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Piers–Rubinsztajn reaction to unlock an 8-step synthesis of 7-hydroxy cannabidiol†

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A scalable synthesis of 7-hydroxy cannabidiol (7-OH CBD), a primary metabolite of (–)-cannabidiol (CBD), is highly desirable, from an industrial point of view, to enable future clinical trials. A Piers–Rubinsztajn reaction was key to enable a mild deprotection and a concise synthesis of 7-OH CBD from commercially available CBD, in 31% overall yield.

Introduction

7-Hydroxy-cannabidiol (7-OH CBD, **1**) is a primary metabolite of cannabidiol (CBD, **2**) generated during the first stages of metabolism.¹ Since 2018, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved the first cannabidiol-based drug in pure form for the treatment of two severe forms of drug-resistant childhood epilepsy, or its intake in combination with commonly used antiepileptic drugs. Cannabidiol (CBD) is one of the most abundant phytocannabinoids obtained from *Cannabis sativa* and it is well known as a non-psychotic, analgesic, anticonvulsant, and anti-inflammatory compound. The cannabinoids, and their derivatives, have thus gained increasing attention in both academia and industry.^{2–4} The underlying mechanism by which CBD exerts its therapeutic efficacy has not been fully elucidated,⁵ though some of the observed effects have tentatively been attributed to metabolites including 7-OH CBD **1**. Interest in 7-OH CBD **1** has significantly grown due to a number of effects that were observed in preclinical studies.^{5–7} Due to the lack of a synthesis of industrial interest, 7-OH CBD **1** has only been used as an analytical standard to date. The development of a robust synthesis is, therefore, critical in enabling any future prospect of targeted clinical trials. Of significant note, and inhibiting many synthetic efforts, is that in the presence of acid CBD, and its metabolites, cyclize to form Δ^9 -tetrahydrocannabinol (Δ^9 -THC), and derivatives, it is therefore imperative to plan a feasible synthesis that avoids such acidic reaction

conditions.⁸ The directed oxidation of cannabinoids to obtain hydroxy-derivatives is a reported strategy which involves the use of selenium dioxide (SeO₂) as an oxidizing agent.⁹ Although used for the oxidation of limonene,¹⁰ the selectivity of oxidation was low giving a mixture of different regioisomeric hydroxylation products. To the best of our knowledge, the first multistep synthesis of 7-OH CBD **1** was reported by Mechoulam and co-workers starting from commercially available CBD **2**.^{11,12} The authors obtained the target compound in 8 steps, with a key limitation being the demethylation of the protected aryl OH groups requiring the use of methyl magnesium iodide in neat conditions at 210 °C. The forcing nature of this deprotection concisely highlights the challenge that lies in the final deprotection, where acidic conditions are to be avoided.

We were interested in developing a synthesis of 7-OH CBD **1** that could be of industrial interest and generate enough material to undertake preclinical studies. Following preliminary discussions and a series of considerations, such as an established industrial process for the preparation of CBD **2** by our industrial partner, (–)-CBD **2** was selected as a key starting material, similarly to Mechoulam's route. At the outset, it was decided that the forcing conditions of the final deprotection had to be avoided, and the route would benefit from being shortened. Therefore, a redesign of the synthesis, along with alternative strategies for the final deprotection, was undertaken. Herein we report a 8-step synthesis to 7-hydroxy cannabidiol **1** starting from (–)-CBD **2** featuring two telescoped transformations, that avoids harsh deprotection conditions (Scheme 1). The application of a Piers–Rubinsztajn reaction, involving B(C₆F₅)₃ (BCF) as a catalyst¹³ in the presence of pentamethyl disiloxane, allowed us to successfully carry out an acid-free deprotection of cannabidiol derivative under mild conditions.

