A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2021**, part iv, 198-205

Mitsonobu reaction of cannabidiol. Synthesis of water-soluble cannabidiol derivatives

Thomas Ziegler[a]* and Eric Cosky[b]

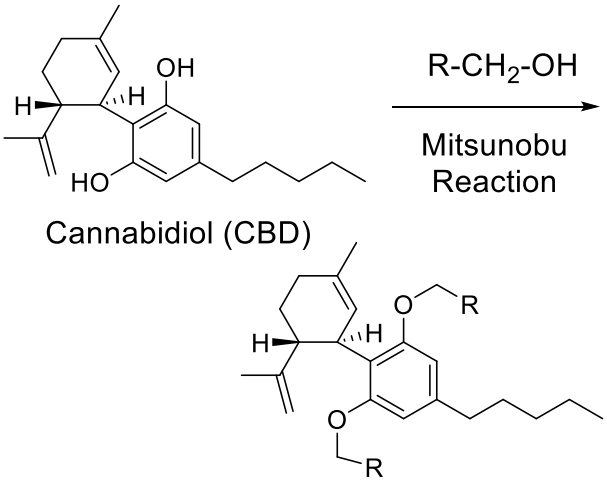
[a]*Institute of Organic Chemistry, University of Tuebingen, Auf der Morgenstelle 18, 72071 Tuebingen, Germany.*
[b]*Tresco Labs GmbH, Uhlandstrasse 24, 70182 Stuttgart, Germany*
Email: Thomas.ziegler@uni-tuebingen.de

Dedicated to Professor Horst Kunz on the occasion of his 80th birthday

Received 08-31-2020 **Accepted** 10-21-2020 **Published on line** 11-19-2020

Abstract

Mitsunobu reactions of cannabidiol (CBD) as the acid component and primary alcohols, for example benzyl, allyl, propargyl and methyl glycolate as the alcohol component gave the corresponding bis-alkylated CBD derivatives which were also obtained by alkylating CBD with the corresponding alkyl bromides. Alkylation of CBD with methyl bromoacetate followed by saponification of the two ester moieties and neutralization of the di-carboxylic acid afforded a water-soluble CBD bis-acetate bis-potassium salt.



Keywords: cannabinoids, cannabidiol, Mitsunobu reaction, water-soluble CBD

DOI: https://doi.org/10.24820/ark.5550190.p011.347

Introduction

Cannabidiol (CBD) is a phenolic monoterpene which is, beside the psychotropic tetrahydrocannabinol (THC), one of the major constituents among the more than 113 cannabinoids found in the resin from hemp (*cannabis sativa*).[1] Although not psychoactive itself, CBD reduces the effect of THC on the nervous system by binding agonistically to the cannabinoid receptors CB1 and CB2 and inhibiting them in an allosteric fashion.[2,3] Pure CBD isolate is also used for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age and older.[4] Through CBD's binding affinity for other G protein-coupled receptors, such as GPR18, 55, 119, 5HT1A, and TRPV2, it may be of pharmaceutical importance for the treatment of numerous medical conditions, like for instance, arthritis, cancer and diabetes.[5,6] Unfortunately, a significant hurdle for the medical application of CBD and other cannabinoids is the high lipophilicity of these compounds and thus, their poor water solubility. In an effort to overcome the poor water solubility of CBD and other cannabinoids, suspensions of CBD nanoparticles[7] or micellar systems[8] were developed. Other groups have described various procedures to solubilize CBD in water by, for example, deprotonating the phenolic alcohol groups in the resorcinol moiety of CBD. However, only CBD concentrations up to 78 mg/l could be achieved this way and the deprotonated CBD species were extremely sensitive toward oxidation, resulting in dark tar-like material.[9] In this paper we describe the chemical synthesis of a CBD derivative which is highly water soluble. Furthermore, a hitherto not described Mitsunobu protocol for modification of CBD is presented as well.[10]

