Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Enantioselective Total Synthesis of Cannabinoids—A Route for Analogue Development

Zachary P. Shultz,[†] Grant A. Lawrence,[†] Jeffrey M. Jacobson,[†] Emmanuel J. Cruz,[†] and James W. Leahy*[,†,‡,§]

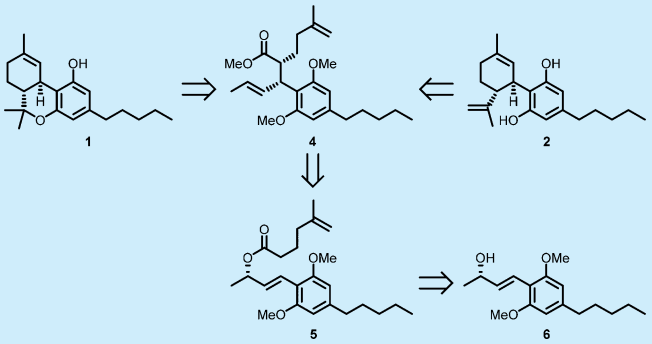
[†]Department of Chemistry, University of South Florida, 4202 East Fowler Avenue, CHE 205, Tampa, Florida 33620, United States

[‡]Center for Drug Discovery and Innovation, University of South Florida, 3720 Spectrum Boulevard, Suite 303, Tampa, Florida 33612, United States

[§]Department of Molecular Medicine, Morsani College of Medicine, University of South Florida, MDC 7, 12901 Bruce B. Downs Boulevard, Tampa, Florida 33612, United States

Supporting Information

ABSTRACT: A practical synthetic approach to Δ^9-tetrahydrocannabinol (**1**) and cannabidiol (**2**) that provides scalable access to these natural products and should enable the generation of novel synthetic analogues is reported.



Plants of the genus *Cannabis* have been of interest to humans since at least the Neolithic era.[1] While cloth made of hemp has been recovered that dates back to the Chou dynasty,[2] the earliest use of the plants for medicinal purposes has been ascribed to Shennong as recorded in *Shen Nong Ben Cao Jing* nearly 2000 years ago.[3] In the intervening millennia, it has reached at least six continents and gained a reputation for, among other things, having been grown by the first president of the United States[4] and being used on Easter Island for raising their moai statues.[5]

The biological effects from the consumption of *Cannabis* plants are considerably complex, presumably because of the large number of natural products produced by the plants.[6] These cannabinoids, which vary greatly in number and concentration among different strains, parts of the plant, and even gender, exhibit their biological effects on mammalian and microbial systems.[7] The therapeutic potential for this class of compounds has been under investigation since the discovery of Δ^9-tetrahydrocannabinol (THC, **1**) (Figure 1) in 1964.[8] Since then, attempts to establish a structure−activity relationship as well as the pharmacokinetic and pharmacodynamic properties of the cannabinoids have been well-studied.[9] The subsequent discovery and characterization of human cannabinoid receptors such as CB1 and CB2 and the entire endocannabinoid system has only increased the interest in pursuing small-molecule therapeutics that modulate this system.[10] Various formulations of **1**, under the generic name dronabinol, have been approved by the U.S. Food and Drug Administration for the treatment of nausea and vomiting as well as AIDS-related anorexia.[11] Meanwhile, an orally available formulation of cannabidiol (CBD, **2**) is currently in phase 3 clinical trials in Canada.[12] While many of the other cannabinoids also demonstrate biological activity, they have not been well-studied, in part because of their limited quantities. A synthetic source of them, as well as of unnatural analogues, would allow for a greater understanding of these subtle effects.

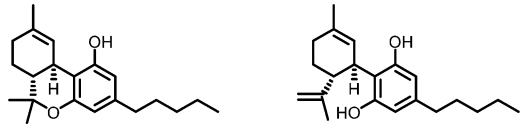


Figure 1. Structures of THC and CBD.

Our own interest in the cannabinoids was piqued by the observation that they possess activity against the free-living amoeba *Naegleria fowleri*,[13] known colloquially as "the brain-eating amoeba." This free-living amoeba is ubiquitously found in bodies of warm, fresh water and can infect humans by entering through the nose and attacking the brain.[14] More than 97% of these infections are fatal,[15] which is why the discovery that cannabinoids such as **1** and **2** inhibit the proliferation of

Received: November 26, 2017

DOI: 10.1021/acs.orglett.7b03668
Org. Lett. XXXX, XXX, XXX−XXX

N. fowleri led us to search for a synthetic route that would allow us to identify novel analogues that might be used to treat such infections.

