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Levonantradol: asymmetric synthesis and structural analysis†

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The first asymmetric synthesis of a synthetic cannabinoid levonantradol was accomplished, and the 3-D solution structure of its core architecture was confirmed by NMR and computational methods.

The use of cannabis for therapeutic and recreational purposes dates back several millennia, but its role in the modern society remains a topic of great debate and controversy.[1] Clinically, cannabinoids have been approved for use as anti-emetics and analgesics for cancer, glaucoma and multiple sclerosis sufferers; potential therapeutic uses have also been suggested for the treatment of epilepsy,[2a] Tourette's syndrome,[2b] Huntington disease[2c] and cancer.[2d,e] However, long-term use of cannabis has also been associated with undesirable psychiatric side effects such as schizophrenia, bipolar disorder and major depression.[2f] Consequently, there is a great deal of interest in the development of synthetic variants that can activate CB_1 and CB_2 cannabinoid receptors without inducing psychosis.[3]

Delta-9-tetrahydrocannabinol (Δ^9-THC) is the principal psychoactive ingredient in cannabis, from which levonantradol (CP-50,556-01) was derived in the 1980s by Pfizer scientists (Fig. 1).[4] As a structurally novel synthetic cannabinoid, levonantradol is 30 times more potent than THC in activating the CB_1 and CB_2 receptors and possesses analgesic and antiemetic properties with 9–14 times greater potency than morphine.[5]

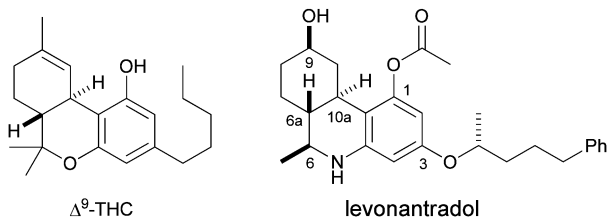

Fig. 1 Structures of THC and levonantradol.

The analgesic potency of the molecule was found to be highly stereospecific, being dependent upon the *trans*-(6a, 10a) stereochemistry along with β-orientation of substituents at C-6 and C-9.[6] Optically pure form of the compound was found to be twice as potent as its racemic mixture, while the epimeric form, containing the opposite stereochemistry at the C-3 side chain, is ten times less efficacious. Although the clinical use of levonantradol was curtailed by its unacceptable toxicity,[7] it remains an important tool for the study of the pharmacology of cannabinoid compounds.[8]

The synthesis of levonantradol was reported more than 30 years ago,[4c] where the optically active form of the compound was obtained by performing four kinetic resolutions over the course of the synthesis consisting of 10 linear synthetic steps (overall yield unspecified). Despite plethora of works devoted to the investigation of the biological activities of levonantradol, an improved synthesis has never been reported; moreover, the characterisation data for levonantradol are surprisingly scant. Most notably, the stereochemistry of levonantradol was assigned based on an unpublished X-ray structure of 3′-epilevonantradol;[4a] independent verification of its structure has never been reported.

Herein, we will report the first enantioselective synthesis of levonantradol, followed by its full characterisation and verification of its conformational and stereochemical structures by a combination of computational and NMR techniques.

It was envisaged that the core structure of the target molecule could be constructed enantioselectively in three key steps (Fig. 2). The key idea was to use the stereocenter created at C-3 in the *aza*-Michael adduct (corresponds to C-6 in **2**) to direct the selectivity at C-6a, 9 and 10a in a chiral relay process.

The chirality on the C-3 side chain required the preparation of (*S*)-5-phenyl-2-pentanol, (*S*)-**1**. This could be achieved by asymmetric synthesis, however, such approaches are either time-consuming or too expensive.[9] Conversely, kinetic resolution of the precursor can be achieved by using a lipase,[10a] or by the resolution of the hemiphthalate derivative using (+)-brucine.[10b] In this work, an effective procedure was devised using the less toxic and inexpensive α-methylbenzylamine as the resolving agent (Scheme 1). This approach afforded (*S*)-(+)-**1** in 97% optical purity, from which corresponding mesylate **6** can be derived.

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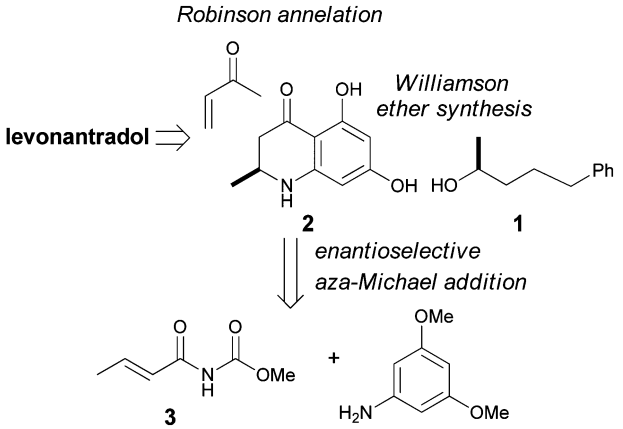
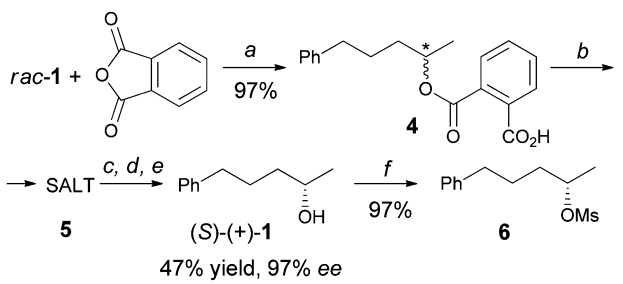


Fig. 2 Retrosynthesis of levonantradol.

