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THE CONVERSION OF 3,4-*CIS*- TO 3,4-*TRANS*-CANNABINOIDS[1]

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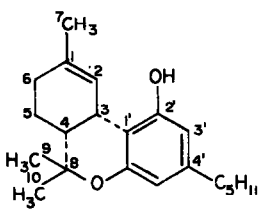
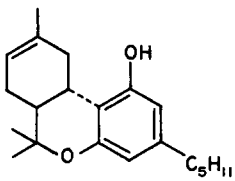
Abstract—An investigation of the conversion of Δ^1-3,4-*cis*-THC **1a** to Δ^6-3,4-*trans*-THC **2a** with BBr_3 is described. By use of **1a** of known optical purity it was determined that the main epimerization occurs at C-4. The small loss of optical purity observed during formation of **2a** results from either competitive epimerization at C-3 or a racemization process. The conversion of 3,4-*cis*- to 3,4-*trans*-HHCs proceeds with exclusive C-4 inversion.

In 1969 Razdan and Zitko[1b] reported the first example of the conversion of a *cis*- to a *trans*-tetrahydrocannabinol (THC).[2] They found that (±)-Δ^1-3,4-*cis*-THC **1** was converted to (±)-Δ^6-3,4-*trans*-THC **2** on treatment with BBr_3.[3] It was proposed that this transformation involved cleavage of the ether bond followed by probable inversion at C-4 rather than at C-3. At the time this work was carried out optically active Δ^1-3,4-*cis*-THC, needed to resolve this point, was unknown and the study of the mechanism of this transformation was not continued. We have recently synthesized[5] (+)-Δ^1-3,4-*cis*-THC **1a** of known absolute configuration (3*S*, 4*R*) from 1*S*,2*S*,3*R*,6*R*-carene-2-oxide and olivetol. The optical purity of this material was determined to be greater than 95% according to the procedure of Dale *et al.*[6] As a result, we have reinvestigated the conversion of *cis*- to *trans*-THCs.



1a-(+)-3*S*,4*R**
1b-(−)-3*R*,4*S*



2a-(+)-3*S*,4*S**
2b-(−)-3*R*,4*R*

*The **a** refers to the compound shown and **b** to its enantiomer. Compounds referred to by number only are racemic.

