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Total Synthesis of 1″- and 2″-Hydroxycannabidiol Metabolites

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Herein we report a new practical and efficient multistep syntheses of 1″- and 2″-hydroxycannabidiol metabolites. Both products and intermediates were fully characterized, and the target metabolites were produced in good overall yields.

Introduction

Cannabidiol (CBD) is one of the main constituents of the *Cannabis sativa L.* and it is currently the most examined non-psychoactive cannabinoids owing to its plethora of properties such as the antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, analgesic and anticancer ones.[1] On the other hand, a very small attention has been targeted towards the pharmacological properties of the CBD metabolites, which could be the effective responsible of some of the important pharmacological effects observed after CBD administration. In particular, the hydroxylated derivatives constitute one of the major CBD metabolites,[2] and the 7-hydroxycannabidiol (**7-OH-CBD**) is the most abundant, nevertheless the formation of others monohydroxylated metabolites such as **6-α-OH-CBD**, **6-β-OH-CBD**, **1′′-OH-CBD**, **2′′-OH-CBD**, **3′′-OH-CBD**, **4′′-OH-CBD**, and **5′′-OH-CBD**, were detected by Watanabe et al. in human liver microsomes.[3]

Although many of these metabolites are well known since the early 70s, they are achieving a growing attention only in recent years, thanks to the increasing interests on cannabidiol usage in therapy (e.g. **1″-OH-CBD** was discovered to be one of the main metabolites in which CBD is converted by cardiac cytochromes CYP2J2).[4]

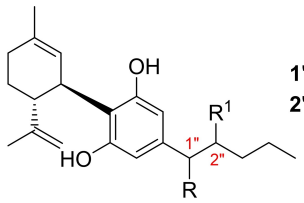
On the other hand, the emptiness in the metabolites research activities can be a consequence of the lack of synthetic protocols for preparing these compounds. In fact, except a contribution provided by Mechoulam and Tchilibon, who implemented an eight-steps procedure to prepare **7″-OH-CBD**,[5] only a limit number of methodologies to prepare hydroxylated cannabidiol derivatives are present in the literature.[6]

In this view and following our studies concerning the synthesis of cannabinoids,[7] we have now developed and report herein, a new multistep and straightforward synthesis of 1″- and 2″-hydroxycannabidiol (Figure 1).

Results and Discussion

Our synthetic approach is based on four steps starting from the triflate derivative **4**, molecule easily synthesized *via* Friedel-Crafts reaction of (+)-*p*-mentha-2,8-dien-1-ol **1** and phlorogucinol **2** followed by the esterification of the adduct **3** using trifluoromethanesulfonic anhydride (Scheme 1).[8] In details, the steps involve (*I*) the protection of the hydroxyl groups of **4** as pivalic esters to form the adduct **5**, (*II*) a Sonogashira reaction between **5** and 1-pentyne, (*III*) the hydration of alkyne **6** to give regioisomeric ketones **7** and **8**, (*IV*) the conversion of these latter into the corresponding title targets **1″-OH-CBD** and **2″-OH-CBD** in almost ~52% of overall yield starting from **4**.

(*I Step*) In view of our synthetic strategy, we began our study exploring the esterification of **4** into its protected derivative **5**. Inspired by the study of Aisa and co-workers,[8] we focused our attention on protecting the two hydroxyl groups as pivalic esters. In fact, as reported by authors, this protection does not seem to affect the reactivity of the triflate moiety concerning a successive coupling reaction. However, we slightly modified the reaction conditions replacing pivaloyl chloride and



1"-OH-CBD R = OH, R^1 = H
2"-OH-CBD R = H, R^1 = OH

Figure 1. General structure of **1″-OH-CBD** and **2″-OH-CBD** metabolites.