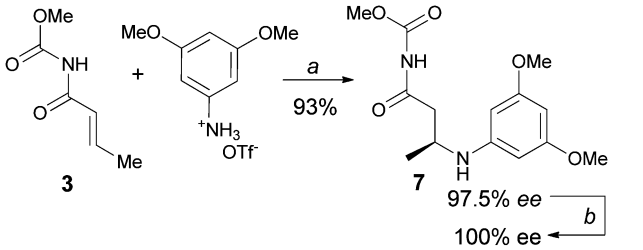
Asymmetric conjugate addition of 3,5-dimethoxyaniline to a chelating Michael acceptor **3** was achieved by using a Pd-catalyzed process developed in our laboratory.[11] Guided by our previous work,[11c] the (*R*)-isomer of the catalyst was employed to induce the requisite (*S*)-stereochemistry at C-3 in **7** (Scheme 2). Due to the nucleophilicity of the aniline substrate, triflate salt was employed in conjunction with the dimeric $[(R\text{-BINAP})Pd(\mu\text{-OH})]_2[OTf]_2$, relying on the Brønsted basicity of the catalyst to control the release of the nucleophile during the reaction.[12] Competitive uncatalyzed process was further suppressed by conducting the reaction at low temperature. Under these conditions, the Michael adduct **7** can be obtained with excellent yield (93%) and enantioselectivity (97.5% ee). Optically purity can be achieved after a single recrystallization from toluene.

With the chiral precursors in hand, the final assembly of the target molecule commenced with the hydrolysis of the Michael adduct **7** to the *N*-aryl amino acid **8**. Treatment of **8** with HBr–acetic acid mixture triggered an electrophilic cyclisation, accompanied by the spontaneous deprotection of the phenolic groups, to afford the quinolone **2** (Scheme 3).

Coupling between **2** (100% ee) and **6** (97% ee) was conducted in the presence of a weak inorganic base. The single diastereoisomer **9** was obtained with complete inversion of the *S*-stereochemistry at C-2′ centre of C-3 chain with 97% ee (verified by chiral HPLC; see ESI†). Further deprotonation of **9** with sodium hydride followed by the treatment with methyl formate resulted in the introduction of *N*-formyl and α-formyl ketone groups; the latter had the requisite reactivity to undergo conjugate addition reaction with



Scheme 1 Kinetic resolution of alcohol **1** and preparation of optically pure precursor **6**. (a) Phthalic anhydride, Py, 94 °C; (b) (*S*)-α-methylbenzylamine, EtOAc, 60 °C; (c) recrystallization (Table S1, ESI†); (d) 1.5 M aq. HCl; (e) 3.75 M aq. NaOH; (f) MsCl, NEt_3, THF, 0 °C to RT.



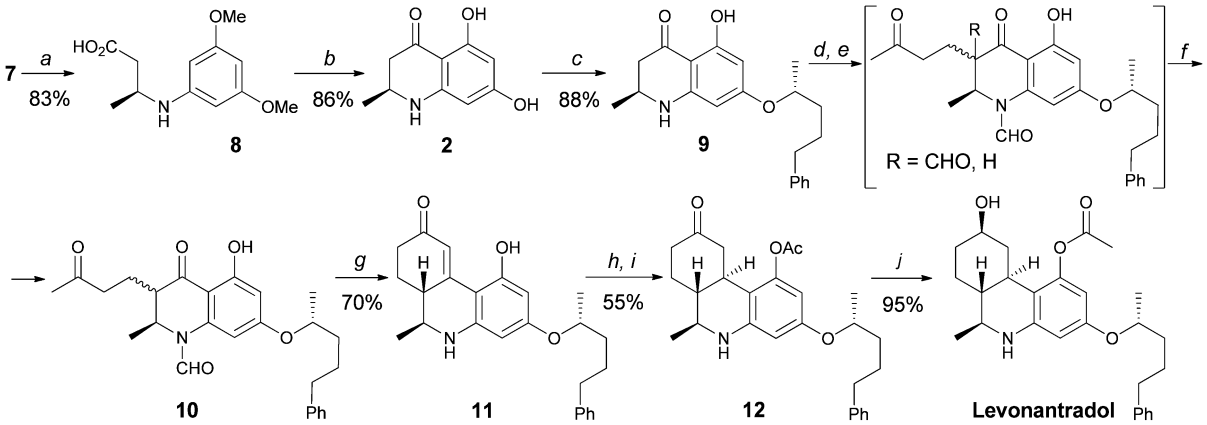
Scheme 2 Asymmetric Pd-catalysed *aza*-Michael reaction. (a) $[(R\text{-BINAP})Pd(\mu\text{-OH})]_2[OTf]_2$ (2 mol%), THF, −10 °C, 48 h, then 0 °C, 24 h; (b) single recrystallization from toluene.