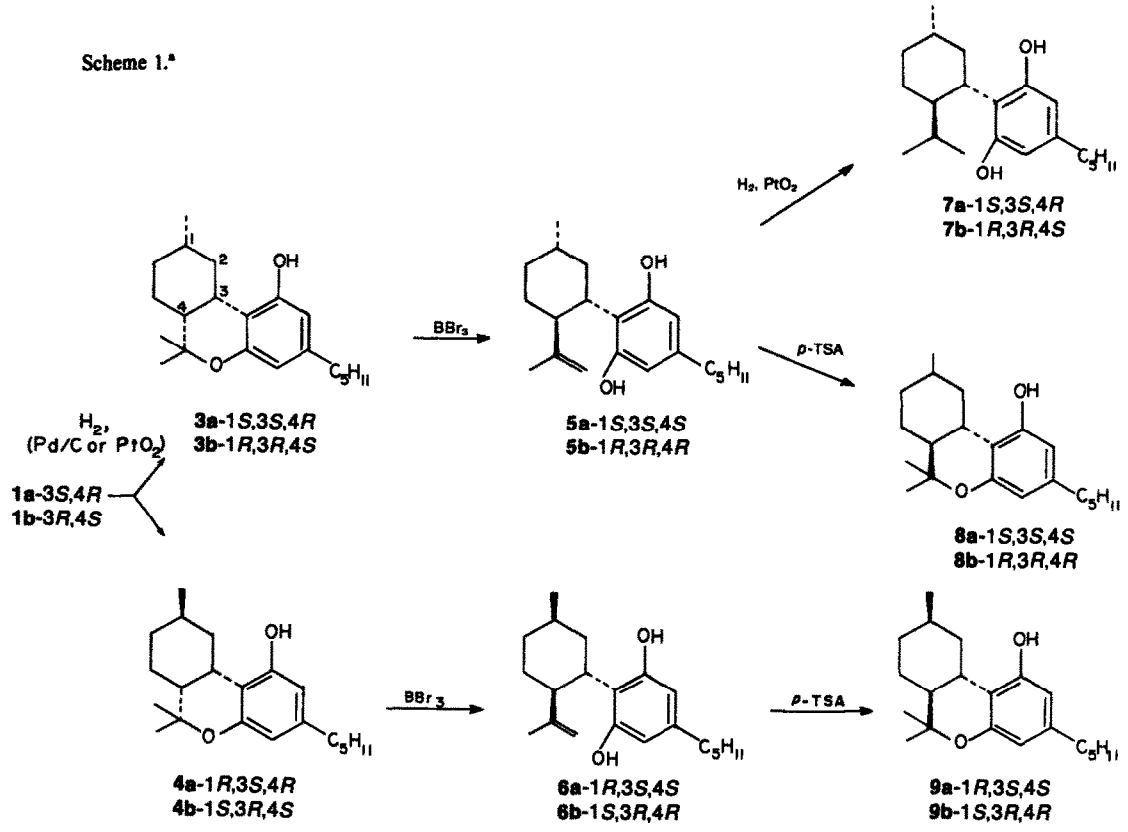
Inasmuch as the products formed by epimerization of **1a** at C-3 (Δ^6-3*R*,4*R*-THC, **2b**) and at C-4 (Δ^6-3*S*,4*S*-THC, **2a**) are enantiomers, preference for epimerization at either site will be reflected in the sign and magnitude of the optical rotation of the product. Hence, a sample of THC **1a** ($[\alpha]_D$ +108°, optical purity 89%) was allowed to react with BBr_3 at −20°C. The product (Δ^6-*trans*-THC, 33% yield) had a rotation of +123° (EtOH), which corresponds[7] to a mixture of 24% enantiomer **2b** and 76% enantiomer **2a** (corrected for the presence of 5.5% Δ^1-3*R*,4*S*-THC **1b** in the starting material). Epimerization at C-4 is thus the favored process and is accompanied by a lesser amount of C-3 epimerization or racemization.

To determine if removal of the carbocyclic unsaturation affects the stereochemical outcome of the conversion, **1a** ($[\alpha_D]$ +121°; >95% optically pure) was hydrogenated over PtO_2 catalyst to give a mixture of *cis* hexahydrocannabinols[8] (HHCs **3a** and **4a**, Scheme 1) in which one epimer predominated to the extent of 94%. The major epimer should be **3a**, the product of *cis* addition of hydrogen to the less hindered side of **1a**. However, because the isomer ratio was found to depend on the nature of the catalyst (Pd/C reversed the ratio to 35:65) the relative configurations of **3a** and **4a** were uncertain. After being separated by high pressure liquid chromatography (HPLC) the minor epimer from the reduction with PtO_2 was treated with BBr_3. GLC analysis of the crude product indicated that the reaction had proceeded only as far as the dihydrocannabidiol stage. The reaction mixture was treated with *p*-toluenesulfonic acid (*p*-TSA) to effect ring closure and give *trans*-HHC **9a** as the product. Its diastereomers **8a** and **8b**, the possible products of C-4 epimerization in **3a** and C-3 epimerization in **4a**, respectively, were not found (GLC comparison with authentic[9,10] **8b** and **9b** prepared from **2b**). Furthermore, the optical rotation of the product (+90°) revealed that it possessed the absolute stereochemistry shown for **9a** and that it was approximately[11] 85% optically pure (by comparison with the (−)-isomer **9b**[9]). Diastereomer **9a** can be formed only by epimerization at C-4 in **4a** (barring the unlikely inversion of C-1 in **3a**). Accordingly, the major and minor epimers from the hydrogenation of **1a** with PtO_2 are assigned structures **3a** and **4a**, respectively.

Having thus established the absolute stereochemistry of **3a** and **4a** corroboration of our epimerization results could be obtained from the more readily available racemic forms (**3** and **4**). Reaction of **3** with BBr_3 gave 3,4-*trans*-dihydrocannabidiol **5** identified by its NMR and GLC characteristics and by conversion to the known tetrahydrocannabidiol **7**.[12a,b] Cyclization of **5** with *p*-TSA gave *trans*-HHC **8**. In a similar series of reactions **4** was converted to **6** and then to **9**. Since no "crossover" products were observed by GLC (i.e. **9** from **3** and **8** from **4**), inversion at the ring junction in **3** and **4** occurs exclusively at C-4.