There have been a number of successful approaches to the total synthesis of **1**.[16] In fact, we were initially attracted to the report by Dethe that the selective formation of the ring systems of **1** or **2** could be achieved from **3** and the appropriate resorcinol derivative simply by controlling the Lewis acid cyclization conditions (Figure 2). In our hands (where R = *n*-

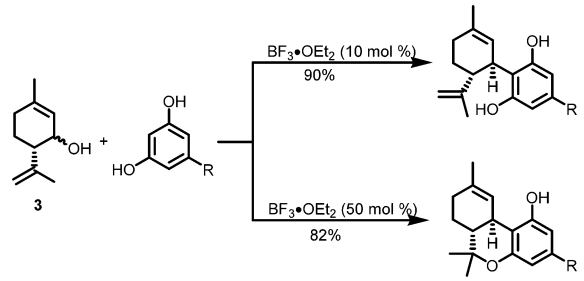


Figure 2. Dethe cannabinoid synthesis.

pentyl), unfortunately, we repeatedly obtained complex mixtures that required extensive HPLC purification to obtain any pure products, though we were able to detect both THC and CBD using both conditions. We therefore sought a practical approach that would not only enable the exclusive formation of **1** or **2** but also be amenable to the generation of novel analogues. The formation of the common cyclohexene via an olefin methathesis reaction, used elegantly by both Trost and Dogra[17] and Carreira and co-workers,[18] was a particularly attractive approach. We envisioned that the requisite diene precursor could be prepared via an Ireland−Claisen rearrangement,[19] thus allowing all of the stereocenters to be derived from a single stereocenter such as **6** (Figure 3). Upon seeing Kim's stereoselective total synthesis of perrottetinine,[20] we were confident that this strategy would prove viable.

We tested our Ireland−Claisen hypothesis by acylating cinnamyl alcohol (**7**) with known acid **8** (Scheme 1).[21] The Ireland−Claisen rearrangement was then conducted by

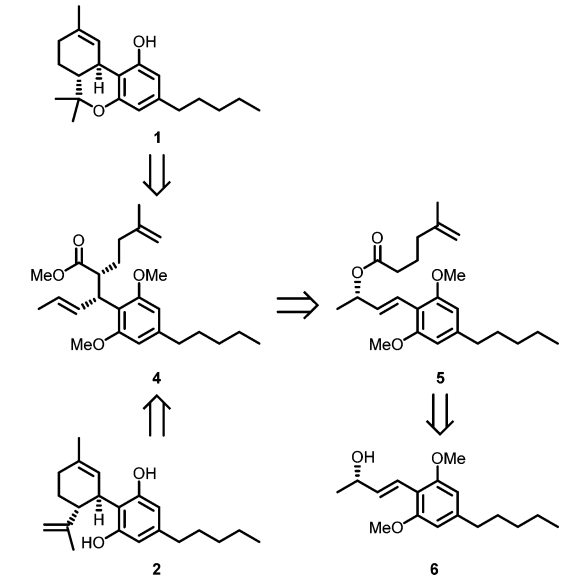
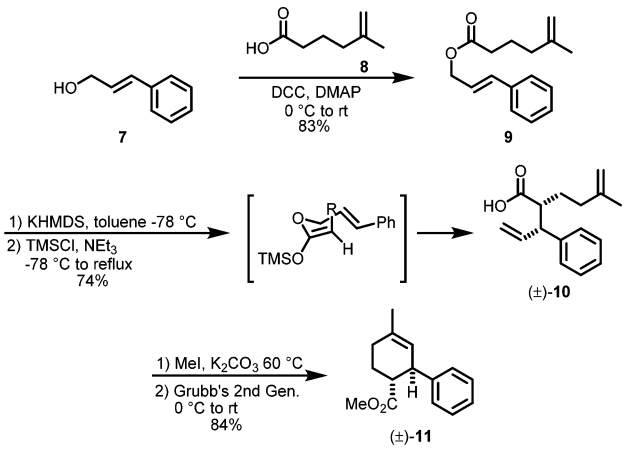


Figure 3. Retrosynthetic analysis of **1** and **2**.

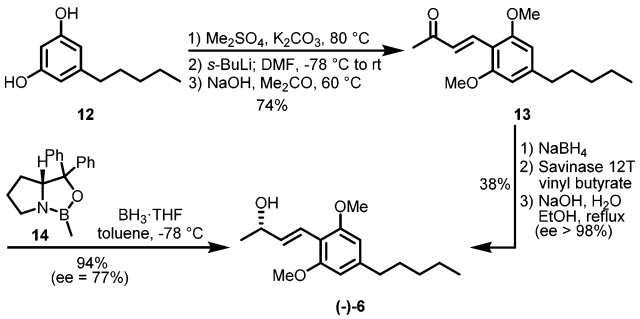
Scheme 1. Model Ireland−Claisen System Synthesis



generation of the corresponding silyl ketene acetal under kinetic conditions without HMPA prior to heating the reaction to reflux.[22] We were pleased to note that the corresponding product was formed as a single diastereomer. We used an amine base in an effort to avoid generation of any HCl during the formation of the silyl ketene acetal, which we believed would be crucial in the real system where a potential stabilized carbocation could be formed using an electron-rich aryl ring.[20] Following esterification of the acid, Grubbs olefin metathesis[23] generated the anticipated cyclohexene **11**, setting the stage for us to try this approach for the cannabinoids.

