

Total Synthesis

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Synthesis of (–)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone through Gold(I)-Catalyzed Cycloisomerization

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Dedicated to Professor Miquel A. Pericàs on the occasion of his 65th birthday

Abstract: The first total synthesis of cannabimovone from *Cannabis sativa* and anhydrocannabimovone was achieved by means of a highly stereoselective gold(I)-catalyzed cycloisomerization. The results led to reassignment of the structure of anhydrocannabimovone.

The herbaceous plant *Cannabis sativa* has been used in medicine for centuries and still attracts significant interest due to the biological and pharmaceutical activity of many of its metabolites.^[1] More than 60 compounds, known as cannabinoids (a group of C₂₁ terpenophenolic compounds), are exclusively found in *Cannabis sativa*.^[2] Owing to the development of synthetic cannabinoids,^[3,4] the unique components of *Cannabis sativa* are known as phytocannabinoids. The most abundant compound is Δ⁹-tetrahydrocannabinol (THC, **1**; Figure 1), which shows interesting pharmacological activity as an analgesic, antiemetic, and appetite stimulant, among others, besides its well-known psychotropic effects.^[5] Several total syntheses of **1** have been accomplished to date.^[6]

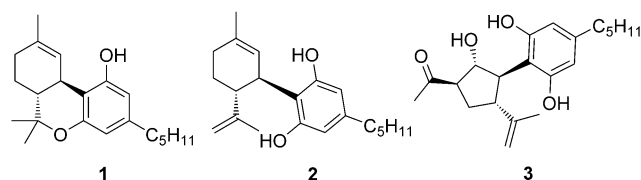
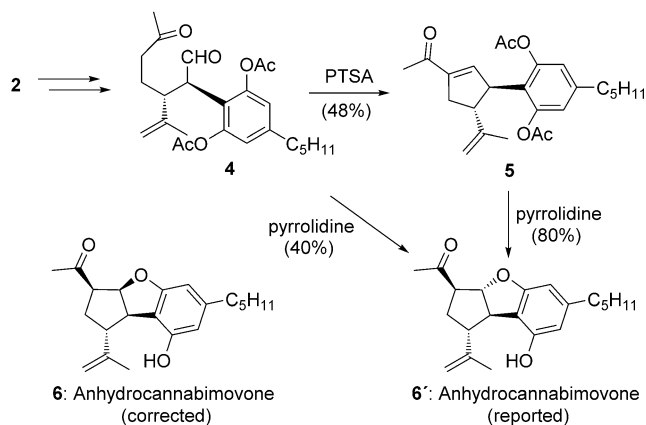


Figure 1. Cannabinoids THC (**1**), CBD (**2**), and cannabimovone (**3**).

Cannabidiol (CBD, **2**) is another important phytocannabinoid with great potential as a drug^[7] since it modulates the undesired effects of THC when they are administrated together.^[8]

A structurally different cannabinoid named cannabimovone (**3**) has recently been isolated by the groups of Tagliatalata-Scafati and Appendino from a nonpsychotropic variety of hemp (*Cannabis sativa* L.; Figure 1).^[9] In their attempt at preparing **3** from CBD (**2**) through an intramolecular aldol reaction of keto aldehyde **4** under mild acidic conditions, the product of dehydration (**5**) was formed instead (Scheme 1). Under basic conditions, the novel cannabinoid



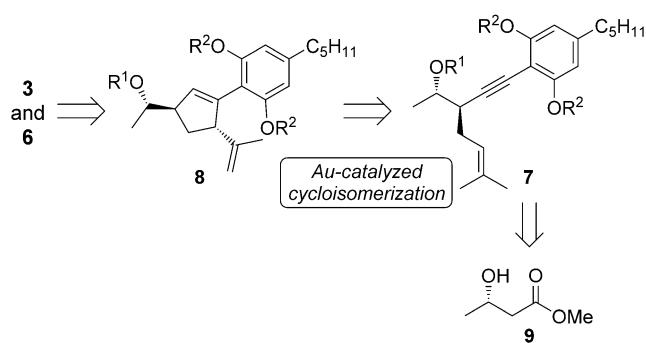
Scheme 1. Synthesis of anhydrocannabimovone (**6**) from cannabidiol (CBD, **2**).^[9]

anhydrocannabimovone (**6**) was directly formed through an intramolecular oxy-Michael addition of one of the phenol groups to the intermediate enone. Synthetic **6** was found to be active against metabotropic and ionotropic cannabinoid receptors, showing a similar biological profile to THC, whereas cannabimovone (**3**) has affinity only for ionotropic receptors.^[9]