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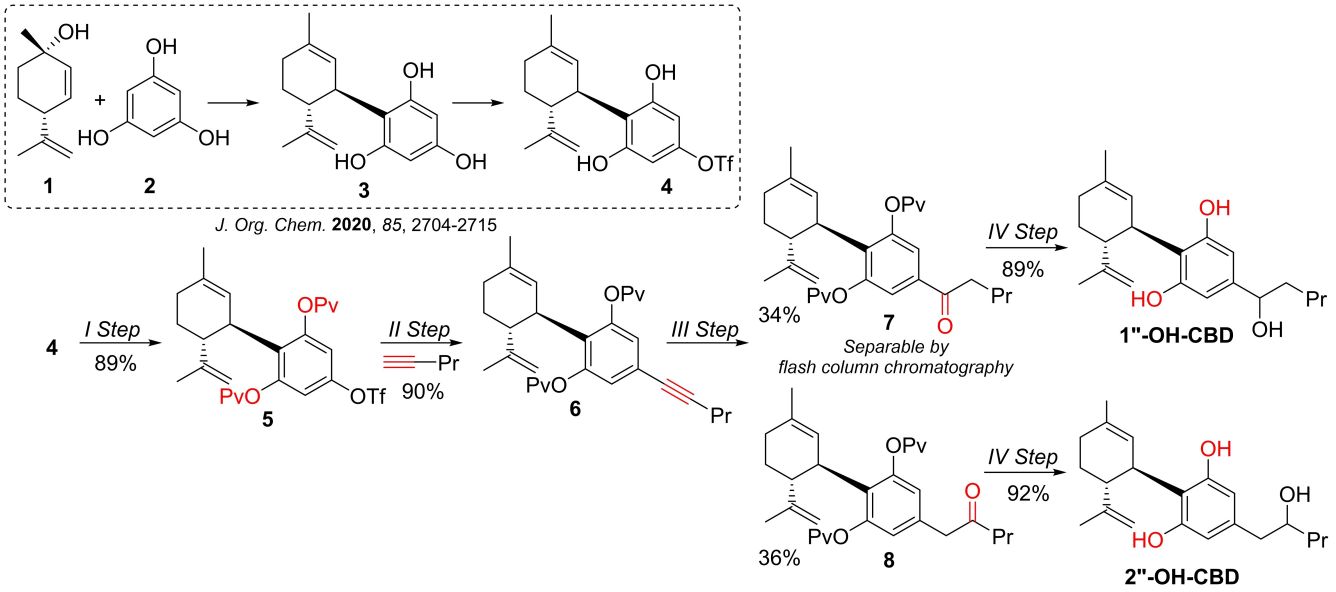

Scheme 1. Multistep approach for the synthesis of **1"-OH-CBD** and **2"-OH-CBD** metabolites.

pyridine with the more manageable and less toxic pivalic acid and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC). In particular, the best yield (89%) was obtained in the presence of 2.4 eq. of pivalic acid, 4 eq. of EDC, 0.4 eq. of DMAP, and conducing the reaction for 18 hours in dry dichloromethane (0.15 M) at room temperature. The reaction was also examined using *N,N'*-dicyclohexylcarbodiimide (DCC) or *N,N'*-diisopropylcarbodiimide (DIC) instead of EDC. In both cases **5** was isolated in lower yield (78% and 76% respectively), nevertheless the reaction performed in the presence of DDC completed just after 5 hours, while 48 hours were needed to finish for the reaction promoted by DIC.

(*II Step*) Then, we faced the Sonogashira reaction between the triflate **5** and 1-pentyne. In this regard, we recorded the best result (90% yield) applying the conditions used by Yu *et al.* for a similar substrate.[9] In particular, the reaction was carried out overnight in a sealed vial, using catalytic amounts of CuI (0.1 eq.) and $Pd(PPh_3)_2Cl$ (0.1 eq.), 5 eq. of 1-pentyne, 3.3 eq. of DIPEA and using dry DMF as the solvent (0.1 M) at 70 °C. An increasing of the temperature to 90 °C did not produce any yield improvement (87%), while a lowering of the temperature to 40 °C or replacing DMF with acetonitrile made the coupling reaction quite ineffective (35% and 40%). Finally, we replayed the reaction at 70 °C using palladium-tetrakis(triphenylphosphine) as catalyst, nevertheless the product yield was significantly lower (25%, overnight).[10]

(*III Step*) Successively, we examined the third step, namely the hydration of alkyne **6** to synthesize ketones **7** and **8**. With this aim, we firstly tested the conditions reported by Li,[11] consisting in the use of catalytic amount of triflic acid (0.2 eq.) in 2,2,2-trifluoroethanol and in the presence of water (2 eq.). However, no product was detected both performing the reaction at room temperature or at 50 °C. Then, we explored the use of $AuCl(PPh_3)$, AgOTf in 1,4-dioxane at room temperature.[12] Under these conditions the formation of the compound **7** was observed, but only in trace amounts. Finally, a slight modification of the Shen's conditions[13] permitted to produce ketones **7** and **8** in almost 1:1 ratio and in a 72% of overall yield. Specifically, the hydration of **6** was attempted using a 4% sulfuric acid water solution, $HgSO_4$ and ethanol as solvent at 70 °C. The two regioisomers presented a significant different retention factor (R_f = 0.32 and 0.16 for compounds **7** and **8** respectively) and they could be easily separated by flash column chromatography (hexane:ethyl acetate = 95:5).