methyl vinyl ketone. Decarbonylation of the Michael adduct occurred under very mild conditions to give compound **10** as a 3 : 2 mixture of epimers. This material was subjected to cyclization accompanied by concomitant removal of the *N*-formyl group under basic conditions, furnishing the target tricycle **11**. The *endo*-cyclic C=C bond was then reduced under dissolved Li-metal conditions to afford a 2 : 1 mixture of *trans–cis*-isomers across the fused six-membered rings (at C-6a and C-10a). Following acylation of the phenol group, the requisite *trans*-isomer **12** was isolated in 55% yield. Finally, reduction of the ketone at C-9 with sodium borohydride at −60 °C ensued with excellent stereoselectivity to give a single diastereoisomer of levonantradol with enantiomeric purity of 99% which was confirmed by chiral HPLC (see ESI†).

The prepared levonantradol was converted into the hydrochloride salt and its melting point and optical rotation corresponded well with the values reported by Pfizer in 1981,[13] however, further comparisons with a genuine sample were not possible.[14] Nevertheless, the ^1H and ^{13}C NMR spectra of the synthesised molecule contain distinct resonance signals, which can be fully assigned by COSY, HMQC and HMBC experiments (Table S2, ESI†). This allowed the relative stereochemistry of levonantradol to be established based on the NOE experiments. Relative positions of all the α-Hs in the carbocyclic ring C can be established by the selective irradiation of the H-9 resonance signal, while the irradiation of H-6 and H-10a confirmed their positions relative to the *S*-configuration at C-6 (ESI†).

Consequently, 3-dimensional structure of levonantradol can be simulated computationally by applying a Hartree–Fock energy-minimisation using a 3-21G basis set. The optimised structure was subjected to DFT calculations by employing GAIO method with the B3LYP/6-311+(2d,p) basis set, to predict NMR properties. Pleasingly, the predicted δ and J values (Tables S2 and S3 respectively; ESI†) fitted well with that observed experimentally. Simultaneously, the model also provided inter-proton distances that showed excellent correlation with the observed NOE values (Table S4, ESI†). There is very good evidence that the fused rings B and C of levonantradol are locked in a rigid, flattened boat–chair conformation in solution (Fig. 3). Most notably, the carbocyclic ring C in levonantradol (a boat conformation) is significantly different from the equivalent cyclohexene ring in the *O*-tosyl derivative of Δ^9-THC (a distorted screw boat).[15]

In summary, asymmetric synthesis of levonantradol is achieved, for the first time, in 11 linear steps with 16.2% overall yield. This was accomplished by devising a new kinetic resolution process for the preparation of the (*S*)-**1**, combined with an



Scheme 3 Final assembly of levonantradol. (a) 1.0 M KOH–MeOH, 3 h; (b) AcOH–HBr (1 : 1, v/v), reflux, 1.5 h; (c) **6**, K_2CO_3, DMF, 80 °C, 2.5 h; (d) NaH, toluene, HCO_2Me, 20 h; (e) MVK, NEt_3, CH_2Cl_2, 20 h; (f) K_2CO_3, MeOH, 0 °C, 4 h (76% over steps d–f); (g) MeONa, MeOH, reflux, 48 h; (h) Li–NH_3, THF, −70 °C, 20 min; (i) Ac_2O, NEt_3, 4-DMAP, CH_2Cl_2, 0 °C, 1 h; (j) $NaBH_4$, EtOH–THF (1 : 1, v/v), −60 °C, 30 min.

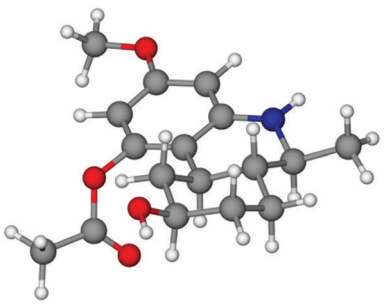


Fig. 3 Solution structure of levonantradol's fused rings established by computational chemistry and NMR (C-3 side chain was omitted).

enantioselective *aza*-Michael reaction for the preparation of quinolone intermediate **2**. The two precursors were then used to construct the target molecule in a chiral relay process, thus eliminating the need for costly separation processes during the synthesis. It is envisaged that structural modifications can be easily introduced for future medicinal chemistry programmes. Finally, the solution structure of levonantradol was derived successfully from a combination of NMR experiments with DFT calculations, providing confirmation of its stereochemistry and conformation. Interestingly, the 3-D structure of levonantradol was found to be significantly different from Δ^9-THC from which it was derived. This may have important implications in the understanding of its biological activity, and the subsequent development of non-toxic, but equally or more potent analogues.

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