The unprecedented *abeo*-menthane terpenoid structure of cannabimovone (**3**) includes a densely functionalized cyclopentane with four contiguous stereocenters. The novel structure of **3**, coupled with its lability towards dehydration under acidic or basic conditions and the interesting biological profiles of both **3** and **6**, inspired us to develop a total synthesis that could allow access to a wide variety of analogues. Herein, we report the first total synthesis of enantiopure cannabimovone (**3**) and also revise the structure originally assigned to anhydrocannabimovone from *trans*-fused **6'** to *cis*-tetrahydro-1*H*-cyclopenta[*b*]benzofuran **6**. Our

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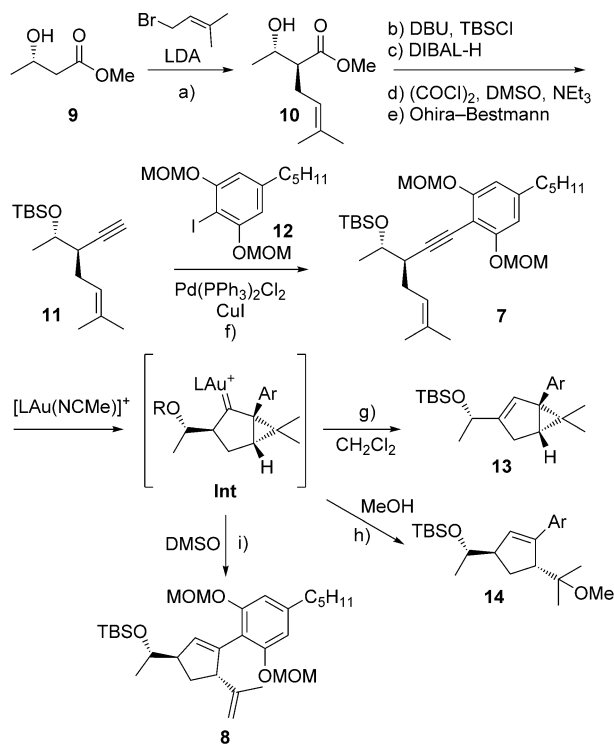


Scheme 2. Retrosynthetic analysis for **3** and **6**.

approach to the synthesis of these compounds relies on a gold(I)-catalyzed cycloisomerization^[10–15] of aryl-substituted 1,5-enyne **7**, which could be obtained in a few steps from commercially available (+)-methyl (*S*)-3-hydroxybutyrate (**9**; Scheme 2).

The synthesis commenced with alkylation of the lithium enolate of **9** with prenyl bromide to provide known compound **10** with excellent diastereoselectivity (98:2) by following a slight modification of the reported procedure^[16] (Scheme 3). Protection of the alcohol of **10** as a silyl ether, conversion of the ester into an aldehyde by a two-step procedure (DIBAL reduction/Swern oxidation), and subsequent homologation with the Ohira–Bestmann reagent led to 1,5-enyne **11** (31 % over 5 steps). Sonogashira coupling of **11** with iodo arene **12**, prepared in two steps from olivetol, gave **7** in 83 % yield on a multi-gram scale. The gold(I)-catalyzed cyclization of 1,5-enyne **7** was highly solvent dependent. Exposing **7** to the cationic gold(I) complex [(JohnPhos)Au(MeCN)]SbF₆ in CH₂Cl₂ led to bicyclic compound **13** (49 %). A similar result was obtained using other solvents such as Et₂O or toluene. Reaction in MeOH afforded methyl ether **14** (93 %). However, when the reaction was performed in DMSO, cyclopentene **8** was obtained in excellent yield (88 %). This reaction was performed up to a 2.1 g scale. A similar result was observed when the reaction was performed in DMF (79 %). Presumably, the initial intermediate of the gold(I)-catalyzed cyclization (**Int**) undergoes proton elimination assisted by the solvent to give **8** after protodeauration. Notably, the gold-catalyzed cyclization led exclusively to the product with the correct relative configuration, thereby setting two of the final four stereocenters.