(*IV Step*) Finally, the separated ketones **7** and **8** were converted into the corresponding target cannabidiol metabolites **1"-OH-CBD** and **2"-OH-CBD**. In particular, the former metabolite was isolated in 89% yield as yellow oil, while **2"-OH-CBD** was obtained in 92% yield as pale pink oil. Both metabolites were isolated as an inseparable ca. 1:1 epimeric mixture, as determined by the analysis of the $^{13}C\{H\}$ NMR spectra (see Supporting Information).

Conclusions

In conclusion, we accomplished a new practical and efficient multistep synthesis of cannabidiol metabolites **1"-OH-CBD** and **2"-OH-CBD**. The procedure involves four steps and can be profitably used for preparing the title targets in good overall yield, thus opening new opportunities to implement new studies concerning both the investigation of cannabinoids metabolism, and the possible direct use of the two metabolites in therapy. Moreover, both the alkyne **6** and ketones **7** and **8** can be further manipulated to potentially generate a huge assortment of CBD analogues, functionalized on the alkyl chain.

Experimental Section

General Remark. ^{1}H NMR analyses were recorded at 400 MHz on a Varian Mercury Plus 400. ^{13}C NMR analyses were recorded at 100 MHz. NMR calibration was accomplished by referring to the TMS signal. Deuterated Chloroform was purchased from Eurisotop. IR spectrum were recorded with a Perkin-Elmer FT-IR spectrometer Spectrum Two UATR. Microanalyses were performed with a CHNS-O analyzer Model EA1108 from Fisons Instruments.

Synthetic procedure for the preparation of 5. DMAP (0.17 g, 1.4 mmol) was added to a solution of **4** (1.39 g, 3.54 mmol) and pivalic acid (0.87 g, 8.5 mmol) in anhydrous dichloromethane (17 mL). The temperature was lowered to 0 °C and EDC (2.7 g, 14.2 mmol) was added in one portion. The mixture was stirred for 18 hours while reaching room temperature. Water was added (20 mL), the two layers were separated, and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over dry Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product **5**, which was purified by chromatography on silica gel (Hexane : EtOAc = 95 : 5; R_f = 0.42).

Pale white oil; yield: 1.764 g (89 %). IR (neat): 1759, 1603, 1425, 1210, 1141, 1082, 1035, 980 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.79 (s, 2H), 5.21 (s, 1H), 4.54 (t, 1H, *J* = 1.6 Hz), 4.51 (s, 1H), 3.59 (d, 1H, *J* = 12.8 Hz), 2.73–2.63 (m, 1H), 2.15–2.01 (m, 2H), 1.88–1.80 (m, 1H), 1.76–1.66 (m, 1H), 1.62 (s, 3H), 1.53 (s, 3H), 1.34 (s, 18H). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 176.1, 147.2, 146.5, 133.2, 130.4, 123.6, 111.3, 45.0, 39.3, 38.6, 30.6, 29.2, 27.1, 23.3, 19.8. MS (70 eV): = 560 ([M$^+$], 4), 457 (8), 85 (24), 57 (100), 41 (13). Anal. Calcd for $C_{27}H_{35}F_3O_7S$ (560.63): C, 57.85; H, 6.29; S, 5.72; Found: C, 57,89; H, 6.32; S, 5.70.

Synthetic procedure for the preparation of 6. DIPEA (0.58 mL) and 1-pentyne (0.41 g, 0.57 mL, 5 mmol) were added to an anhydrous solution of DMF (14 mL) containing $Pd(PPh_3)_2Cl_2$ (0.070 g, 0.1 mmol), CuI (0.020 g, 0.1 mmol) and **5** (0.56 g, 1 mmol) maintained under argon atmosphere in a sealed vial. The resulting mixture was stirred overnight at 70 °C, then a saturated solution of NH_4Cl (30 mL) was added and the aqueous layer extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over dry Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product **6**, which was purified by flash column chromatography on silica gel (Hexane : EtOAc = 98 : 2; R_f = 0.47).