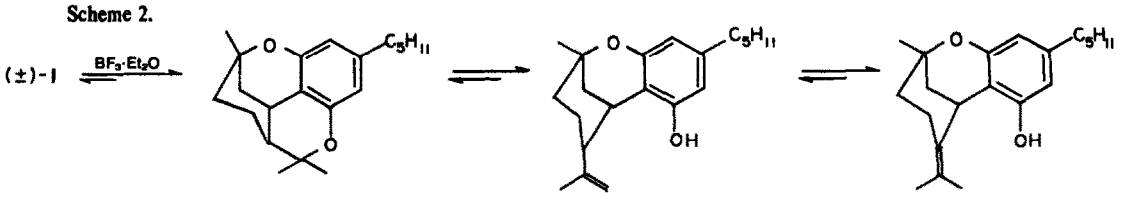
In the presence of BF_3·etherate, *cis*-Δ^1-THC **1** forms an equilibrium mixture of cannabinoids **10–12** (Scheme 2) *via* intramolecular cyclization followed by pyran ring cleavage.[12c] No Δ^1- or Δ^6-*trans*-THCs are found even on treatment of this mixture with BBr_3 for 2h at −20°C. The formation of *trans*- products from **1a** when initiated by BBr_3, then, follows a different path, which probably involves, as a first step, cleavage of the pyran ring rather than cyclization.[13] The resulting equilibrium (Scheme 3) is driven to the relatively stable isomer **2a** *via* epimerization at C-4.[16] Friedel–Crafts cleavage of the C-3–C-1′ bond in **13a** or **14a** followed by recombination leads

Scheme 1.[a]

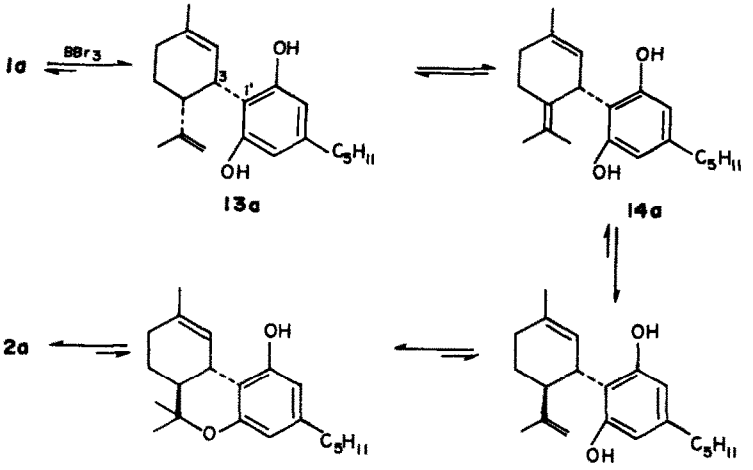


[a]The a refers to the compound shown and b to its enantiomer. Compounds referred to by number only are racemic.

Scheme 2.



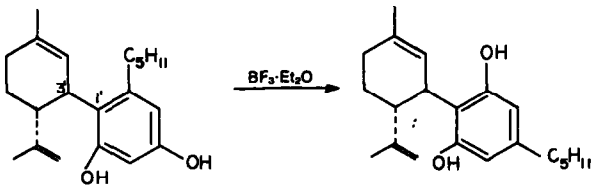
Scheme 3.



to C-3 epimerization in the former and racemization of the latter.

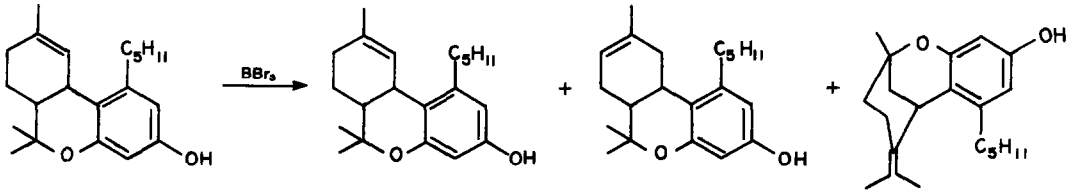
A retro-Friedel–Crafts $_{1,3}$ mechanism has been postulated[17] to account for the formation of (−)-"normal"-*trans*-CBD **16**[18] from its (−)-"abnormal"-counterpart **15** with BF_3·etherate (Scheme 4). In this case rotation of the resorcinyl group and formation of "normal" products is diagnostic for cleavage of the

Scheme 4.



