Improved Procedure for the Preparation of Chiral 1,2-Epoxybutanes: Total Synthesis of (*S*)-3′-Hydroxy-Δ^9-tetrahydrocannabinol, A Highly Active Metabolite of Δ^9-Tetrahydrocannabinol

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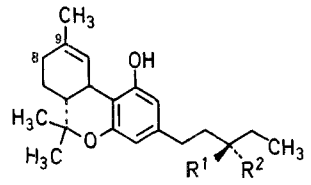
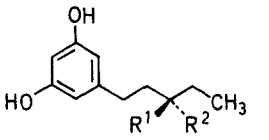
We have previously reported[1] that the metabolite 3′-hydroxy-Δ^9-tetrahydrocannabinol **(1)** (as a diastereomeric mixture at C-3′) is two to three times more active than Δ^9-tetrahydrocannabinol itself in behavioral tests. The individual stereoisomers, however, have not been evaluated for biological activity. We describe here efficient routes to (*R*)- and (*S*)-3′-hydroxy-Δ^9-tetrahydrocannabinol **(1a)** and **(1b)** via the intermediates (*R*)- and (*S*)-3′-acetoxyolivetol **(2a)**

and **(2b)** [(*R*)- and (*S*)-5-(3′-acetoxypentyl)-1,3-benzenediol]. In preliminary pharmacological tests the (*S*)-isomer is much more active than the (*R*)-isomer.



1a R^1 = OH, R^2 = H
b R^1 = H, R^2 = OH
c R^1 = OAc, R^2 = H
d R^1 = H, R^2 = OAc

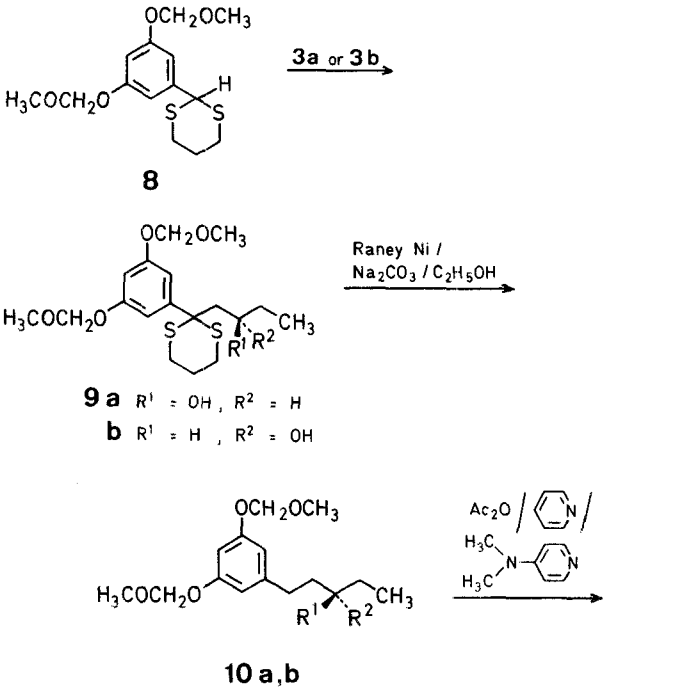


2a R^1 = OAc, R^2 = H
b R^1 = H, R^2 = OAc

We introduced the required chirality into the *n*-pentyl side chain of **1** via chiral 1,2-epoxybutanes **(3a)** and **(3b)**. Our high yield synthesis of **3a** and **3b** (Scheme **A**) incorporates some noteworthy improvements following the route of Coke and Rice[2,8]. Racemic 1-dimethylamino-2-butanol **(4)** was obtained using our new procedure[3] from 1,2-epoxybutane, **(3)**, and lithium dimethylamide. This racemic compound from ethanol as the (−)-dibenzoyl-L-tartrate salt **5a** (96% yield). The optically enriched **4a** ($[\alpha]_D^{25}$: −15.5°) was obtained in 69% yield by treatment of **5a** with hydrochloric acid followed by base and ether extraction. The reaction of **4a** with methyl iodide gave **6a** quantitatively. Conversion of the iodide salt to the hydroxide salt **7a** has previously been accomplished[2] in moderate yield with silver(I) oxide. In our hands ion-exchange chromatography provided simple and efficient access to **7a**. Thermolysis[2] then gave (*R*)-1,2-epoxybutane **(3a)** (72% yield from **6a**), which was used immediately without purification.