Brown oil; yield: 0.430 g (90 %). IR (neat): 2230, 1757, 1615, 1555, 1480, 1094, 1034, 892 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.83 (s, 2H), 5.26 (s, 1H), 4.57–4.54 (m, 2H), 3.54 (d, 1H, *J* = 10.0 Hz), 2.73–2.65 (m, 1H), 2.35 (t, 2H, *J* = 5.6 Hz), 2.19–2.09 (m, 1H), 2.08–2.00 (m, 1H), 1.87–1.80 (m, 1H), 1.76–1.66 (m, 1H), 1.64–1.58 (m, 5H), 1.56 (s, 3H), 1.35 (s, 18H), 1.04 (t, 3H, *J* = 6.0 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 176.4, 147.7, 132.4, 129.5, 124.5, 122.8, 111.0. 91.3, 79.2, 45.2, 39.2, 38.7, 30.7, 29.5, 27.2, 23.2, 22.1, 21.3, 19.9, 13.5. MS (70 eV): *m*/z (%) 478 ([M$^+$], 12), 393 (21), 311 (14), 227 (29), 85 (14), 57 (100), 29 (5). Anal. Calcd for $C_{31}H_{42}O_4$ (478.67): C, 77.79; H, 8.84. Found: C, 77.83; H, 8.87.

Synthetic procedure for the preparation of 7 and 8. To a solution of **6** (0.30 g, 0.61 mmol) in EtOH (6 mL) an aqueous 4 % H_2SO_4 solution (3 mL, 0.365 mmol, 0.6 eq.) was added and the mixture was stirred for 4 hours at 70 °C. Then, the pH of the solution was adjusted to ~7–8 using $NaHCO_3$ sat. solution (10 mL) and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over dry Na_2SO_4, filtered and evaporated under reduced pressure to give a 45 : 55 regioisomeric mixture of ketones **7** and **8**, which was purified by flash column chromatography on silica gel (Hexane : EtOAc = 97 : 3).

Compound **7**. Yellow oil; R_f = 0.32; yield 0.161 g (32 %). IR (neat): 3078, 1754, 1688, 1645, 1615, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (s, 2H), 5.24 (s, 1H), 4.55 (s, 2H), 3.63 (d, 1H, *J* = 12.5 Hz), 2.91 (t, 2H, *J* = 7.5 Hz), 2.79–2.71 (m, 1H), 2.21–2.11 (m, 1H), 2.09–2.03 (m, 1H), 1.89–1.82 (m, 1H), 1.76–1.67 (m, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.48–1.29 (m, 20H), 0.96 (t, 3H, *J* = 7.5 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 198.4, 176.5, 147.4, 136.0, 134.8, 132.9, 123.7, 111.2, 45.1, 39.2, 39.0, 38.1, 30.7, 29.4, 27.2, 26.1, 23.2, 22.3, 19.7, 14.0. MS (70 eV): *m*/z (%) = 496 ([M$^+$], 9), 411 (29), 369 (9), 327 (13), 245 (14), 85 (23), 57 (100), 29 (4). Anal. Calcd for $C_{31}H_{44}O_5$ (496.69): C, 74.96; H, 8.93. Found: C, 75.00; H, 8.96.

Compound **8**. Yellow oil; R_f = 0.16; yield 0.197 g (40 %). IR (neat): 3076, 1752, 1716, 1645, 1622, 1103 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.64 (s, 2H), 5.24 (s, 1H), 4.53 (d, 2H, *J* = 0.8 Hz), 3.59 (s, 2H), 3.54 (d, 1H, *J* = 8.8 Hz), 2.73–2.61 (m, 1H), 2.40 (t, 2H, *J* = 7.2 Hz), 2.15–2.07 (m, 1H), 2.05–1.97 (m, 1H), 1.85–1.78 (m, 1H), 1.74–1.66 (s, 1H), 1.62–1.54 (m, 8H), 1.33 (s, 18H), 0.85 (t, 3H, *J* = 7.4 Hz). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 207.9, 176.6, 147.8, 133.0, 132.4, 128.0, 124.6, 110.9, 49.3, 45.1, 43.8, 39.2, 38.6, 30.7, 29.4, 27.2, 23.3, 20.0, 17.1,13.6. MS (70 eV): *m*/z (%) = 496 ([M$^+$], 11), 411 (33), 329 (13), 242 (16), 85 (10), 57 (100), 29 (4). Anal. Calcd for $C_{31}H_{44}O_5$ (496.69): C, 74.96; H, 8.93. Found: C, 74.99; H, 8.90.