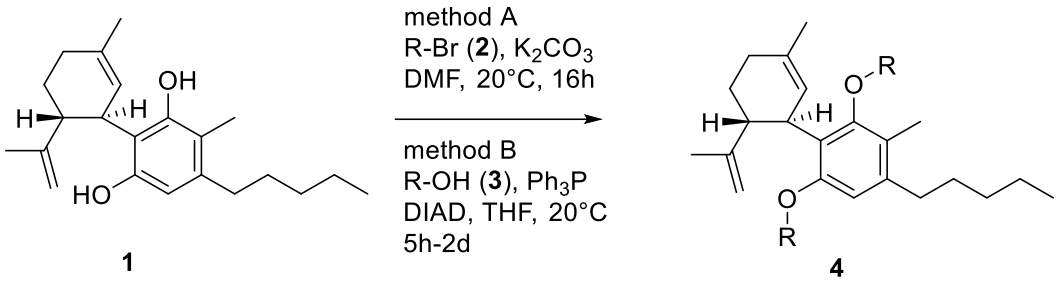
CBD was first isolated in 1940 from *cannabis sativa* by Adams, Hunt and Clark[11] and from *cannabis indica* by Jacob and Todd.[12] Its structure was proven and its stereochemistry unambiguously assigned by Mechoulam and Shvo in 1963.[13] The configuration of naturally occurring CBD and CBD-analogues has since been confirmed multiple times by several enantioselective total syntheses.[14] Due to the broad spectrum of possible medical applications of CBD a large number of naturally occurring and synthetic CBD derivatives are described in the scientific literature and in numerous patents.[15-19] In general, two major types of chemical modifications of CBD had been described so far: modifications of the monoterpene ring or of the resorcinol moiety. For the latter modification, mainly the hydroxyl groups were either alkylated or acylated by various reagents and we are pursuing this modification avenue as well.

Results and Discussion

For the preparation of *O*-alkylated CBD derivatives (alkyl-CBD-ethers) we compared the classical alkylation of phenolic hydroxyls with alkyl bromides with a Mitsunobu protocol with the corresponding alcohols in which the phenolic hydroxyl groups of CBD act as the acid component. Mitsunobu reactions between alcohols and phenols are well documented in the literature.[20-24] However, to the best of our knowledge, no Mitsunobu reaction of cannabinoids has been described so far. Thus, we reacted CBD (**1**) with bromides **2** and K_2CO_3 in DMF, and with primary alcohols **3** using a Mitsunobu protocol to give alkylated CBD derivatives **4** (Scheme 1). Table 1 shows the results.

In general, alkylations of CBD with alkyl bromides **2** proceeded smoothly affording the corresponding alkylated derivatives **4** in 63-99% yield (table 1). In case of propargyl bromide (**2c**) the medium yield was likely due to the instability of propargyl bromide. With the exception of methyl glycolate (**3d**) (table 1, entry 4), all primary alcohols **3** gave comparable yields of alkylated CBD derivatives **4** under Mitsunobu conditions. For the failure of the Mitsunobu reaction of **3d** we do not have any reasonable explanation.

Attempts to react Δ^9-tetrahydrocannabinol (Δ^9-THC) with benzyl alcohol (**3a**) under Mitsunobu conditions (Ph_3P, DIAD, THF, 20°C) failed. No alkylated THC could be detected. In contrast, smooth alkylation of CBD occurred when it was reacted with **3a**. Most likely, the failure of the Mitsunobu reaction of THC is due to the different acidities of THC and CBD. The pKa of CBD is approximately 8.0–8.3[9] while the pKa of THC is 10.6.[25] Therefore, THC is not acidic enough for acting as the acid component in a Mitsunobu condensation. Whether more basic phosphane reagents or other azodicarboxylates enable THC to participate in a Mitsunobu reaction needs to be tested in the future.