Results and discussion

The forward synthesis was started with protecting (–)-CBD **2** on the two phenolic groups with methyl tosylate¹⁴ to generate

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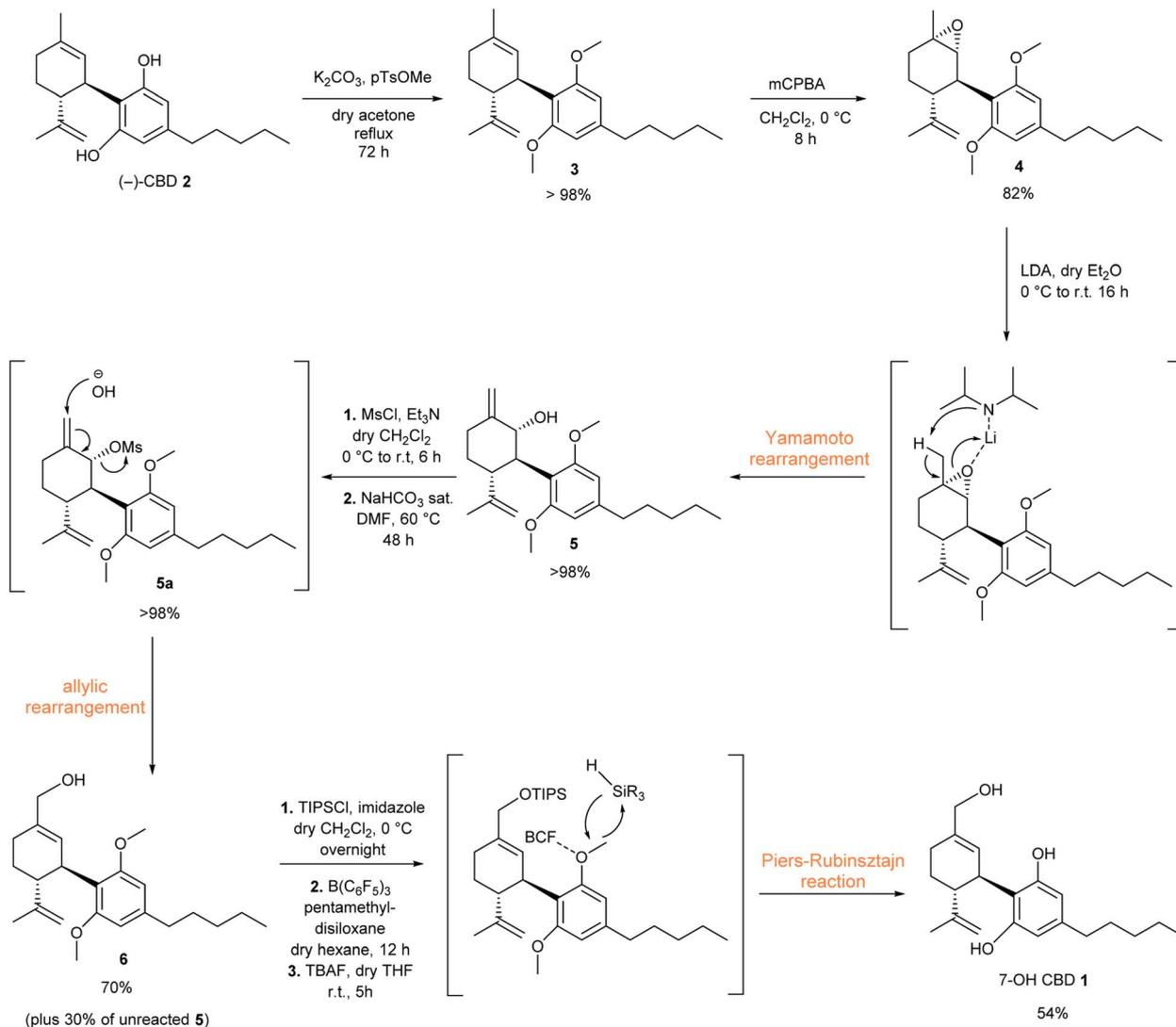
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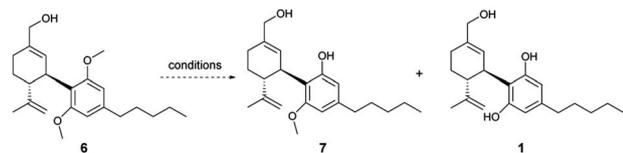


Scheme 1 Overall synthesis of 7-hydroxy-cannabidiol 1.