Enone **13** could be readily prepared in short order from olivetol (**12**) via a known formylation/aldol process (Scheme 2).[17] A number of chiral catalysts and reagents are available for

Scheme 2. Installation of the Chiral Allylic Alcohol



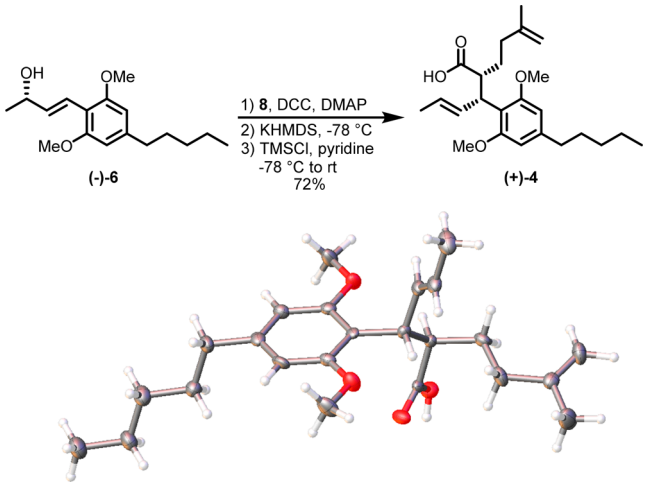
the asymmetric reduction of ketones,[24] and while we tried a number of readily available methods, the best results we obtained were via CBS oxazaborolidine **14**,[25] which proceeded to give (−)-**6** with 77% ee. While this was adequate to allow us to prepare **1** and **2** with high enantiopurity because of the presence of a crystalline intermediate (**4**; vide infra), we were interested in developing a scalable and economically practical approach to generate products with high enantiopurity. We therefore sought to explore an enzymatic approach that would use an inexpensive and readily available enzyme. Simple reduction of **13** with sodium borohydride provided the requisite racemic alcohol, and acylation with vinyl buyrate in the presence of Savinase 12T provided the ester with >98% ee in 38% overall yield for the three steps. While we were also able to acylate (±)-**6** using activated esters of **8** with high enantiopurity under enzymatic conditions,[26] the ready availability of vinyl butyrate compared with the cost of

DOI: 10.1021/acs.orglett.7b03668
Org. Lett. XXXX, XXX, XXX−XXX

generating the requisite activated esters made the former approach more practical on a large scale.

With a viable source of (−)-**6** in hand, acylation with **8** proceeded smoothly, and the Ireland−Claisen rearrangement proceeded as expected (Scheme 3). While we explored a

Scheme 3. Ireland−Claisen Rearrangement

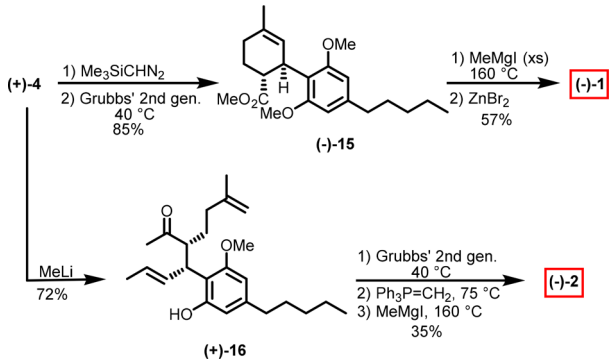


variety of different conditions to effect this transformation, the only discernible factor that resulted in a negative impact on the reaction was the strict requirement for anhydrous conditions, without which we observed a significant loss of diastereoselectivity. We were pleased to find that carboxylate **4** was a crystalline product, which allowed us to obtain an X-ray structure that confirmed the formation of the relative stereocenters at both positions as expected. This also allowed us to recrystallize all of our initial material into high enantiopurity in an overall 48% yield of recrystallized **4** from **6** (ee = 77%). Furthermore, this product served as the common intermediate for our synthesis of both **1** and **2**.

Esterification of **4** and metathesis cyclization with Grubbs' second-generation catalyst afforded cyclohexene **15**, which could be converted into **1** by exhaustive treatment with methylmagnesium iodide followed by Lewis acid-mediated cyclization (Scheme 4).[27,28] Similarly, methylation of **4** led to the formation of ketone **16**, which could be cyclized and then converted into **2** via Wittig methylenation and deprotection.

