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Improved accessibility to the desoxy analogues of Δ^9-tetrahydrocannabinol and cannabidiol

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ABSTRACT

Desoxy analogues of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been reported to provide a novel mode of analgesia whilst avoiding the psychotropic side effects associated with most cannabinoid drugs. A detailed and improved synthesis of desoxy THC, desoxy CBD and didesoxy CBD is reported here. The key improvements include a concentration-dependent boron trifluoride mediated electrophilic aromatic substitution which was used to synthesize both THC and CBD analogues. The synthetic route is general and could be applied to the development of a library of modified desoxy THC and desoxy CBD analogues.

Plants of the *Cannabis* genus have been outlawed by many nations due to the psychoactive properties and abuse liability of their flowers and leaves, collectively termed marijuana. However, legitimate medicinal use of marijuana remains a last option for the numerous chronic pain sufferers who do not respond to traditional treatment options. The diverse pharmacology of marijuana is attributable to the plethora of cannabinoids (68 known) present in *Cannabis* spp.

The major psychoactive constituent of cannabis is Δ^9-tetrahydrocannabinol (THC, **1**, Fig. 1),[1] the primary pharmacological effects of which include psychosis, analgesia, motor impairment and hypothermia.[2,3] These effects result from the activation of two G-protein coupled cannabinoid receptors; the cannabinoid type-1 receptor (CB1, K_i 41 nM) and the cannabinoid type-2 receptor (CB2, K_i 36 nM).[4,5] Cannabidiol (CBD, **2**, Fig. 1) exists as the main non-psychoactive pharmacological constituent of cannabis, with a loss of psychotropic activity attributed to its 100-fold decreased affinity to both cannabinoid receptors.[4] Despite its lack of psychotropic activity, CBD **2** has shown therapeutic applications as an anti-arthritic and a neuroprotective antioxidant.[6,7]

The CB1 receptor is widely distributed in the central nervous system (CNS) and is thought to be responsible for the psychotropic response to cannabinoids. The CB2 receptor is almost exclusively expressed in immune cells and may play a role in suppressing inflammatory and neuropathic pain.[8] Selective CB2-agonists have been synthesized[9] in the hope of developing therapeutic agents that avoid the often undesirable psychoactivity of marijuana, based on the observation that CB1 knockout mice still exhibit THC-mediated analgesia.[10] A recent study by Xiong et al. reported a novel mode of analgesic action for cannabinoids, showing that THC **1**, desoxy THC **3** and desoxy CBD **4** bind strongly to the α1 and α3 subunits of spinal glycine receptors, thereby potentiating the ability of these receptors to dampen pain signals to the brain.[11] Furthermore, the desoxy analogues **3** and **4** show a significantly reduced binding affinity to the CB1 receptor. When all the oxygen atoms are removed from THC **1**, the resulting didesoxy CBD **5** shows no affinity for CB1 or CB2 receptors. In addition, didesoxy

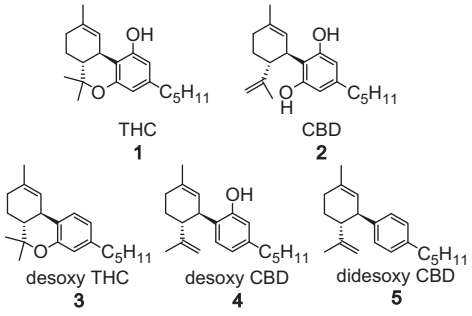

Figure 1. THC (**1**) and CBD (**2**) and their desoxy analogues.