The published route [2] to (*S*)-1,2-epoxybutane, **(3b)**, requires the use of the (+)-dibenzoyl-D-tartrate salt and reapplication of the procedure described above. We found that treatment of the mother liquors from the ethanol recrystallization of **5a** provided the aminoalcohol **4b** in 63% yield ($[\alpha]_D^{25}$: +18.0°). This was converted, as described above for **3a**, to epoxide **3b** (86% yield from **6b**).

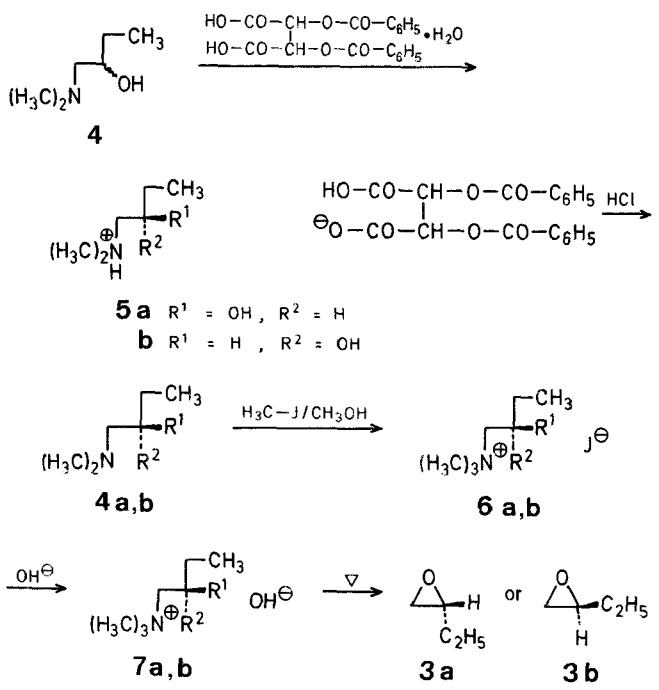
Reaction of epoxide **3a** with the lithium anion formed from 2-(3,5-bis[methoxymethoxy]phenyl)-1,3-dithiane **(8)**[4] at −78°C produced dithianyl alcohol **9a**, which was deprotected and acetylated to give **11a** in a 51% overall yield from **3a**. Acetate **11b** was synthesized in an analogous fashion from **3b** in 48% yield. (Scheme **B**).



