of **6** (1.62 g, 6.13 mmol) in anhydrous DCM (20.4 mL), DMAP (0.37 g, 3.07 mmol), EDC·HCl (2.12 g, 11.0 mmol) and 5-methylhex-5-enoic acid (1.24 mL, 9.20 mmol) were added. Anhydrous triethylamine (1.53 mL, 11.0 mmol) was added dropwise and the solution was stirred for 16 hours. The mixture was washed with HCl (14 mL, 1 M) and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 75:25) to provide **5** (1.83 g, 80% yield) as a clear colorless solid. R_f 0.32; $[\alpha]^{27}_D = -28.2$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, J = 16.2, 1.2 Hz, 1H), 6.60 (dd, J = 16.2, 7.1 Hz, 1H), 6.36 (s, 1H), 5.56-5.49 (m, 1H), 4.73–4.68 (m, 2H), 3.83 (s, 6H), 2.57 (t, J = 7.8 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 2.05 (t, J = 7.5 Hz, 2H), 1.79 (p, J = 7.8 Hz, 2H), 1.71 (s, 3H), 1.63-1.55 (m, 2H), 1.41–1.31 (m, 5H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.63, 159.17, 145.64, 144.58, 132.11, 122.84, 111.70, 111.22, 104.83, 73.57, 56.31, 37.77, 37.03, 34.88, 34.16, 23.59, 23.08, 22.86, 21.43, 14.62. HRMS (ESI) *m/z* $[M+Na]^+$ 397.2562 (calcd for $C_{23}H_{34}O_4Na$, 397.2355).

Synthesis of (2*R*,3*R*,*E*)-3-(4-butyl-2,6-dimethoxyphenyl)-2-(3-methylbut-3-en-1-yl)hex-4-enoic acid 4: A solution of TMS–Cl (3.95 mL, 31.6 mmol) and triethylamine (3.95 mL, 28.3 mmol) in anhydrous THF (24 mL) was prepared at −78 °C under nitrogen atmosphere. A solution of **5** (2.41 g, 6.44 mmol) in anhydrous THF (97 mL) at −78 °C was added and then a solution of LDA (9.66 mL, 9.66 mmol, 1 M in THF/hexane) in anhydrous THF (9.66 mL) at −78 °C was added dropwise. The mixture was stirred at −78 °C for 90 min, then at room temperature for 1 hour and then at reflux for 5 hours. It was quenched with NH_4Cl and HCl (80 mL, 1 M) and the aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 9:1) to provide **4** as white solid (2.06 g, 5.50 mmol, 85% yield). R_f 0.22; $[\alpha]^{27}_D = +14.3$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 2H), 5.90–5.71 (m, 1H), 5.55 (dq, J = 12.8, 6.3 Hz, 1H), 4.71 (d, J = 10.8 Hz, 2H), 4.06 (t, J = 10.0 Hz, 1H), 3.75 (s, 6H), 3.18 (td, J = 10.8, 3.2 Hz, 1H), 2.56-2.52 (m, 2H), 2.00 (t, J = 7.6 Hz, 2H), 1.88–1.77 (m, 1H), 1.73 (s, 3H), 1.68-1.54 (m, 5H), 1.38 (h, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.84, 158.64, 146.08, 143.29, 131.61, 127.68, 116.73, 110.82, 105.60, 56.51, 48.29, 42.68, 36.85, 36.35, 34.11, 30.17, 23.24, 23.06, 18.59, 14.65. HRMS (ESI) *m/z* $[M+Na]^+$ 397.2364 (calcd for $C_{23}H_{34}O_4Na$, 397.2355).

Synthesis of (2*S*,3*R*,*E*)-3-(4-butyl-2,6-dimethoxyphenyl)-2-(3-methylbut-3-en-1-yl)hex-4-enoic acid 4: To a solution of KHMDS (1.96 mL, 1.96 mmol, 1 M THF) in anhydrous Tol (5.3 mL) at −78 °C under nitrogen atmosphere was added a solution of **5** (245 mg, 0.65 mmol) in anhydrous Tol (5.5 mL) and the mixture was stirred at −78 °C for 1 h. Then a solution prepared at 0 °C of anhydrous pyridine (0.24 mL, 2.93 mmol) and TMS–Cl (0.413 mL, 3.27 mmol) in anhydrous Tol (5 mL) was added to the reaction. After 10 min of stirring, the temperature was warmed at room temperature for 4 h. The reaction was quenched with NH_4Cl and HCl (8 mL, 1 M) and the

aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 8:2) to provide **4** (179 mg, 73% yield) as white solid. R_f 0.31; $[\alpha]^{27}{}_D = +2.4$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 2H), 5.78 (ddd, *J* = 15.21, 9.65, 1.87 Hz, 1H), 5.53 (dq, *J* = 15.15, 6.36 Hz, 1H), 4.68 (d, *J* = 10.90 Hz, 2H), 4.03 (t, *J* = 10.04 Hz, 1H), 3.73 (s, 6H), 3.17–3.06 (m, 1H), 2.56–2.47 (m, 2H), 1.98 (dd, *J* = 9.54, 6.17 Hz, 2H), 1.85–1.72 (m, 1H), 1.70 (s, 3H), 1.69–1.49 (m, 6H), 1.37 (p, *J* = 7.38 Hz, 2H), 0.93 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.76, 158.11, 145.57, 142.78, 131.07, 127.18, 116.20, 110.28, 105.08, 56.00, 47.70, 42.16, 36.33, 35.82, 33.58, 29.67, 22.71, 22.54, 18.07, 14.12. HRMS (ESI) *m/z* $[M+Na]^+$ 397.2362 (calcd for $C_{23}H_{34}O_4Na$, 397.2355).

Synthesis of (3*R*,4*R*,*E*)-4-(4-butyl-2,6-dimethoxyphenyl)-3-(3-methylbut-3-en-1-yl)hept-5-en-2-one 13: A solution of **4** (2.05 g, 5.48 mmol) in anhydrous ether (55 mL) was cooled at 0 °C and methyllithium (8.6 mL, 13.7 mmol, 1.6 M in ether) was added dropwise. The mixture was stirred at 0 °C for 1 hour and at room temperature for 3 hours. Then, the reaction was quenched with NH_4Cl (10 mL) and the aqueous layer was extracted with DCM (3× 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 95:5) to provide **13** (1.59 g, 4.27 mmol, 78% yield) as a colorless oil. R_f 0.38; $[\alpha]^{18}{}_D = +17.2$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 2H), 5.81 (ddt, *J* = 15.2, 9.4, 1.6 Hz, 1H), 5.60–5.53 (m, 1H), 4.74–4.70 (m, 2H), 4.02 (dd, *J* = 10.7, 9.4 Hz, 1H), 3.83 (s, 6H), 3.30 (td, *J* = 10.7, 3.4 Hz, 1H), 2.56–2.53 (m, 2H), 1.97-1.92 (m, 2H), 1.93-1.81 (m, 4H), 1.74–1.73 (m, 3H), 1.69–1.65 (m, 4H), 1.61–1.57 (m, 2H), 1.42–1.35 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.44, 157.75, 145.88, 143.02, 131.38, 126.94, 116.01, 110.12, 104.94, 55.85, 54.86, 42.25, 36.32, 36.00, 33.61, 29.59, 28.99, 22.64, 22.51, 18.08, 14.11. HRMS (ESI) *m/z* $[M+Na]^+$ 395.2571 (calcd for $C_{24}H_{36}O_3Na$, 395.2562).

Synthesis of 1-((1*R*,2*R*)-4′-butyl-2′,6′-dimethoxy-5-methyl-1,2,3,4-tetrahydro-[1,1′-biphenyl]-2-yl)ethan-1-one 3: Umicore M73 SIMes catalyst (35.5 mg, 6.7 μmol, 14% w/w) was added to a solution of **13** (50 mg, 0.134 mmol) in anhydrous DCM (6.7 mL) under nitrogen atmosphere. The reaction mixture was stirred for 10 hours at 40 °C and then another portion of Umicore M73 SIMes catalyst (35.5 mg, 6.7 μmol, 14% w/w) was added. The mixture was stirred for further 5 hours at 40 °C. The solvent was removed under *vacuum* and the crude was purified on silica gel (eluent: *n*-Hex/EtOAc 95:5) to provide 3 (40 mg, 0.121 mmol, 90% yield) as a colorless oil. R_f 0.25; $[\alpha]^{18}{}_D = -54.5$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 2H), 5.15-5.14 (m, 1H), 4.16 (dtd, *J* = 8.8, 4.4, 2.3 Hz, 1H), 3.74 (s, 6H), 3.27 (ddd, *J* = 12.9, 10.5, 3.0 Hz, 1H), 2.54 (t, *J* = 7.8 Hz, 2H), 2.24–2.13 (m, 1H), 2.09–1.92 (m, 1H), 1.89 (s, 3H), 1.87–1.77 (m, 2H), 1.66 (s, 3H), 1.58 (ddd, *J* = 15.4, 8.8, 6.4 Hz, 2H), 1.40–1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.50, 142.82, 131.12, 124.86, 117.19, 104.93, 55.93, 51.13, 36.21, 34.67, 33.55, 29.56, 28.64, 26.61, 23.35, 22.55, 14.03. Carbonyl carbon not detected because out of ppm range. HRMS (ESI) *m/z* $[M+Na]^+$ 353.2099 (calcd for $C_{21}H_{30}O_3Na$, 353.2093).