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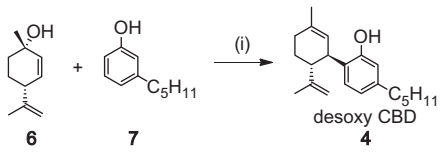
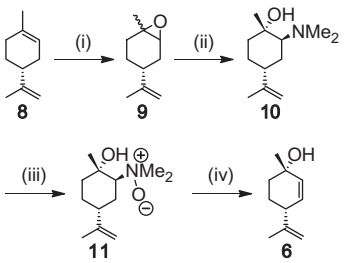
CBD **5** is ineffective at potentiating glycine receptors and instead selectively antagonizes the THC-induced potentiation of these sites. The reduced CB1 receptor affinity of these desoxy THC analogues suggest that psychoactivity may also be attenuated, offering the prospect of novel cannabinoid analgesics without abuse liability. A rapid and practical synthesis of these THC analogues is necessary for further biological studies, and could provide access to completely novel and structurally-elaborated analogues of desoxy THC **3** and desoxy CBD **4**.

The synthesis of desoxy THC **3** has previously been reported through the deoxygenation of THC **1**.[12,13] Unfortunately, the same route cannot be utilized for the synthesis of desoxy CBD **4** due to the presence of two phenol groups on the aromatic ring. The synthesis of desoxy CBD **4** by Xiong and coworkers,[11] involved the coupling of *p*-mentha-2,8-dien-1-ol (**6**) and *m*-pentylphenol (**7**) by a DMF–dineopental acetal-mediated condensation (Scheme 1).[14,15] Consequent Lewis acid mediated cyclization of CBD **4** gave desoxy THC **3**. Although this approach provides access to desoxy THC **3** and desoxy CBD analogues, in our hands, this reaction failed to yield appreciable quantities of the desoxy CBD **4**. It was suggested that a major by-product of this reaction is the irreversible formation of the *p*-mentha-1,8-dien-3-yl 3-*n*-pentylphenyl ether resulting from alkylation of the phenol with *p*-mentha-2,8-dien-1-ol (**6**).[14] Furthermore, fragments **6** and **7** have limited commercial availability and there is little precedence for their preparation in the chemical literature. The inconsistent and problematic nature of this crucial coupling step in the synthesis of desoxy THC **3**, desoxy CBD **4** and didesoxy CBD **5** led us to investigate an alternative access to this novel class of analgesic agents. Specifically, we sought practical and inexpensive routes to **6** and **7**, and a more reliable means for their coupling.

p-Mentha-2,8-dien-1-ol (**6**) was originally synthesized in one step from the natural oil (+)-limonene (**8**) using photosensitized O_2-transfer.[16] A drawback of this procedure is the difficulty of isolating the desired alcohol (produced in moderate yields) from the pool of regioisomeric alcohols generated in the reaction. A stepwise synthetic approach from (+)-limonene (**8**) provided more regioselectivity and control via a selenoxide elimination to install the alkene.[17] We decided to pursue this stepwise approach utilizing a Cope elimination to yield the allylic alcohol **6** as an alternative to the use of highly toxic selenium (Scheme 2).[18]



Scheme 1. Acetal-mediated synthesis of desoxy CBD **4**.[14] Reagents and conditions: (i) DMF–dineopental acetal, CH_2Cl_2, rt, 63 h, 22%.



Scheme 2. Synthesis of *p*-mentha-2,8-dien-l-ol (**6**). Reagents and conditions: (i) *m*CPBA, $CHCl_3$, 0 °C, 2 h, 62%; (ii) 40% $HNMe_{2(aq)}$, 80 °C, 18 h, 88% based on the trans isomer; (iii) 30% H_2O_2, 50% aq CH_3CN, rt, 2 h, quant.; (iv) Δ, 180 °C, 1 mmHg, 74%.