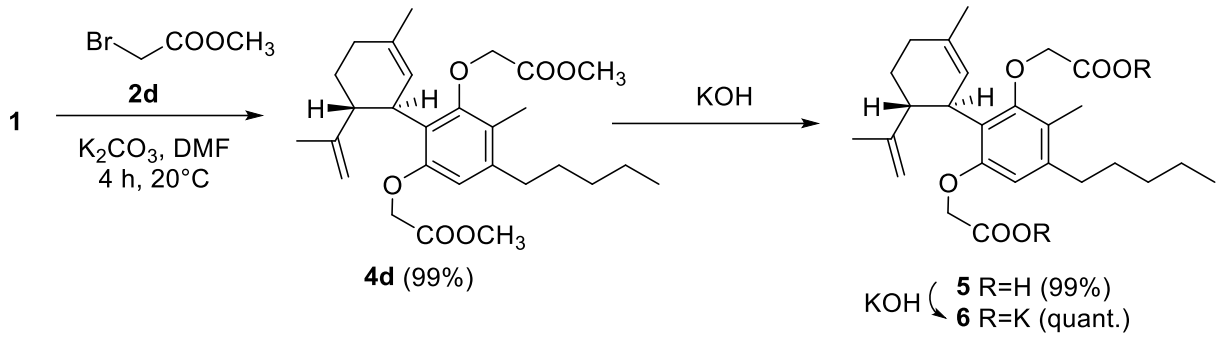
Scheme 1. Reaction of CBD with alkyl bromides (method A) and with primary alcohol under Mitsunobu conditions (method B).

Table 1

Entry	R-Br **2**	R-OH **3**	yield **4** Meth. A[a]	Yield **4** Meth. B[a]
1	Br-CH_2-Ph (**2a**)	HO-CH_2-Ph (**3a**)	93%	94%
2	Br-CH_2-CH=CH_2 (**2b**)	HO-CH_2-CH=CH_2 (**3b**)	84%	37%
3	Br-CH_2-C≡CH (**2c**)	HO-CH_2-C≡CH (**3c**)	63%	65%
4	Br-CH_2-$COOCH_3$ (**2d**)	HO-CH_2-$COOCH_3$ (**3d**)	99%[c]	-[b]

[a]Method A: **1**, **2**, K_2CO_3 in DMF; Method B: **1**, **3**, Ph_3P, DIAD in THF. [b]Tlc indicated an intricate mixture of products. [c]No chromatography was necessary.

For the synthesis of water-soluble CBD-derivatives we planned to attach a carboxylic acid to CBD which allows to form an anionic species and thus, increase the water solubility. For that purpose, we chose bis-acetate derivative **4d**. Since for mainly practical reasons, like for instance reaction conditions and purification procedures, classical alkylations of CBD with alkylbromides were regarded as being superior to a Mitsunobu protocol we reacted 41 g of CBD (**1**) with methyl bromoacetate (**2d**) under the conditions of method A in scheme 1 to obtain CBD derivative **4d** in virtually quantitative yield (scheme 2). A similar mono ethyl acetate of CBD had been described in a patent but no experimental details were given.[17] Next, CBD di-ester **4d** was saponified with ethanolic KOH to give the free di-acid **5** (99%). Quantitative deprotonation of the latter with an equimolar amount of KOH finally gave the di-potassium salt **6** which is highly soluble in water up to 60% by weight.



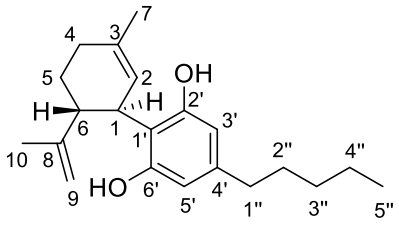
Scheme 2

Conclusions

We could show that cannabidiol (CBD) functions in Mitsunobu reactions as the acid component affording upon reaction with primary alcohols the corresponding bis-alkylated cannabidiols. The same products can be obtained by O-alkylation of CBD with alkyl bromides. The bis-hydroxycarbonylmethylated CBD derivative forms highly water-soluble potassium salts. No Mitsunobu reaction takes place with Δ^9-tetrahydrocannabinol.