dimethoxy CBD 3 in quantitative yield; a subsequent regioselective epoxidation of the endocyclic double bond on the terpene moiety produced epoxide 4 in high yield. The choice of the protecting group on the phenolic hydroxy groups was restricted to methyl to enable the subsequent epoxide ring-opening reaction,¹¹ as also confirmed in our labs. A Yamamoto rearrangement, enabled a concomitant ring-opening of the epoxide with the removal of the methyl hydrogen, smoothly producing cyclohexanol derivative 5. A strong, bulky base was found to be key for high regio- and chemoselectivity in the epoxide ring-opening reaction.¹⁵ LDA proved to be efficient and cost effective for the purpose, providing allylic alcohol 5 in quantitative yield, without any purification needed. An allylic rearrangement of 5, that would directly afford primary alcohol 6, was envisaged; if successful, this would indeed provide an advanced intermediate to 7-OH CBD 1. A conjugated nucleophilic substitution¹⁶ on the mesylated-derivative 5a was attempted using hydroxide as a nucleophile in aqueous conditions; to our delight, alcohol 6 was obtained in good yields in

a telescoped procedure. It should be noted that, given the multiple steps, complex, biphasic solvent and reagent mixture, the yield of the reaction is scale dependent. Care must be taken to ensure all vessel and mixing parameters are matched. To our delight, the remaining mass balance was unreacted allylic alcohol 5 that could be recovered and subjected to the allylic rearrangement again. To afford 7-OH CBD 1 as the final product, the removal of the methoxy-protecting groups on the phenolic moieties posed a stimulating challenge. Indeed, strong acids or acidic conditions induce a tertiary carbocation formation on the isopropenyl substituent resulting in a cyclization to give the THC skeleton, while strong bases in oxidizing conditions give hydroxy-1,4-benzoquinone derivatives as byproducts. A number of different approaches that would avoid the aforementioned conditions were tested (Scheme 2). Mild Lewis acids were tested, such as FeCl_3 and AlCl_3 alone or in combination with Et_3N or NaI ; di-ether 6 was recovered unreacted or the reaction led to decomposition. Attention was then turned to the use of nucleophilic reagents including



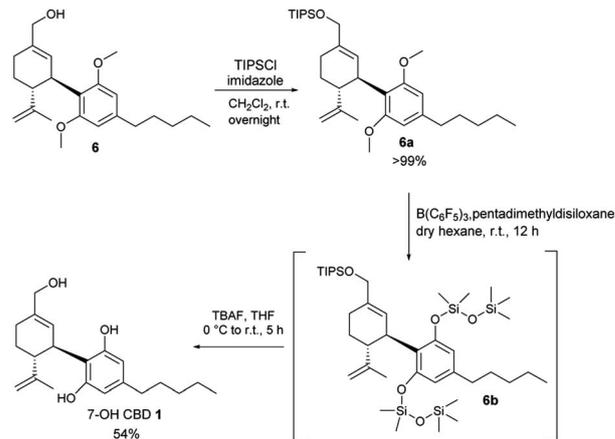


- $\text{AlCl}_3/\text{Et}_3\text{N}$ 1:2.85, DCM: no reaction
- AcCl/NaI 5:6, acetonitrile/THF 1:1: no reaction
- FeCl_3 1 eq, Ac_2O : decomposition
- AlCl_3 3.5 eq, DCM: decomposition
- HPPH_2 4 eq, tBuOK 4 eq, DMF: 7 (85%)
- EtSNa 6 eq, DMF: 1 (traces)
- EtSNa 20 eq, DMF 140 °C, then EtSNa 30 eq, DMF, 145 °C, 1 (5%)
- EtSNa 20 eq, DMF, 140 °C, then Ac_2O , Et_3N , DMAP, DCM, then EtSNa 30 eq, DMF, 145 °C: 7
- EtSNa 20 eq, DMF, 140 °C, then MeCOOH 10.5 eq, then EtSNa 30 eq, DMF, 145 °C: 7

Scheme 2 Attempted reaction conditions to deprotect methoxy groups on **6**.