Synthetic procedure for the preparation of 1″-OH-CBD and 2″-OH-CBD. $LiAlH_4$ (0.031 g, 0.805 mmol, 5 eq.) was added to a stirred solution of **7** (or **8**) (0.080 g, 0.161 mmol) in dry THF (5 mL) under N_2 atmosphere at 0 °C. The reaction was stirred for 4 hours and then diluted with H_2O (10 mL), extracted with ethyl acetate (3×20 mL), filtered and evaporated under reduced pressure to give target compound **1″-OH-CBD** (or **2″-OH-CBD**), which was purified by flash column chromatography on silica gel (Hexane : EtOAc 75 : 25).

1″-OH-CBD (diastereomeric mixture). Yellow oil; R_f = 0.36; yield 0.047 g (89 %). IR (neat): 3415, 1624, 1586, 1440, 1025, 755 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.36 (s, 2H), 6.06 (br s, 2H), 5.53 (d, 1H, *J* = 6.4 Hz), 4.60–4.51 (m, 1H), 4.47–4.27 (m, 2H), 3.96–3.90 (m, 1H), 2.41 (dt, 1H, *J* = 10.5, 4.0 Hz), 2.26–2.17 (m, 1H), 2.12–2.05 (m, 1H), 1.89–1.53 (m, 5H), 1.78 (s, 3H), 1.66 (s, 3H), 1.36–1.22 (m, 4H), 0.89–0.80 (m, 3H). ^{13}C{H} NMR ($CDCl_3$, 100 MHz): δ = 148.5, 148.4, 144.5, 144.4, 140.0, 124.0, 115.8, 115.7, 111.0, 74.6, 46.3, 46.2, 38.1, 38.0, 36.6, 36.5, 30.4, 28.2, 28.0, 23.7, 22.6, 19.7, 19.6, 14.0, 13.9. MS (70 eV): *m*/z (%) = 330 ([M$^+$], 9), 247 (100), 229 (10), 205 (10), 121 (11). Anal. Calcd for $C_{21}H_{30}O_3$ (330.47): C, 76.33; H, 9.15. Found: C, 76.36; H, 9.12.

2″-OH-CBD (diastereomeric mixture). Pale pink oil; R_f = 0.31; yield 0.049 g (92 %). IR (neat): 3422, 1626, 1584, 1444, 1027, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.40 (br s, 1H), 6.22 (s, 2H), 6.07 (br s, 1H), 5.54 (s, 1H), 4.55 (s, 1H), 4.48–4.43 (m, 1H), 3.98–3.89 (m, 1H), 3.81–3.71 (m 1H), 2.66 (dt, 1H, *J* = 13.2, 3.6 Hz), 2.47–2.37 (m, 2H), 2.30–2.16 (m, 2H), 2.13–2.03 (m, 1H), 1.83–1.73 (m, 2H), 1.78 (s, 3H), 1.67 (s, 3H), 1.53–1.17 (m, 4H), 0.97–0.81 (m, 3H). ^{13}C{H} NMR $CDCl_3$, 100 MHz): δ = 148.6, 148.3, 139.8, 139.7, 138.0, 137.9, 124.2, 124.1, 114.9, 114.8, 111.0, 110.9, 72.7, 72.4, 46.4, 46.3, 43.7, 43.6, 38.7, 38.7, 36.3, 36.2, 30.3, 29.7, 28.3, 23.7, 19.6, 19.4, 19.0, 14.0. MS (70 eV): *m*/z (%) = 330 ([M$^+$], 10), 247 (100), 209 (7), 175 (35), 121 (12), 55 (7). Anal. Calcd for $C_{21}H_{30}O_3$ (330.47): C, 76.33; H, 9.15. Found: C, 76.37; H, 9.18.