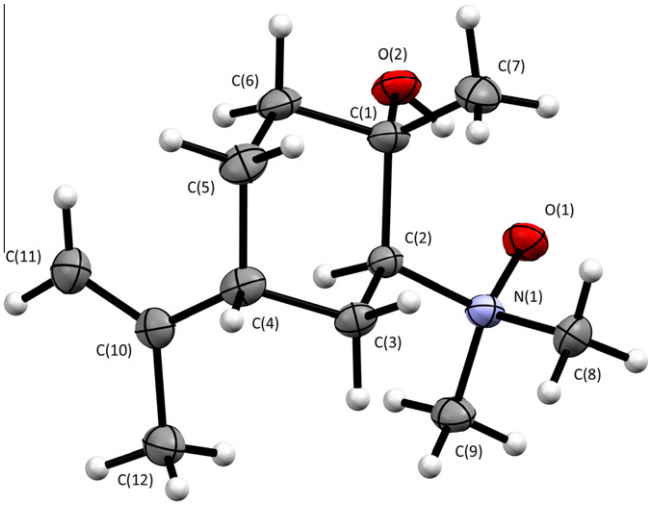


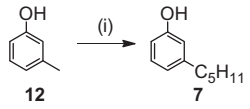
Figure 2. An ORTEP[24] depiction of a representative molecule of **11** from the asymmetric unit with 50% displacement ellipsoids (CCDC 838074).

Starting with inexpensive and abundant (+)-limonene (**8**), the trisubstituted alkene was regioselectively epoxidized via a Prilezhaev reaction to generate cyclic epoxide **9** as an enantiomeric mixture.[19] The *trans*-epoxide was regio- and enantioselectively opened with aqueous dimethylamine to generate optically pure *trans*-aminoalcohol **10** in 88% yield (based on the *trans*-epoxide).[†] The *cis*-epoxide remained largely unreacted and could be recovered. The enantioselectivity of the epoxide opening arises from the energy associated with the respective transition states required to achieve axial epoxide opening.[20–22] The *trans*-epoxide adopts a favored chair-like transition structure, whilst the *cis*-epoxide must take on an unfavored boat-like transition state. Coincidentally, if the same reaction is performed at higher temperatures using a sealed tube, the *cis*-epoxide undergoes ring-opening to form the unwanted regioisomer which proved difficult to separate from the desired *trans*-aminoalcohol **10**. The tertiary amine of *trans*-aminoalcohol **10** underwent acetonitrile-assisted oxidation to generate the hygroscopic cyclohexamine oxide **11** in quantitative yield.[23] Single crystal X-ray analysis of the amine oxide **11** (Fig. 2) confirmed the absolute stereochemistry and supported the regio- and enantioselectivity of the epoxide opening. Interestingly, the bulky isopropenyl group adopts an axial rather than equatorial conformation, likely stabilized by intramolecular hydrogen bonding between the amine oxide and the alcohol. Pyrolysis of cyclohexamine oxide **11** went smoothly to yield *p*-mentha-2,8-dien-1-ol (**6**) in 74% yield via Cope elimination. In addition to completely circumventing the use of selenium, this synthetic route provided cyclohexenol **6** from (+)-limonene oxide (**9**) in an improved yield (64% over three steps) compared to the selenoxide route (45% over three steps).[17]

The *m*-pentylphenol **7** (used to couple with *p*-mentha-2,8-dien-1-ol **6**) was prepared by the alkylation of *m*-cresol (**12**) Scheme 3. This reaction proceeded through a dimetallation of *m*-cresol to produce a di-anion that selectively reacted with bromobutane at the carbanion in 70% yield.[11,25]

With both fragments in hand, a Lewis acid mediated coupling was attempted using boron trifluoride–diethyl etherate to facilitate elimination of the tertiary alcohol.[26–28] The use of a 1% solution of boron trifluoride–diethyl etherate yielded desoxy THC **3** in 46% yield in a single step (Scheme 4). The reaction is

[†] The stereochemistry of the epoxide and consequent terpenoid structures will be referred to as *cis* and *trans* which represent the relative stereochemistry of the isopropenyl and methyl group on the cyclohexyl ring (as is referred to in most related literature) and not the stereochemistry of the epoxide.