Experimental Section

General. All reactions were performed under an atmosphere of nitrogen using solvents dried by standard procedures. Reaction progress was monitored by TLC on Polygram SIL G/UV_{254} silica gel plates from Macherey & Nagel. Detection of spots was effected by charring with sulfuric acid (5% in ethanol), staining by spraying the plates with an alkaline aqueous solution of potassium permanganate, staining plates in a iodine chamber or by inspection of the TLC plates under UV light (254 nm). Preparative chromatography was performed on silica gel (0.032–0.063 mm) from Macherey & Nagel. NMR spectra were recorded with the following spectrometers: Bruker Avance III HD 400 (^{1}H: 400.2 MHz; ^{13}C: 100.6 MHz), Bruker Avance III HDX 600 (^{1}H: 600.2 MHz; ^{13}C: 150.9 MHz) and Bruker Avance III HDX 700 (^{1}H: 700.3 MHz; ^{13}C: 176.1 MHz); and calibrated for the solvent signal (^{1}H: $CDCl_3$: δ = 7.26 ppm; acetone-d_6: δ = 2.05 ppm; dichlormethane-d_2: δ = 5.32 ppm; DMSO-d_6: δ = 2.50 ppm; ^{13}C: $CDCl_3$: δ =77.16 ppm; acetone-d_6: δ = 29.92 ppm; dichlormethane-d_2: δ = 54.0 ppm; DMSO-d_6: δ = 39.51 ppm). CBD derivatives are formally numbered according to scheme 5 and ref. 26. ESI-TOF-HRM spectrometry was performed on a Bruker MAXIS 4G spectrometer. Elemental analyses were obtained from a HEKAtech Euro EA 3000 apparatus. Optical rotations were determined with a Perkin-Elmer Polarimeter 341 in a 10 cm cuvette at 20 °C with a wavelength of 589 nm (Na-lamp). Melting points were measured with a Büchi Melting Point M-560 apparatus.



Scheme 5. Numbering of CBD (**1**).

General Procedure Method A

A suspension of CBD (**1**) (1 mol equivalent), alkyl bromide (**2**) (3 mol equivalents) and K_2CO_3 (3 mol equivalents) in DMF was vigorously stirred under an atmosphere of nitrogen at room temperature for 16 h. The mixture was filtered through a glass filter and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate and the resulting solution was washed 3 times with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated in vacuo. If necessary, the product **4** was purified by chromatography with mixtures of petrol ether and ethyl acetate on silica gel.

General Procedure Method B

A solution of CBD (**1**) (1 mol equivalent), alcohol **3** (2 mol equivalents) and Ph_3P (2 mol equivalents) in THF was stirred under nitrogen at 0°C for 0.5 h. Diisopropyl azodicarboxylate (2 mol equivalents) was added and stirring was continued at room temperature until TLC (petrol ether/ethyl acetate 3/1) revealed complete consumption of the starting material. The solution was concentrated in vacuo, the residue re-dissolved in dichloromethane, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated again. The residue was chromatographed with mixtures of petrol ether and ethyl acetate to afford **4**.

2-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-yl-1-cyclohex-2-enyl]-1,3-dibenzyloxy-5-pentylbenzene (4a). According to the General Procedure Method A, CBD (**1**) (200 mg, 0.63 mmol), benzyl bromide (**2a**) (257 mg, 178 µl, 1.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (2 ml) and chromatography with petrol ether/ethyl acetate 3/1 afforded **4a** (290 mg, 93%). $[\alpha]_D^{20}$ = -125.2 (C=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=0.91 (t, *J* 6.9 Hz, H-5‘‘, 3H), 1.23-1.40 (m, H-3‘‘,4‘‘, 4H), 1.50-2.00 (m, H-4,5,2‘‘,7,10, 12H), 2.55 (t, *J* 7.7 Hz, H-6, 1H), 2.96 (td, *J* 10.4, 4.8 Hz, H-1‘‘, 2H), 4.07-4.18 (m, H-1, 1H), 4.39-4.50 (m, H-9, 2H), 5.01 (s, CH_2O, 4H), 5.33 (br s, H-2, 1H), 6.45 (s, H3‘,5‘, 2H), 7.28-7.51 (m, H-Ph, 10H). ^{13}C NMR ($CDCl_3$) δ 14.1 (C-5‘‘), 19.5 (C-10), 22.6 (C-4‘‘), 23.4 (C-7), 29.5, 30.6, 31.0, 31.6, 36.4 (C-1‘‘,2‘‘3‘‘,4,5), 36.6 (C-6), 44.6 (C-1), 77.2 (CH_2O, 2C), 105.8 (C-3’5’, 2C), 109.9 (C-9), 119.3 (C-1’), 119.3 (C-4’), 126.5, 127.3, 128.3 (C-Ph), 131.4, 137.9, 142.1 (C-1’,4’, Ph), 149.7 (C-8). HRMS: *m/z* calcd. for $[M+Na]^+$ 517.3077; found 517.3077.