8

9a R^1 = OH, R^2 = H
b R^1 = H, R^2 = OH

10a,b



4

5a R^1 = OH, R^2 = H
b R^1 = H, R^2 = OH

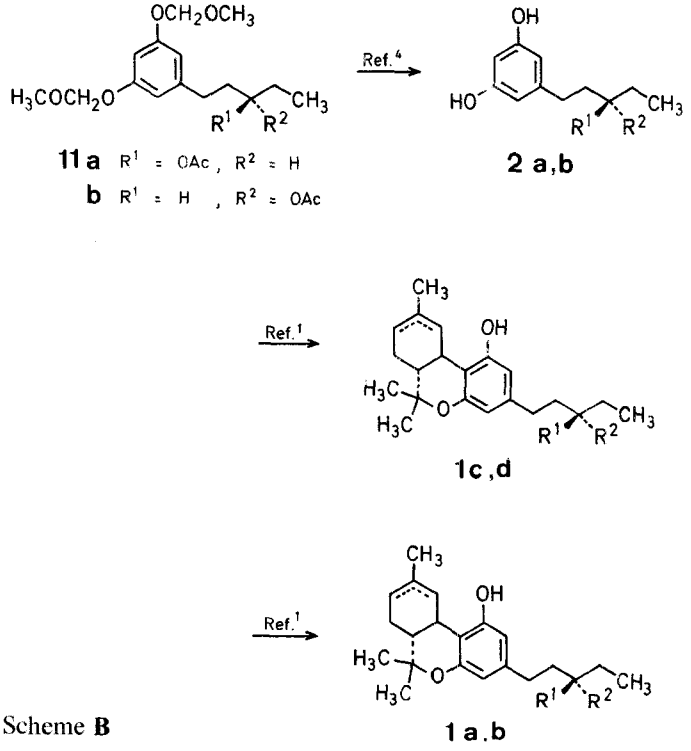
4a,b

6a,b

7a,b

3a **3b**

Scheme **A**



11a R^1 = OAc, R^2 = H
b R^1 = H, R^2 = OAc

2a,b

1c,d

1a,b

Scheme **B**

Completion of the total synthesis required deprotection[4] of **11a** and **11b** to **2a** and **2b**, respectively, followed by condensation with (+)-*cis*-*p*-menth-2-ene-1,8-diol and separation of the Δ^9-, Δ^8-isomeric mixture by H.P.L.C., as previously reported by us[1]. We have now found that separation by rapid flash chromatography[6] was just as efficient as H.P.L.C. (ratios of 9:1 of Δ^9- to Δ^8-3′-hydroxy-tetrahydrocannabinols can be obtained) and overall yields are similar. We feel this is the procedure of choice for the purification of these metabolites. The identity of compounds **1a** and **1b** was confirmed by high-resolution mass spectral analysis and equal retention times on G.L.C. as compared with an authentic sample of unresolved **1**[1].

In a variety of behavioral tests, (*S*)-3′-hydroxy-Δ^9-tetrahydrocannabinol **(1b)** proved to be six to seven times more active than the (*R*)-isomer, **1a**. Details of the pharmacological testing will be the subject of a separate publication.

(*R*)-1,2-Epoxybutane (3a) and (*S*)-1,2-Epoxybutane (3b):

Tartrate salts **5a** and **5b**: To a solution of (−)-dibenzoyl-L-tartaric acid monohydrate (Aldrich; 4.62 g, 123 mmol) in warm ethanol (103 ml) is added a solution of (±)-1-dimethylamino-2-butanol[3] (**4**; 15.0 g, 128 mmol) with stirring. After storage at 10 °C overnight, the precipitated solid is filtered to give white crystals (48.0 g). Recrystallization from ethanol (200 ml) affords the salt **5a** as a white crystalline solid; yield: 29.1 g (48%); m.p. 106–110 °C (Lit.[2], m.p. 109–112 °C).

The combined mother liquors are concentrated in vacuo to give **5b** as a sticky white foam; yield: 28.8 g (47%).

(R)- *and* (S)-*1-Dimethylamino-2-butanol* **(4a)** *and* **(4b)**: The salt **5a** (29.1 g) is dissolved in 10% hydrochloric acid (60 ml) and ether (80 ml) is added. The ether layer is extracted with water, and the combined aqueous layers are basified with sodium hydroxide (9.7 g), and saturated with sodium chloride. Repeated extraction with ether, drying with anhydrous magnesium sulfate, and distillation at atmospheric pressure affords the amino alcohol **4a** as a colorless liquid; yield: 5.18 g (69%); b.p. 140–144 °C/760 torr (Lit.[2], b.p. 142–143 °C/754 torr); $[\alpha]_D^{25}$: −15.5° (*c* 2.0, ethanol); ee[2]: 70%.

Similar treatment of **5b** gives **4b**; yield: 4.70 g (63%), $[\alpha]_D^{25}$: +18.0° (*c* 2.1, ethanol); ee: 81%.