Synthesis of (1*R*,2*R*)-4′-butyl-2′,6′-dimethoxy-5-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1′-biphenyl 14: *n*-BuLi (0.145 mL, 0.232 mmol, 1.6 M) was added dropwise to a solution of $MePPh_3Br$ (83 mg, 0.232 mmol) in anhydrous THF (2.43 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 45 min and **3** (60 mg, 0.184 mmol) was added. The reaction was stirred at room temperature for further 18 hours. The reaction was quenched with NH_4Cl and the aqueous layer was extracted with *n*-Hex (3× 15 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 97:3) to provide **14** (34 mg, 0.103 mmol, 56% yield) as a yellow oil. R_f 0.41; $[\alpha]^{18}{}_D = -56.3$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 2H), 5.23 (s, 1H), 4.51–4.42 (m, 2H), 4.07–3.95 (m, 1H), 3.76 (s, 6H), 2.93 (td, *J* = 10.72, 4.11 Hz, 1H), 2.62–2.52 (m, 2H), 2.21 (dd, *J* = 13.76, 7.46 Hz, 1H), 2.01 (d, *J* = 16.78 Hz, 1H), 1.81–1.72 (m, 2H), 1.69 (s, 3H), 1.66–1.56 (m, 6H), 1.39 (h, *J* = 7.33 Hz, 2H), 0.96 (t, *J* = 7.33 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.77, 150.22, 142.50, 131.86, 126.60, 119.59, 110.24, 105.52, 56.60, 45.86, 36.83, 36.76, 34.18, 31.42, 30.38, 24.12, 23.23, 19.72, 14.69. HRMS (ESI) *m/z* $[M+Na]^+$ 351.2307 (calcd for $C_{22}H_{32}O_2Na$, 351.2300).

Synthesis of cannabidiol-C_4 1: *a*) Sodium ethanethiolate (360 mg, 4.26 mmol) was added to a solution of **14** (70.0 mg, 0.213 mmol) in anhydrous DMF (2.13 mL) into sealed tube under nitrogen atmosphere. The reaction mixture was stirred at 140 °C for 24 hours. Once cooled, the reaction was quenched with $NaHCO_3$ and the aqueous layer was extracted with Et_2O (3×2 mL). The combined organic layers were washed with water (1×2 mL), brine (1×2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 99:1 to 85:15) to provide the methyl ether of **1** (53.0 mg, 0.169 mmol, 79% yield) as pale-yellow oil. *b*) Sodium ethanethiolate (610 mg, 7.25 mmol) was added to a solution of the methyl ether of **1** (76.0 mg, 0.242 mmol) in anhydrous DMF (4.00 mL) into sealed tube under nitrogen atmosphere. The reaction mixture was stirred at 145 °C for 18 hours. Once cooled to room temperature, the reaction was quenched with $NaHCO_3$ and the aqueous layer was extracted with EtO_2 (3×2 mL). The combined organic layers were washed with water (1×2 mL), brine (1×2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on silica gel (eluent: *n*-Hex/EtOAc 99:1 to 85:15) to provide **1** (20.4 mg, 0.080 mmol, 28% yield) as a pale-yellow oil. HPLC Analysis on Agilent 1100 Series System: ZORBAX SB–C8 (3.5 μm x 4.6 x 150 mm), gradient flow from water/MeOH 2:8 to water/MeOH 1:9 in 10 min followed by 2.5 min isocratic at 90% of MeOH, flow 1 mL/min, λ = 228 and 210 nm. R_f 0.20; $[\alpha]^{16}{}_D = -220.7$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36–5.92 (m, 2H), 5.60 (s, 1H), 4.63 (d, *J* = 39.38 Hz, 2H), 3.88 (ddq, *J* = 10.48, 4.48, 2.20 Hz, 1H), 2.53–2.37 (m, 3H), 2.27 (ddd, *J* = 18.90, 9.53, 4.11 Hz, 1H), 2.12 (dp, *J* = 15.27, 2.75 Hz, 1H), 1.83 (d, *J* = 13.33 Hz, 4H), 1.69 (s, 3H), 1.57 (q, *J* = 7.62 Hz, 2H), 1.35 (q, *J* = 7.27 Hz, 2H), 0.93 (t, *J* = 7.31 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.12, 149.32, 142.98, 140.01, 124.16, 113.77, 110.85, 108.48, 46.17, 37.20, 35.19, 33.11, 30.40, 28.41, 23.68, 22.33, 20.47, 13.96. IR (cm^{-1}) 3421, 2926, 1629, 1584, 1441. HRMS (ESI) *m/z* $[M+Na]^+$ 323.1992 (calcd for $C_{20}H_{28}O_2Na$, 323.1987).

Deposition Number 2161746 (for **4**) contains 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.

Acknowledgements

Open Access Funding provided by Universita degli Studi di Milano within the CRUI-CARE Agreement.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cannabidiol · Claisen-Ireland rearrangement · Metathesis · Natural products · Total synthesis

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Manuscript received: March 31, 2022
Revised manuscript received: May 4, 2022
Accepted manuscript online: May 10, 2022