According to the General Procedure Method B, CBD (**1**) (200 mg, 0.63 mmol), benzyl alcohol (**3a**) (140 mg, 1347µl, 1.3 mmol), PPh_3 (230 mg, 1.3 mmol) and DIAD (260 mg, 152 µl, 1.3 mmol) in THF (2 ml) and chromatography with petrol ether/ethyl acetate 3/1 afforded **4a** (292 mg, 94%).

2-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-yl-1-cyclohex-2-enyl]-1,3-diallyloxy-5-pentylbenzene (4b). According to the General Procedure Method A, CBD (**1**) (200 mg, 0.63 mmol), allyl bromide (**2b**) (182 mg, 127 µl, 1.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (2 ml) and chromatography with petrol ether/ethyl acetate 3/1 afforded **4b** (208 mg, 84%). $[\alpha]_D$ = -122.9 (c=2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=0.89 (t, *J* 6.9 Hz, H-5‘‘, 3H), 1.22-1.37 (m, H-3‘‘,4‘‘, 4H), 1.47-2.21 (m, H-4,5,2‘‘,7,10, 12H), 2.45 (t, *J* 7.7 Hz, H-6, 1H), 2.48-2.87 (m, H-1‘‘, 2H), 3.39-4.03 (m, OCH_2, 2H), 4.35-4.58 (m, H-1, 9, 3H), 5.21 (br s, H-2, =CH, 3H), 5.21 (s, =CH, 2H), 6.44 (s, H3‘,5‘, $=CH_2$, 5H). ^{13}C NMR ($CDCl_3$) δ=14.2 (C-5‘‘), 19.3 (C-10), 22.7 (C-4‘‘), 23.7 (C-7), 29.5, 30.8, 31.0, 31.7, 36.2 (C-

1'',2''3'',4,5), 36.3 (C-6), 44.6 (C-1), 45.6 (OCH_2, 2C), 110.2 (C-3'5'9, 3C), 130.9 (C-1'), 119.3 (C-4'), 131.8 (=CH), 142.0 (C-1',4'), 149.3 (C-8, $=CH_2$). HRMS: *m/z* calcd. for $[M+Na]^+$ 417.5888 found 417.5893.

According to the General Procedure Method B, CBD (**1**) (100 mg, 0.315 mmol), allyl alcohol (**3b**) (36.6 mg, 43 μl, 0.63 mmol), PPh_3 (165 mg, 0.63 mmol) and DIAD (130 mg, 126 μl, 0.63 mmol) in THF (2 ml) and chromatography with petrol ether/ethyl acetate 3/1 afforded **4b** (45.5 mg, 37%).