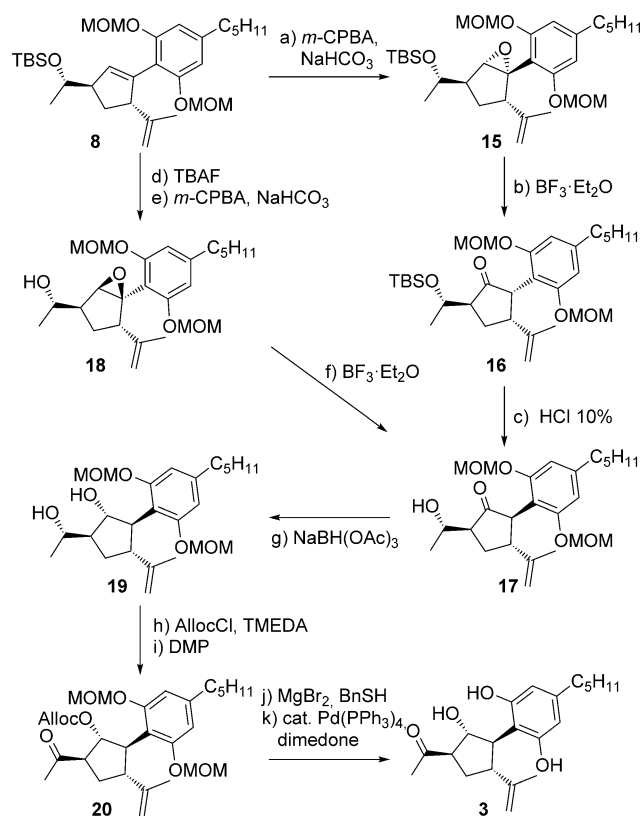
Although deprotection of the TBS group of **8** followed by oxidation of the alcohol to the methyl ketone could be carried out uneventfully, isomerization to form the α,β -unsaturated ketone failed under all the conditions we examined with this and with other intermediates with different phenol protecting groups. Fortunately, the desired functionality in the five-membered ring could be introduced by epoxidation with *m*-CPBA and NaHCO₃ to exclusively form **15**, followed by Meinwald rearrangement with stoichiometric BF₃·Et₂O to give ketone **16** (2,3-*cis*). Epimerization and cleavage of the silyl ether was achieved with aqueous HCl to give **17** (Scheme 4). The relative configuration of **17** was determined by NMR studies and was confirmed by preparation of the



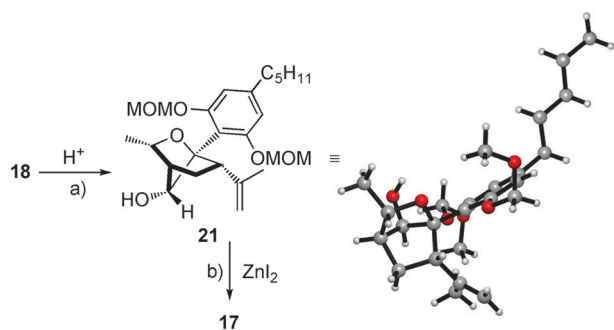
Scheme 3. a) LDA, HMPA, prenyl bromide, THF, -70°C to -10°C , 3 h, 81 %; b) TBSCl, DBU, CH₂Cl₂, 25°C , 14 h, 89 %; c) DIBAL-H, Toluene, -78°C to -50°C , 4 h, 84 %; d) Oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, -60°C to 25°C , 1 h; e) Ohira–Bestmann reagent, K₂CO₃, MeOH, 25°C , 5 h, 51 % (2 steps); f) Pd(PPh₃)₂Cl₂ (5 mol %), CuI (10 mol %), Et₃N/*i*Pr₂EtN (1:1), 25°C , 16 h, 83 %; g) [(JohnPhos)Au(MeCN)]SbF₆ (5 mol %), CH₂Cl₂ 1 M, 25°C , 30 min, 49 %; h) [(JohnPhos)Au(MeCN)]SbF₆ (5 mol %), MeOH 1 M, 25°C , 30 min, 93 %; i) [(JohnPhos)Au(MeCN)]SbF₆ (5 mol %), DMSO 0.5 M, 25°C , 3 h, 88 %. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, THF = tetrahydrofuran, TBSCl = *tert*-butyldimethylsilyl chloride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylalane, DMSO = dimethyl sulfoxide, JohnPhos = (2-biphenyl)-di-*tert*-butylphosphine.