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Conflict of Interests

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: cannabinoids · synthetic cannabinoids · cannabidiol metabolites · total synthesis · hydroxycannabidiol derivatives

[1] a) P. Consroe, A. Wolkin, *J. Pharmacol. Exp. Ther.* **1977**, *201*, 26; b) R. Mechoulam, L. A. Parker, R. Gallily, *J. Clin. Pharmacol.* **2002**, *42*, 11; c) J. Elikottil, P. Gupta, K. Gupta, *J. Opioid. Manag.* **2009**, *5*, 341; d) A. W. Zuardi, J. A. S. Crippa, J. E. C. Hallak, S. Bhattacharyya, Z. Atakan, R. Martin-Santos, P. K. McGuire, F. S. Guimarães, *Curr. Pharm. Des.* **2012**, *18*, 5131; e) A. Batalla, H. Janssen, S. S. Gangadin, M. G. Bossong, *J. Clin. Med.* **2019**, *8*, 1058; f) S. Atalay, I. Jarocka-Karpowicz, E. Skrzydlewska, *Antioxidants* **2020**, *9*, 21; g) G. D. Silva, F. Borelli Del Guerra, M. De Oliveira Lelis, L. Figueira Pinto, *Front. Neurol.* **2020**, *11*, 531939; h) M. Wright, P. Di Ciano, B. Brands, *Cannabis Cannabinoid Res.* **2020**, *5*, 191; i) E. S. Seltzer, A. K. Watters, D. MacKenzie Jr, L. M. Granat, D. Zhang, *Cancers* **2020**, *12*, 3203; j) F. R. Henshaw, L. S. Dewsbury, C. K. Lim, G. Z. Steiner, *Cannabis Cannabinoid Res.* **2021**, *6*, 177; k) S. D. Lichestein, *Curr. Addict. Rep.* **2022**, *9*, 473; l) S.-H. Lee, H.-S. Lee, G. Tamia, H.-J. Song, C.-I. Wei, *Curr. Dev. Nutr.* **2022**, *6*, 246; m) Y. Román-Vargas, J. D. Porras-Arguello, L. Blandón-Naranjo, L. D. Pérez-Pérez, D. M. Benjumea, *Molecules* **2023**, *28*, 4299.
[2] I. Ujváry, L. Hanuš, *Cannabis Cannabinoid Res.* **2016**, *1.1*, 90.
[3] R. Jiang, S. Yamaori, S. Takeda, I. Yamamoto, K. Watanabe, *Life Sci.* **2011**, *89*, 165.
[4] W. R. Arnold, A. T. Weigle, A. Das, *J. Inorg. Biochem.* **2018**, *184*, 88.
[5] a) S. Tchilibon, R. Mechoulam, *Org. Lett.* **2000**, *2*, 3301; b) L. O. Hanus, S. Tchilibon, D. E. Ponde, A. Breuer, E. Fride, R. Mechoulam, *Org. Biomol. Chem.* **2005**, *3*, 1116.
[6] a) W. R. Arnold, A. T. Weigle, A. Das, *J. Inorg. Biochem.* **2018**, *184*, 88; b) W. A. Kinney, M. E. McDonnell, H. M. Zhong, C. Liu, L. Yang, W. Ling, T. Qian, Y. Chen, Z. Cai, D. Petkanas, D. E. Brenneman, *ACS Med. Chem. Lett.* **2016**, *7(4)*, 424; c) N. Lander, Z. Ben-Zvi, R. Mechoulam, B. Martin, M. Nordqvist, S. Agurell, *J. Chem. Soc. Perkin Trans. 1* **1976**, 8.
[7] E. Chiurchiù, S. Sampaolesi, P. Allegrini, D. Ciceri, R. Ballini, A. Palmieri, *Eur. J. Org. Chem.* **2021**, *2021*, 1286.
[8] X. Gong, C. Sun, M. A. Abame, W. Shi, Y. Xie, W. Xu, F. Zhu, Y. Zhang, J. Shen, H. A. Aisa, *J. Org. Chem.* **2020**, *85*, 2704.
[9] Y. Zhu, Z. Shen, W. Li, B. Yu, *Org. Biomol. Chem.* **2016**, *14*, 1536.
[10] L.-P. Sun, X.-H. Huang, W.-M. Dai, *Tetrahedron* **2004**, *60*, 10983.
[11] W. Liu, H. Wang, C.-J. Li, *Org. Lett.* **2016**, *18*, 2184.
[12] J. Jeong, D. Ray, C. H. Oh, *Synlett* **2012**, *23*, 897.
[13] C. Wu, Y. Wang, F. Yang, W. Shi, Z. Wang, L. He, Y. He, J. Shen, *ChemMedChem* **2019**, *14*, 2042.

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