2-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-yl-1-cyclohex-2-enyl]-1,3-propargyloxy-5-pentylbenzene (4c). According to the General Procedure Method A, CBD (**1**) (200 mg, 0.63 mmol), propargyl bromide (**2b**) 80% in toluene (230 μl, 1.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in DMF (2 ml) and chromatography with petrol ether/ethyl acetate 3/1 afforded **4c** (156 mg, 63%). $[\alpha]_D$ = -160.8 (c=1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* 6.9 Hz, H-5'', 3H), 1.17-1.44 (m, H-3'',4'', 4H), 1.48-1.69 (m, H-4,5,2'',7,10, 12H), 1.89-2.05 (m, H-6, 1H), 2.40-2.58 (m, CH, 2H), 2.93 (dd, *J* 15.5. 10.2 Hz, H-1'', 2H), 3.96-4.13 (m, H-1, 9, 3H), 5.33-4.54 (m, H-2, OCH_2, 5H), 5.10-5.39 (m, H3',5', 4H). ^{13}C NMR ($CDCl_3$) δ=14.2 (C-5''), 19.4 (C-10), 22.1 (C-4''), 23.6 (C-7), 29.7, 30.9, 31.1, 31.8, 36.5 (C-1'',2''3'',4,5), 36.4 (C-6), 45.2 (C-1), 69.5 (OCH_2, 2C), 110.0 (C-3'5'9, 3C), 126.5 (HC=), 131.2 (C=), 131.5 (C-1'), 119.6 (C-4'), 141.8 (C-1',4'), 149.9 (C-8, $=CH_2$). HRMS: *m/z* calcd. for $[M+Na]^+$ 413.2457 found 413.2452.

According to the General Procedure Method B, CBD (**1**) (100 mg, 0.315 mmol), propargyl alcohol (**3c**) (35.3 mg, 37 μl, 0.63 mmol), PPh_3 (165 mg, 0.63 mmol) and DIAD (130 mg, 126 μl, 0.63 mmol) in THF (2 ml) and chromatography with petrol ether/ethyl acetate 3/1 afforded **4b** (80.2 mg, 65%).

Methyl 2-[(1R,6R)-3-methyl-6-prop-1-en-2-yl-1-cyclohex-2-enyl]-5-pentylbenzo-1,3-dioxy-diacetate (4d). According to the General Procedure Method A, CBD (**1**) (41 g, 0.13 mol), methyl bromoacetate (**2d**) (59.7 g, 0.39 mol) and K_2CO_3 (53.9 g, 0.39 mol) in DMF (500 ml) and workup without chromatography afforded **4e** (59.2 g, 99%). $[\alpha]_D$ = -112.6 (c=0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* 7 Hz, H-5'', 3H), 1.25-1.32 (m, H-3'', 2H), 1.32-1.31 (m, H-4'', 2H), 1.50-1.71 (m, H-4,5,2'',7,10, 12H), 2.20-2.26 (m, H-6, 1H), 2.46 (td, *J* 10, 4.9 Hz, H-1'', 2H), 3.78 (s, OCH_3, 6H), 4.06-4.09 (m, H-1, 1H), 4.45-4.52 (m, H-9, 2H), 5.21 (s, CH_2O, 4H), 5.33 (br s, H-2, 1H), 6.25 (s, H3',5', 2H). ^{13}C NMR ($CDCl_3$) δ 14.0 (C-5''), 18.9 (C-10), 22.4 (C-4''), 23.4 (C-7), 29.3, 30.5, 30.8, 31.4, 36.0 (C-1'',2''3'',4,5), 36.2 (C-6), 45.0 (C-1), 52.0 (OCH_3, 2C), 66.4 (CH_2O, 2C), 109.9 (C-3'5', 2C), 120.6 (C-9), 125.1 (C-4'), 141.7 (C-4'), 131.4, 137.9, 142.1 (C-1'), 149.1 (C-8). HRMS: *m/z* calcd. for $[M+H]^+$ 431.2434; found 431.2443.

According to the General Procedure Method B, CBD (**1**) (100 mg, 0.315 mmol), methyl glycolate (**3d**) (302.8 mg, 0.63 mmol), PPh_3 (165 mg, 0.63 mmol) and DIAD (130 mg, 126 μl, 0.63 mmol) in THF (2 ml) gave an inseperable mixture of products.