same compound by a different route, namely cleavage of the TBS group of **8** followed by epoxidation to give **18**, which underwent Meinwald rearrangement to provide **17**. Diastereoselective reduction of β -hydroxy ketone **17** by Sakseña–Evans reaction with NaBH(OAc)₃ in CH₂Cl₂ afforded diol **19**. Protection with AllocCl, which proceeded with moderate selectivity, followed by Dess–Martin oxidation gave protected cannabimovone **20**. Cleavage of the MOM groups using MgBr₂ and BnSH,^[17] followed by Pd⁰ deprotection of the allyl carbonate provided **3** (53 % over 2 steps). The spectral data and optical rotation of the synthetic cannabimovone (**3**) matched those reported for the natural compound.^[18]

Whereas the synthesis of **3** fully supported the assigned configuration for all of the intermediates, a crystalline oxabicyclic intermediate **21** was obtained through treatment of epoxide **18** with a Brønsted acid, which led to opening of the epoxide and trapping of the benzylic carbocation by the free alcohol (Scheme 5). The molecular structure of **21** was determined by X-ray diffraction, which confirmed the relative configuration between the isopropenyl and the hydroxyethyl



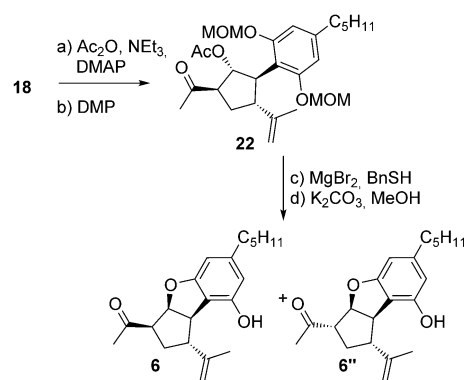
Scheme 4. a) *m*CPBA, NaHCO₃, CH₂Cl₂, 0°C to 25°C, 3 h, 57%; b) BF₃·OEt₂, THF, 25°C, 30 min, 93%; c) HCl dil./THF, 25°C, 1 h, 88%; d) TBAF, THF, 25°C, 14 h, 83%; e) *m*CPBA, NaHCO₃, CH₂Cl₂, 0°C to 25°C, 4 h, 58%; f) BF₃·OEt₂, THF, 25°C, 1 h, 48%; g) NaBH(OAc)₃, CH₂Cl₂, 25°C, 48 h, 48% (77% brsm); h) AllocCl, TMEDA, CH₂Cl₂, −40°C, 1.5 h, 41% (72% brsm); i) DMP, NaHCO₃, CH₂Cl₂, 25°C, 1.5 h, 87%; j) MgBr₂, BnSH, Et₂O, 25°C, 30 h, 62%; k) Pd(PPh₃)₄ (5 mol %), dimedone, THF, 25°C, 1 h, 85%. *m*CPBA = *m*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride, Alloc = allyloxycarbonyl, TMEDA = tetramethylethylenediamine, DMP = Dess–Martin periodinane.



Scheme 5. a) *m*-ClC₆H₄CO₂H, CH₂Cl₂, 25°C, 1 h, 77%; b) ZnI₂, (NaBH₄), (CH₂Cl)₂, 25°C, 14 h, 63%. X-Ray structure for **21**.

substituents.^[19] Treatment of **21** with ZnI₂ effected a pinacol rearrangement to give ketone **17**.

The synthesis of anhydrocannabimovone (**6**) was carried out from acetate **22** by MOM cleavage followed by treatment with K₂CO₃ to promote the oxy-Michael addition. Under these conditions, two separable epimers (**6** and **6''**) were formed in a 4:1 ratio (Scheme 6). Surprisingly, although



Scheme 6. a) Ac₂O, Et₃N, DMAP, CH₂Cl₂, −30°C, 1 h, 50% (56% brsm); b) DMP, NaHCO₃, CH₂Cl₂, 25°C, 1 h, 73%; c) MgBr₂, BnSH, Et₂O, 25°C, 24 h, 82%; d) K₂CO₃, MeOH, 25°C, 15 min, 60% (**6**) and 19% (**6''**).