In summary, we have achieved an enantiospecific synthesis of both THC and CBD from a common intermediate in which the chirality can be derived from a single stereocenter

Scheme 4. Synthesis of THC and CBD



generated with the inexpensive and readily available enzyme Savinase 12T. Efforts to use these methods for the generation of novel cannabinoid analogues will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03668.

Experimental details for the preparation and analysis of all compounds (PDF)

Accession Codes

CCDC 1588045 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: (813) 974-4642. E-mail: jwleahy@usf.edu.

ORCID

James W. Leahy: 0000-0003-3647-4489

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for support of this research by the University of South Florida Office of Research and Innovation and the Florida Center of Excellence for Drug Discovery and Innovation. We gratefully acknowledge the efforts of the University of South Florida X-ray Crystallography Core Facility, and especially Dr. Lukasz Wojtas and Gaurav Verma of the University of South Florida X-ray Crystallography Core Facility, in obtaining the crystal structure of **16**.

■ REFERENCES

(1) Abel, E. L. *Marihuana—The First Twelve Thousand Years*; Plenum Press: New York, 1980.
(2) Li, H.-L. *Econ. Bot.* **1974**, *28*, 437.
(3) Brand, E. J.; Zhao, Z. *Front. Pharmacol.* **2017**, *8*, 108.
(4) George Washington Grew Hemp. http://www.mountvernon.org/george-washington/the-man-the-myth/george-washington-grew-hemp (accessed July 23, 2017).
(5) Lipo, C. P.; Hunt, T. L.; Haoa, S. R. *J. Archaeol. Sci.* **2013**, *40*, 2859.
(6) Atakan, Z. *Ther. Adv. Psychopharmacol.* **2012**, *2*, 241.
(7) Appendino, G.; Gibbons, S.; Giana, A.; Pagani, A.; Grassi, G.; Stavri, M.; Smith, E.; Rahman, M. M. *J. Nat. Prod.* **2008**, *71*, 1427.
(8) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646.
(9) Compton, D. R.; Rice, K. C.; De Costa, B. R.; Razdan, R. K.; Melvin, L. S.; Johnson, M. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 218.
(10) Mallipeddi, S.; Janero, D. R.; Zvonok, N.; Makriyannis, A. *Biochem. Pharmacol. (Amsterdam, Neth.)* **2017**, *128*, 1.
(11) U.S. Food and Drug Administration. Marinol. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018651s021lbl.pdf (accessed July 23, 2017).
(12) CTV News. Canadian Researchers To Study Cannabis Oil To Treat Kids' Epilepsy. http://www.ctvnews.ca/lifestyle/canadian-

DOI: 10.1021/acs.orglett.7b03668
Org. Lett. XXXX, XXX, XXX−XXX

researchers-to-study-cannabis-oil-to-treat-kids-epilepsy-1.3321008 (accessed July 23, 2017).
(13) Pringle, H. L.; Bradley, S. G.; Harris, L. S. *Antimicrob. Agents Chemother.* **1979**, *16*, 674.
(14) Contis-Montes de Oca, A.; Carrasco-Yepez, M.; Campos-Rodriguez, R.; Pacheco-Yepez, J.; Bonilla-Lemus, P.; Perez-Lopez, J.; Rojas-Hernandez, S. *Parasite Immunol.* **2016**, *38*, 481.
(15) Capewell, L. G.; Harris, A. M.; Yoder, J. S.; Cope, J. R.; Eddy, B. A.; Roy, S. L.; Visvesvara, G. S.; Beach, M. J.; Fox, L. M. *J. Pediatric Infect Dis Soc.* **2015**, *4*, e68.
(16) See: Dethe, D. H.; Erande, R. D.; Mahapatra, S.; Das, S.; B., V. K. *Chem. Commun.* **2015**, *51*, 2871 and references cited within. A practical synthesis of **2** and analogues has also been reported. See: Kobayashi, Y.; Takeuchi, A.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 2699.
(17) Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861.
(18) Schafroth, M. A.; Zuccarello, G.; Krautwald, S.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13898.
(19) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939.
(20) Song, Y.; Hwang, S.; Gong, P.; Kim, D.; Kim, S. *Org. Lett.* **2008**, *10*, 269.
(21) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1997**, *62*, 67.
(22) Conducting the reaction in the absence of HMPA allows for the generation of the (*E*)-silylketene acetal, which results in the desired stereochemical outcome. See: Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650. Kim's use of HMPA allowed for their generation of the (*Z*)-silylketene acetal, which corresponded to the stereochemistry required for perrottetinine.[20]
(23) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760.
(24) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
(25) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(26) Details of this reaction are given in the Supporting Information.
(27) Salzer, W. *Hoppe-Seyler's Z. Physiol. Chem.* **1942**, *274*, 39.
(28) Stoss, P.; Merrath, P. *Synlett* **1991**, *1991*, 553.

DOI: 10.1021/acs.orglett.7b03668
Org. Lett. XXXX, XXX, XXX−XXX