2-[(1*R*,6*R)*-3-Methyl-6-prop-1-en-2-yl-1-cyclohex-2-enyl]-5-pentylbenzo-1,3-dioxy-diacetic acid (5). CBD derivative **4d** (59 g, 0,128 mol) was dissolved in ethanol (200 ml) and a solution of KOH (16.8 g, 0.3 mol) in ethanol (50 ml) was added with stirring at room temperature under an atmosphere of nitrogen and stirring was continued for 16 h. The resulting solution was concentrated in vacuo to about 100 ml and mixed with water (500 ml). The aqueous solution was acidified by addition of 37% aqueous HCl solution (33 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and filtered. Concentration of the filtrate afforded **5** (54.8 g, 99%). $[\alpha]_D$ = -95.6 (c=0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.90 (t, *J* 7.0 Hz, H-5'', 3H); 1.21-1.39 (m, H-3'', 3H), 1.49-1.62 (m, H-4'', 2H), 1.66, 1.67 (2 s, H-7,10, 6H), 1.79 (dd, J=9.7, 4.2 Hz, H-2'', 2H), 2.00 (br s, H-5, 1H), 2.37-2.55 (m, H-1'', 2H), 3.02 (dd, *J* 4.7 Hz, H-1, 1H), 3.80 (s, OCH_3, 6H), 4.47 (s, H-9, 2H), 4.55 (s, OCH_2, 4H), 5.24 (br s, H-2, 1H), 6.27 (br s, H-3',5', 2H). ^{13}C-NMR ($CDCl_3$) δ 14.0 (C-5''), 18.9 (C-10), 22.4 (C-4''), 23.4 (C-7), 29.3, 30,5, 30,8, 31.4 (C-1'',2'',3''5), 36.0 (C-4), 36.2 (C-1), 52.0 (OCH_3), 66.4 (OCH_2), 109.9 (C-9), 120.6 (C-3), 125.1 (C-2,3',5'), 131.7 (C-4'), 142.0 (C-1'), 149.2 (C-8), 169.4 (C1'2',6'). Elemental Analysis calcd. for $C_{25}H_{34}O_6$: C 70.24; H 8.16; found C 69.11; H 8.14.

Di-potassium 2-[(1*R*,6*R*)-3-Methyl-6-prop-1-en-2-yl-1-cyclohex-2-enyl]-5-pentylbenzo-1,3-dioxydiacetate (6). A solution of compound **5** (1 g, 2.3 mmol) in ethanol (10 ml) was neutralized with a 1 N solution of KOH in ethanol (2.3 ml). Concentration of the solution afforded **6** (1.08 g, qant.). $[\alpha]_D$ = -80.2 (c=1, H_2O). HRMS: *m/z* calcd. for $[M+H]^-$ 429.2283 found 429.2287 (dev. 1.17 ppm).

Acknowledgements

We thank Dr. D. Wistuba and Dr. M. Kramer and their teams for measuring the MS and NMR spectra. We also thank P. Schülzle for performing the elemental analyses. Tresco Labs GmbH, Germany is acknowledged for financial support.

Supplementary Material

NMR Data are found in the Supplementary Material

References

1. Aizpurua-Olaizola, O.; Soydaner, U.; Öztürk, E.; Schibano, D.; Simsir, Y.; Navarro, P.; Etxebarria, N.; Usobiaga, A. *J. Nat. Prod*. **2016**, *79*, 324. https://doi.org/10.1021/acs.jnatprod.5b00949
2. Russo, E. B. *Br. J. Pharmacol. **2011**, 163*, 1344. https://doi.org/10.1111/j.1476-5381.2011.01238.x
3. Thomas, A.; Baillie, G. L.; Phillips, A. M.; Razdan, R. K.;Ross, R. A.; Pertwee, R. G. *Br. J. Pharmacol*. **2007**, *150*, 613. https://doi.org/10.1038/sj.bjp.0707133
4. O'Connella, B. K.; Gloss, D.; Devinskya, O. *Epilepsy & Behavior* **2017**, *70*, 341. https://doi.org/10.1016/j.yebeh.2016.11.012
5. Noreen, N.; Muhammad, F.; Akhtar, B.; Azam, F.; Anwar, M. I. *Crit. Rev. Eukar. Gene* **2018**, *28*, 73**.** https://doi.org/10.1615/CritRevEukaryotGeneExpr.2018021528
6. Malfait, A. M.; Gallily, R.; Sumariwalla, P. F.; Malik, A. S,; Andreakos, E.; Mechoulam, R.; Feldmann, M. *PNAS* **2000**, *97*, 9561. https://doi.org/10.1073/pnas.160105897
7. Stukelj, R.; Bencina, M.; Faretti, M.; Valant, M.; Drab, M.; Iglic, A.; Kralj-Iglic, V. *Materials Technology* **2019**, *53*, 543. https://doi.org/10.17222/mit.2018.253
8. Winnicki, R. PCT Int. Appl. (**2013**) WO 2013009928 Al, *Chem. Abstr*. **2013**:81850
9. Metcalf, D. G. United States Patent (**2019**) US 10555914, *Chem. Abstr*. **2020**:267166.
10. Cosky, E. United States Patent Apllication (**2020**) US 63/101,897.
11. Adams, I. R.; Hunt, M.; Clark, J. H. *J. Am. Chem. Soc*. **1940**, *62*, 196. https://doi.org/10.1021/ja01858a058
12. Jacob, A.; Todd, A. R. *J. Chem. Soc*. **1940**, 649.