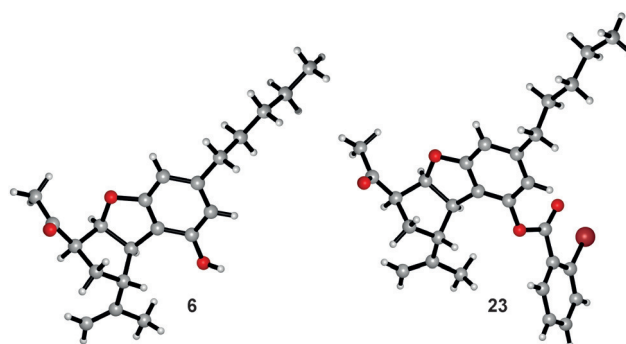


Figure 2. X-Ray structures for **6** and **23**.

¹H NMR of the major isomer **6** was identical to that reported for anhydrocannabimovone, very significant differences were observed in the ¹³C NMR spectrum.^[20] Furthermore, the optical rotation of **6** ([α]_D²² = +40.6° (*c* = 0.29, CHCl₃)) was very different to that reported ([α]_D²² = −17° (*c* = 0.02, CHCl₃)).^[9] The structure of anhydrocannabimovone (**6**) was finally confirmed by X-ray diffraction^[19] and its absolute configuration was assigned on the basis of the X-ray structure of anhydrocannabimovone 2-bromobenzoate (**23**; Figure 2).^[19]

In order to clarify the discrepancy between our structural assignment and that originally reported,^[9] we performed DFT calculations to study the oxy-Michael cyclization. Under basic conditions, oxy-Michael cyclization of the phenolate anion leads to *cis* fusion, which is more favored than the *trans* addition by 19.8 Kcal mol^{−1} (Figure 3).^[21] Furthermore, DFT calculations were employed to predict the expected ¹³C NMR chemical shifts of the different possible products.^[22] Our data were in better agreement with the *cis*-tetrahydro-1*H*-cyclopenta[*b*]benzofuran structure for anhydrocannabimovone (**6**).^[20]

In conclusion, we have accomplished the first total synthesis of cannabimovone (**3**). The four stereogenic centers of the target molecule were set up starting from the stereogenic center present in commercially available

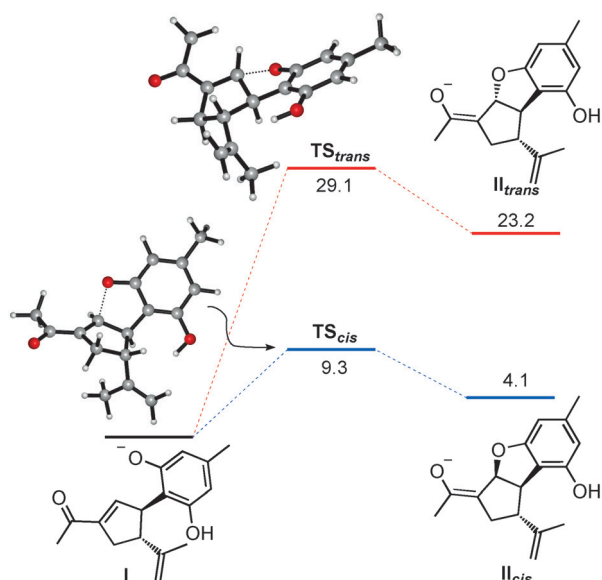


Figure 3. Energy profile (*cis* and *trans*) for the oxy-Michael cyclization. DFT calculations (M06-2x/6-31G(d,p) (MeOH), ΔG (kcal mol⁻¹).

(+)-methyl (*S*)-3-hydroxybutyrate (**9**) and by using a fully diastereoselective gold(I)-catalyzed cyclization. Interestingly, this is the first example of the cycloisomerization of simple 1,5-enynes into 3-vinylcyclopent-1-enes catalyzed by gold in the context of natural product synthesis. We also synthesized anhydrocannabimovone (**6**) and revised the stereochemistry at the ring fusion by X-ray crystallography and DFT calculations. This synthetic endeavor provides ready access to **3** and **6**, as well as other synthetic cannabinoids, for biological testing.

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- [18] See the Supporting Information for more details. Optical rotation: $[\alpha]_D^{28} = -6.8^\circ$ ($c = 0.70$, CHCl_3); (lit. $[\alpha]_D^{22} = -10^\circ$ ($c = 0.07$, CHCl_3)).^[9]
- [19] CCDC 1454956 (**6**), CCDC 1454957 (**21**) and CCDC 1454958 (**23**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
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