(−)-15 (−)-16

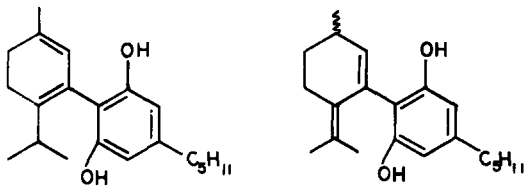
Scheme 5.



(±)-*cis*-17 (±)-*trans*-18 (±)-*trans*-19 (±)-20

C-3–C-1′ bond. However, when (±) "abnormal"-3,4-*cis*-THC **17** was treated with BBr_3 (a more active Friedel–Crafts catalyst than BF_3[19]), only "abnormal"-products (**18–20**)[17,7] were found (Scheme 5). Thus, if this reaction is analogous to that of **1a** with BBr_3, in that C-3 epimerization and/or racemization occurs, then the operation of a retro-Friedel–Crafts mechanism in the conversion of *cis*- to *trans*-THCs is in doubt.

Alternatively, racemization may be brought about by the formation of 1,3- and 2,4(8)-dienes (**21** and **22**), although it is unlikely that such conjugated entities could revert to THC products. In any event, compounds **21** and **22** may contribute to the large amount of tar that accompanies these transformations with BBr_3.



21 **22**

EXPERIMENTAL

NMR spectra were recorded on a Varian T-60 spectrometer, and optical rotations were obtained on a Perkin–Elmer 141. A Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system was used for the high pressure chromatography. The high resolution mass spectrum was recorded on a Dupont CEC-110B instrument and the low resolution spectra on an AEI MS-9 spectrometer. A Varian Aerograph Model 1400 equipped with a 6-ft × 1/8 in. stainless steel column packed with 3% OV-17 on 80–100 mesh Supelcoport and a flame ionization detector was used for GLC analysis. Carrier gas was helium and the column temperature was 240°C for silylated and 260°C for unsilylated samples. Compounds were identified by comparison of their retention times with those of authenic samples (silylated and unsilylated) and by comparison of their retention times relative to those of (−)-Δ^1-3*R*,4*R*-THC (silylated and unsilylated) as a standard. Bis(trimethylsilyl)-trifluoroacetamide was used as the silylating agent.

Reaction of (+)-Δ^1-3*S*,4*R*-*THC* **1a** *with* BBr_3

BBr_3 (100 μl, 1.05 mmol) was added to a stirred solution of (+)-Δ^1-3*S*,4*R*-THC[5] ([α]$_D$ + 108° (EtOH), 75 mg, 0.24 mmol) in 10 ml of CH_2Cl_2 at −20°C. After 2 h the reaction mixture was quenched with 50 ml of liquid NH_3. The NH_3 was allowed to evaporate at room temp. and was replaced by ether. The ethereal solution was washed with 1N HCl and brine and dried over Na_2SO_4. Preparative TLC (silica gel, 20% ether/petroleum ether) gave 50 mg of orange resin. Repeated HPLC on a 7-ft × 3/8-in. column packed with Porasil C, with 3% ether/isooctane as eluant, gave 25 mg (33%) of (+)-Δ^6-3*S*,4*S*-THC **2a**. The capacity factor (k′) was 2.4 and [α]$_D$ was +123° (1.50, EtOH). Except for the optical rotation, this material was identical in all respects (NMR, GLC) to authentic **2b**.