https://doi.org/10.1039/jr9400000649
13. Mechoulam, R.; Shvo, Y. *Tetrahedron* **1963**, *19*, 2073. https://doi.org/10.1016/0040-4020(63)85022-X
14. Jung, B.; Lee, J. K.; Kim, J.; Kang, E. K.; Han, S. Y.; Lee, H.-Y.; Choi, I. S. *Chem. Asian J*. **2019**, *14*, 3749; and references cited therein. https://doi.org/10.1002/asia.201901179
15. Morales, P.; Reggio, P. H.; Jagerovic, N. *Front. Pharmacol*. **2017**, *8*, 422; and references cited therein. https://doi.org/10.3389/fphar.2017.00422
16. Mechoulam, R.; Kogan, N.; Gallily, R.; Breuer, A. PCT Int. Appl. (**2008**), WO 2008107879 A1 20080912; *Chem. Abstr*. **2008**: 1101653.
17. Eisphly, M. A.; Majumdar, S.; Gul, W.; Ashfag, M. K.; Sufka, K. J.; Harris, H. M. PCT Int. Appl. (**2017**), WO 2017132526 A1; *Chem. Abstr.* **2017**:1256603.
18. Ben-Shabat, S.; Hanus, L. O.; Katzavian, G.; Gallily, R. *J. Med. Chem.* **2006,** *49,* 1113. https://doi.org/10.1021/jm050709m
19. Gong, X.; Sun, C.; Abame, M. A.; Shi, W.; Xie, Y.; Xu, W.; Zhu, F.; Zhang, Y.; Shen, J.; Aisa, H. A. *J. Org. Chem*. **2020**, *85*, 2704. https://doi.org/10.1021/acs.joc.9b02880
20. JSmith, J. R. L.; O'Brien, P.; Reginato, G. *Tetrahedron: Asymmetry* **1997**, *8*, 3415. https://doi.org/10.1016/S0957-4166(97)00399-6
21. Boxhall, J. Y.; Page, P. C. B.; Chan, Y.; Hayman, C. M.; Heaney, H.; McGrath, M. J. *Synlett* **2003**, 997.
22. Hodgetts, K. J. *Tetrahedron* **2005**, *61*, 6860. https://doi.org/10.1016/j.tet.2005.04.047
23. Hain, J. J.; Chandrasekaran, V.; Lindhorst, T. K. *Isr. J. Chem*. **2015**, *55*, 383. https://doi.org/10.1002/ijch.201400211
24. Lakoud, S. G.; Djerourou, A. *Arabian Journal of Chemistry* **2016**, *9*, S889. https://doi.org/10.1016/j.arabjc.2011.09.008
25. Garrett, E. R.; Hunt, C. A. *J. Pharm. Sci.* **1974***, 63*, 1056. https://doi.org/10.1002/jps.2600630705
26. Choi, Y. H.; Hazekamp, A.; Peltenburg-Looman, A. M. G.; Frédérich, M.; Erkelens, C.; Lefeber, A. W.; Verpoorte, R. *Phytochem. Anal*. **2004**. *15*, 345. https://doi.org/10.1002/pca.787