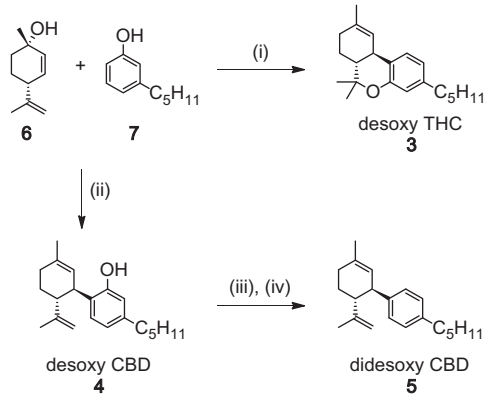


Scheme 3. Synthesis of *m*-pentylphenol. Reagents and conditions: (i) *n*-BuLi, *t*-BuOK, TMEDA, hexane, −50 to −20 °C, 3 h then *n*-BuBr, THF, −60 °C to rt, 20 h, 70%

hypothesized to go via a Friedel–Crafts alkylation of **7** with the cyclohexene **6** to first form desoxy CBD **4**, with the boron Lewis acid then catalysing an intramolecular cyclization/etherification between the phenol and the isopropenyl tail to yield desoxy THC **3**. Unlike the acetal-promoted coupling step (Scheme 1), this Lewis acid mediated coupling is reported to be reversible via a retro-Friedel–Crafts reaction so the formation of certain by-products (such as the ether generated in the acetal-mediated coupling or regioisomers) can be recycled back into the reaction to contribute towards the yield of the desired product.[26] Given that desoxy CBD **4** is generated as an intermediate in this reaction, boron trifluoride–diethyl etherate was deactivated with basic alumina[28] in the hope of trapping desoxy CBD **4**, but only the cyclized desoxy THC **3** and starting material were isolated. However, after systematic exploration of reagent concentrations, reducing the boron trifluoride–diethyl etherate concentration to 0.1% successfully slowed further reaction, allowing the isolation of desoxy CBD **4** in 42% yield (Scheme 2). In addition to improved yields of desoxy THC **3** and desoxy CBD **4** from a common route by judicious selection of reagent concentration, the desired products were prepared more expediently (<2 h) than the acetal-mediated coupling (63 h).

Deoxygenation of desoxy CBD **4** was achieved by phosphorylation of the phenol group followed by a Birch reduction (Scheme 2).[11,13] The didesoxy CBD **5** was obtained in 82% over two steps. NMR spectra of all three desoxy analogues **3–5** were identical to those previously reported in the literature.[11]

In summary, an alternative procedure that improves the synthetic accessibility of desoxy THC **3**, desoxy CBD **4** and didesoxy CBD **5** is described, with several improvements over the previously described methods. The application of boron trifluoride–diethyl etherate to the coupling of key precursory fragments **6** and **7** provided improved yields with significantly shorter reaction times. Furthermore, an alternative and safe synthetic route to the former *p*-mentha-2,8-dien-1-ol (**6**) from inexpensive and abundant (+)-limonene **8** was detailed. This general route is also applicable to the synthesis of novel desoxy THC and desoxy CBD analogues, allowing further development of cannabinoids possessing interesting biological activity.



Scheme 4. Synthesis of desoxy THC and CBD analogues. Reagents and conditions: (i) 1% $BF_3{\cdot}OEt_2$, $MgSO_4$, CH_2Cl_2, −10 °C, 39%; (ii) 0.1% $BF_3{\cdot}OEt_2$, $MgSO_4$, CH_2Cl_2, −78 to −10 °C, 42%; (iii) NaH, $(EtO)_2P(O)Cl$, THF, 0 °C, 1 h, quant.; (iv) $Li_{(s)}$, $NH_{3(l)}$, THF, −78 °C, 2 h, 82%.

Acknowledgements

The X-ray crystal structure was solved by Jason Price of the crystal structure analysis facility at the University of Sydney, NSW, Australia. NMR analysis was aided by Dr. Ian Luck of the NMR facility at the School of Chemistry, the University of Sydney, NSW, Australia. Mass spectrometry results were acquired by Dr. Nick Proschogo and Chris Phippin of the Mass Spectrometry laboratory at the University of Sydney, NSW, Australia. Elemental analysis was performed by Dr. Christopher McRae of the Chemical Analysis Facility at Macquarie University, NSW, Australia.

Supplementary data

Supplementary data (synthesis procedures, spectral data and crystal structure data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.080.

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