Hydrogenation of (+)-Δ^1-3*S*,4*R*-*THC* **1a**

(+)-Δ^1-3*S*,4*R*-THC ([α]$_D$ + 121° (EtOH), 58 mg, 0.18 mmol) in 30 ml of ethanol was hydrogenated at 10 psig over Pd/C (10%) for 2 h. After the solution was filtered through Celite and the solvent removed, GLC analysis of the residue showed two peaks whose retention times (relative to Δ^6-*trans*-THC = 1.00) and % by area were, respectively, 0.68 (65%) and 0.94 (35%) unsilylated, and 0.75 and 0.90 silylated. Preparative separation was achieved by HPLC on a 7-ft × 3/8-in. column of Porasil C with 1.5% ether/isooctane as eluant. The separation factor (α) was 2.1 and the compounds were eluted in the same order as on GLC: (+)-1*R*,3*S*,4*R*-HHC (**4a**, 22 mg, k′ = 1.8, [α]$_{578}$ + 11° (1.12, $CHCl_3$)); NMR ($CDCl_3$) δ: 6.28, 6.08 (dd, 2, J = 2 Hz, aromatics), 4.65 (s, 1, O-H), 3.4–3.0 (br, 2, C2α-H and C3-H), 2.45 (t, 2, J = 8 Hz, α-benzylics), 1.35, 1.22 (2s, 6, C8-$(CH_3)_2$), 0.87 (m, 6, C1-CH_3 and ω-CH_3); 70 eV MS *m/e* (% base peak) 316 (100, M^+), 301 (21, M^+-CH_3·), 273 (94, M^+-C_3H_7·), 260 (82, M^+-C_4H_8), 193 (55); (+)-1*S*,3*S*,4*R*-HHC (**3a**, 12 mg, k′ = 3.8, [α]$_{578}$ + 26° (1.29, $CHCl_3$)); NMR ($CDCl_3$) δ: 6.30, 6.17 (dd, 2, J = 2 Hz, aromatics), 4.65 (s, 1, O-H), 2.95 (dt, 1, J = 12, 6, 6 Hz, C3-H), 2.45 (t, 2, J = 8 Hz, α-benzylics), 1.40 (s, 6, C8-$(CH_3)_2$), 0.95–0.87 (m, 6, C1-CH_3 and ω-CH_3); 70 eV MS *m/e* (% base peak) 316 (100, M^+), 301 (23), 273 (92), 260 (73), 193 (65).

When this hydrogenation was carried out as above, with PtO_2 in place of Pd/C, the percentages of compounds **4a** and **3a** were 6 and 94, respectively. Racemic Δ^1-3,4-*cis*-THC **1** was hydrogenated as above with Pd/C catalyst to give **3** and **4**.

Conversion of (+)-1*R*,3*S*,4*R*-*HHC* **4a** *to* (+)-1*R*,3*S*,4*S*-*HHC* **9a**

To 22 mg (0.07 mmol) of (+)-1*R*,3*S*,4*R*-HHC in 4 ml of CH_2Cl_2 at −20°C was added 25 μl (0.26 mmol) of BBr_3. After 2 h the reaction was quenched with liquid NH_3 and worked up as described for **1a**. GLC analysis of the product indicated that the major component was a dihydrocannabidiol with retention times (relative to Δ^6-*trans*-THC = 1.00) of 0.86 unsilylated, 1.06 monsilylated, and 0.59 disilylated: NMR (CCl_4) δ: 5.97 (s, 2, aromatics), 4.60, 4.38 (br, 4, C9-vinylics and two exchangeable O-H), 1.57 (s, 3, C8-CH_3), 1.18, 1.05 (d, J = 7 Hz, C1-CH_3), 0.88 (t, ω-CH_3). This material (20 mg) was dissolved in 5 ml of benzene and refluxed with *p*-TSA·H_2O (1 mg) for 45 min. The reaction was quenched with solid Na_2CO_3·H_2O and filtered, and the solvent was removed. Separation by HPLC, on a 1-ft × 0.25-in.