HPPH_2 and tBuOK , which have been exploited in mild deprotection protocols of aryl methyl/benzyl/allylethers,¹⁷ but unfortunately only a single phenolic oxygen was deprotected, even under forcing conditions or when subjecting the mono-deprotected product **7** to a second round of the deprotection reaction. Additionally, sodium ethanethiolate has been used to induce a nucleophilic cleavage of the C–O bond, leaving the phenolate as a leaving group. Despite the reported treatment of CBD-ether **3** with 4 equivalents of NaSEt at 150 °C for 5 hours leading to CBD **2**,¹⁸ in our hands it was unsuccessful yielding only mono-deprotection. A similar result was obtained in our trials of NaSEt ; the reaction with dimethoxy derivative **6** afforded only mono-deprotected **7**, with only trace 7-OH CBD **1** detected by ^1H NMR spectroscopy and MS. This issue suggests that in the presence of nucleophiles such as HPPH_2 or NaSEt the first demethylation provides a methoxy phenolate that increases the electron density of the aromatic ring, rendering the second deprotection more difficult. While we were facing this challenge, Passarella and co-workers reported the successful deprotection on small scale of dimethoxy CBD **3** to CBD **2** by using a large excess of NaSEt , in two sequential steps, isolating the monodeprotected intermediate.¹⁹ Unfortunately, the same protocol did not prove successful in our hands for the deprotection of dimethoxy derivative **6**; 7-OH CBD **1** was obtained in very low yield and only detectable by mass spectrometry. Derivatization of phenolate **7** with an easily removable electron-withdrawing group to affect the second deprotection was attempted, along with adjusting the pH, to no avail.

Eventually, we realized that the Piers–Rubinsztajn reaction^{20,21} could be the key to a successful deprotection although it had not been reported for the purpose in the context of cannabinoids. We, therefore, investigated whether it could be employed to our aim. The use of tris(pentafluorophenyl) borane (BCF) as a catalyst in the presence of silyl hydrides constitutes a mild and scalable deprotection methodology for aryl ethers.^{22,23} Lewis basic oxygen species, such as methyl ethers, can attack the activated Si-center of the Lewis complex formed between BCF and a siloxane. A reductive cleavage of both *O*-methyl groups on the phenolic oxygens brings about the release



Scheme 3 Deprotection of **6** in mild conditions employing Piers–Rubinsztajn reaction.

of methane and the formation of Ar–Si bonds in their place, that can be easily cleaved with TBAF in acid-free conditions. More importantly for the case of deprotecting dimethoxy derivative **6**, the instant formation of the silyl ether is a key point; capping the negative charge of the phenolate, thus enabling the intermediate monodeprotected species **7** to undergo a second deprotection *via* nucleophilic attack. Initial tests using CBD-ether **3** as a model substrate were very encouraging; ^1H NMR analysis showed the complete formation of CBD **2** as the main product. Unfortunately, subjecting dimethoxy derivative **6** to the same conditions resulted in the unexpected recovery of CBD **2**. In hindsight, with the reductive cleavage of methyl groups, the unwanted deoxygenation is also promoted by the reaction system. As demonstrated by Yamamoto, primary and allylic alcohols can be reduced to alkanes using BCF and $\text{HSi}(\text{Et})_3$.²⁴ Therefore, a series of protecting groups (see ESI†) were tested on the primary alcohol of an analogue of dimethoxy derivative **6**; these had to be stable under the reaction conditions and, ultimately, be removed during the final step of the Piers–Rubinsztajn sequence. TIPS was eventually selected as the protecting group of choice for compound **6**. After simple quantitative protection with TIPS, crude **6a** is telescoped in the Piers–Rubinsztajn reaction to crude **6b**, that is also telescoped to the final deprotection to **1**. 7-OH CBD **1** was obtained in a satisfying 54% yield over the three steps (Scheme 3).

Conclusions

In conclusion, we report the development of an 8-step synthesis, with two telescoped transformations, of 7-hydroxy-cannabidiol **1** in 31% overall yield. The synthesis features an allylic rearrangement and a Piers–Rubinsztajn reaction as key steps; in particular, the development of the final removal of the *O*-methyl groups was critical to efficiently effect the deprotection reaction under more mild and safer conditions. Interestingly, this type of deprotection of cannabidiol derivatives is reported for the first time, to the best of our knowledge, and we believe that such a mild deprotection will be highly attractive for cannabidiol



chemistry. Further work is underway in our labs to access similar derivatives and undertake research for clinical studies on the pharmacological activity of 7-hydroxy-cannabidiol.