μPorasil column with 1.0% ether/isooctane as eluant, gave (+)-1*R*,3*S*,4*S*-HHC (**9a**, 1.6 mg, 7% yield (90% pure by GLC), k' = 7.5, $[\alpha]_D + 90°$ (0.16, $CHCl_3$)); high resolution mass spectrum: molecular weight calc. for $C_{21}H_{32}O_2$ 316.24023, found 316.24191. The GLC retention times, both silylated and unsilylated, as well as the HPLC retention time of compound **9a** were identical with those of an authentic sample of (−)-1*S*,3*R*,4*R*-HHC (**9b**, $[\alpha]_D - 109°$ ($CHCl_3$)).[9]

Reaction of (±)-1,3,4-*cis*-*HHC* **3** *with* BBr_3

To a solution of (±)-1,3,4-*cis*-HHC (69 mg, 0.22 mmol) in 15 ml of CH_2Cl_2 at −20°C was added BBr_3 (100 μl, 1.05 mmol). After 2 h the reaction mixture was worked up as previously described. Drying and removal of solvent left 45 mg of yellow resin, identified as (±)-1,3-*cis*-4-*trans*-dihydrocannabidiol **5**: NMR (CCl_4) δ: 5.97 (br, 2, aromatics), 4.57, 4.40 (br, 4, C9-vinylics and two exchangeable O-H), 2.30 (br, 2, α-benzylics), 1.53 (s, 3, C8-CH_3), 0.93 (br, 6, Cl-CH_3 and ω-CH_3). GLC retention times of **5** (relative to Δ⁶-*trans*-THC = 1.00) were 0.82 unsilylated, 1.12 monosilylated, and 0.46 disilylated. This material was used in subsequent reactions without further purification.

A portion of the dihydrocannabidiol **5** was hydrogenated over PtO_2 to give (±)-1,3-*cis*-4-*trans*-tetrahydrocannabidiol (**7**), which was identical by GLC with an authentic sample of 1*R*,3*R*,4*S*-tetrahydrocannabidiol **7b**.[12a,b]

Reaction of (±)-1,3-*cis*-4-*trans*-*dihydrocannabidiol* **5** *with p-TSA*

To a solution of (±)-1,3-*cis*-4-*trans*-dihydrocannabidiol (45 mg, 0.14 mmol) in 15 ml of refluxing benzene was added 5 mg of *p*-TSA·H_2O. After 1.5 h the reaction was quenched with $Na_2CO_3 \cdot H_2O$. Filtration and evaporation of the solvent gave 45 mg of resin. Chromatography on Florisil with ether/petroleum ether (5:95) gave 27 mg of (±)-1,3-*cis*-4-*trans*-HHC **8**, identical in all respects other than rotation to (−)-1*R*,3*R*,4*R*-HHC **8b**.[9] Overall yield from HHC **3** was 29%.

Racemic **4** was converted to racemic **9** in similar fashion; the overall yield was 30%.

Reaction of (±)-"*abnormal*"-Δ¹-3,4-*cis*-*THC* **17** *with* BBr_3

A stirred solution of 85 mg (0.27 mmol) of "abnormal"-Δ¹-*cis*-THC at −20°C was treated with BBr_3 (100 μl, 1.05 mmol). After 2 h the reaction was quenched with liquid NH_3 and worked up in the usual manner. Preparative TLC (silica gel, 1:4 ethyl acetate/hexane) gave three major bands, which, after elution, weighed10–15 mg each. Two of these fractions gave useful GLC and NMR spectra. The faster-moving band consisted of "abnormal"-Δ^(6(8))-isoTHC **20** and "abnormal"-Δ⁶-3,4-*trans*-THC **19** in a ratio of 1.8:1.0. Retention times on GLC (relative to Δ⁶-3,4-*trans*-THC = 1.00) were, respectively, 0.78 and 0.82 (unsilylated) and 1.00 and 1.07 (silylated). The second band contained a mixture of "abnormal"-Δ¹-3,4-*trans*-THC **18** and **19** in a ratio of 0.2:1.0. Relative retention times were, respectively, 0.89 and 0.82 (unsilylated) and 1.19 and 1.07 (silylated). The relative quantities determined by GLC of the crude were 11% of **18**, 47% of **19**, and 27% of **20**.

Reaction of an equilibrium mixture of compounds **10–12** *with* BBr_3

To 50 mg of an equilibrium mixture of **10–12** (obtained by treating (±)-Δ¹-3,4-*cis*-THC **1** with BF_3 etherate)[12c] in 10 ml CH_2Cl_2 at −20°C was added 15 μl of BBr_3. After 2 h the reaction mixture was quenched and worked up in the usual manner. Analysis of the product by GLC showed no change in composition.

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