Author contributions

E. C. and D. I. conceptualization, data curation, formal analysis, investigation, methodology. A. B. data curation, formal analysis, investigation, methodology. P. A. supervision. S. P. T. funding acquisition and supervision. F. P. and A. C. conceptualization, project administration, funding acquisition and supervision. D. I. and A. C. writing – original draft. All writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- H. Li, Y. Liu, D. Tian, L. Tian, X. Ju, L. Qi, Y. Wang and C. Liang, *Eur. J. Med. Chem.*, 2020, **192**, 112163.
- A. Maiocchi, J. Barbieri, V. Fasano and D. Passarella, *ChemistrySelect*, 2022, **7**, e202202400.
- J. A. A. Grimm, H. Zhou, R. Properzi, M. Leutzsch, G. Bistoni, J. Nienhaus and B. List, *Nature*, 2023, **615**, 634–639.
- G. Appendino and P. Allegrini, *Chim. Ind.*, 2018, **6**, 12–16.
- J. L. Beers, D. Fu and K. D. Jackson, *Drug Metab. Dispos.*, 2021, **49**, 882–891.

- C. Stott, N. Jones, B. Whalley, G. Stephens and C. Williams, *US Pat.*, US 2017/0209390A1, 2017.
- Y. Li, Q. Wu, X. Li, L. S. Von Tungeln, F. A. Beland, D. Petibone, L. Guo, P. Cournoyer, S. Choudhuri and S. Chen, *Food Chem. Toxicol.*, 2022, **159**, 112722.
- R. K. Razdan, in *The Total Synthesis of Natural Products*, Wiley, 2007, vol. 4, pp. 185–262.
- A. Breuer, C. G. Haj, M. V. Fogaça, F. V. Gomes, N. R. Silva, J. F. Pedrazzi, E. A. D. Bel, J. C. Hallak, J. A. Crippa, A. W. Zuardi, R. Mechoulam and F. S. Guimarães, *PLoS One*, 2016, **11**, e0158779.
- S. Yoshitsugu, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 3348–3349.
- S. Tchilibon and R. Mechoulam, *Org. Lett.*, 2000, **2**, 3301–3303.
- L. O. Hanus, S. Tchilibon, D. E. Ponde, A. Breuer, E. Frideb and R. Mechoulam, *Org. Biomol. Chem.*, 2005, **3**, 1116–1123.
- V. Nori, F. Pesciaoli, A. Sinibaldi, G. Giorgianni and A. Carlone, *Catalysts*, 2022, **12**, 5.
- M. A. Arai, Y. Yamaguchi and M. Ishibashi, *Org. Biomol. Chem.*, 2017, **15**, 5025–5032.
- A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 6513–6514.
- K. McAulay and J. S. Clark, *Chem.–Eur. J.*, 2017, **23**, 9761–9765.
- W. Pan, C. Li, H. Zhu, F. Li, T. Li and W. Zhao, *Org. Biomol. Chem.*, 2021, **19**, 7633–7640.
- K. Abdur-Rashid, W. Jia and K. Abdur-Rashid, WO 2020/232545A1, 2020.
- P. Marzullo, A. Maiocchi, G. Paladino, U. Ciriello, L. Lo Presti and D. Passarella, *Eur. J. Org. Chem.*, 2022, **22**, e202200392.
- S. Rubinsztajn and J. A. Cella, *Macromolecules*, 2005, **38**, 1061–1063.
- J. M. Blackwell, E. R. Sonmor, T. Scoccitti and W. E. Piers, *Org. Lett.*, 2000, **2**, 3921–3923.
- A. A. Torrens, A. L. Ly, D. Fong and A. Adronov, *Eur. J. Org. Chem.*, 2022, e202200570.
- T. A. Bender, J. A. Dabrowski and M. R. Gagne, *ACS Catal.*, 2016, **6**, 8399–8403.
- V. Gevorgyan, M. Rubin, S. Benson, J. X. Liu and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**, 6179–6186.