(R)- *and* (S)-*1,2-Epoxybutane* **(3a)** *and* **(3b)**: (*R*)-1-Dimethylamino-2-butanol (**4a**; 4.86 g, 41.5 mmol), is dissolved in methanol (20 ml) under nitrogen, and a solution of methyl iodide (7.06 g, 49.7 mmol) in methanol (20 ml) is added dropwise at 0 °C. The mixture is allowed to warm to 25 °C, and then refluxed for 5 h. Evaporation gives **6a** as a light yellow solid; yield: 10.75 g (100%); m.p. 168–169 °C (Lit.[2], m.p. 161–162 °C).

The methiodide of the corresponding (*S*)-isomer, also obtained in 100% yield, has m.p. 162–164 °C.

Salt **6a** (10.75 g) is dissolved in water (10 ml) and passed through Amberlite IRA-400 (OH-form) ion-exchange resins (65 g), at a flow rate of two bed volumes per hour. All basic fractions are combined and concentrated below 55 °C. The residual yellow syrup **7a** is heated at 130 °C for 0.5 h. The condensate (6.90 g) is distilled (bulb-to-bulb) at 30 torr pressure and 25 °C to produce 2.67 g of a colorless oil. Redistillation from anhydrous magnesium sulfate gives (*R*)-1,2-epoxybutane **(3a)**[2], contaminated with a small amount of trimethylamine; yield: 2.14 g (72%).

Similar treatment of **6b** affords epoxide **3b**[2]; yield: 2.33 g (86%). The ^{1}H-N.M.R spectra of these epoxides are consistent with that reported for racemic **3**[7].

(*R*)- and (*S*)-2-(3,5-Bis[methoxymethoxy]phenyl)-2-(2-hydroxybutyl)-1,3-dithiane (9a) and (9b):

To a solution of dithiane **8**[4] (8.40 g, 26.5 mmol) in tetrahydrofuran (40 ml) is added dropwise a solution of *n*-butyllithium in hexane (10.7 ml of a 2.23 molar solution, 23.9 mmol) at −78 °C. The resulting dark red-brown solution is stirred for 1 h at −78 °C, and a solution of the crude epoxide **3a** (2.14 g, 29.7 mmol) in tetrahydrofuran (10 ml) is added dropwise over 10 min. The mixture is stirred at −78 °C for an additional 30 min, allowed to stand at −10 °C for 17 h, and finally stirred at 25 °C for 1.5 h. It is then cooled to 0 °C and a saturated solution of ammonium chloride is added. The aqueous phase is extracted several times with ether, and the combined organic layers are washed with a saturated solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered and concentrated to give dithianyl alcohol **9a** as a yellow oil, used in the next step without purification; yield: 10.47 g.

Similarly **8** (9.23 g, 29.2 mmol) and (*S*)-epoxide **3b** (2.33 g, 32.3 mmol) gives **9b**; yield: 12.0 g.

A sample of racemic **9**, prepared in the same manner, was characterized after purification by column chromatography (10–20% ether/petroleum ether) as a viscous yellow oil; yield: 72% from **3**.

$C_{18}H_{28}O_5S_2$	calc.	C 55.64	H 7.26	S 16.50
(388.6)	found	55.51	7.27	16.41

IR (neat): ν = 3440, 2935, 2905, 2880, 1580, 1420, 1265, 1200, 1130, 1070, 1015, 905, 715 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): δ = 7.18 (d, J = 2 Hz, 2H, H—2,6-Ar); 6.60 (t, J = 2 Hz, 1H, H—4-Ar); 5.12 (s, 4H, CH_2O); 3.6–3.9 (br. s, 1H, HCOH); 3.46 (s, 6H, CH_3O); 2.6–2.9 (m, 4H, CH_2S); 1.7–2.3 (m, 5H, $CH_2CHOHCH_2$); 1.84 (t, J = 7 Hz, 3H, CH_3CH_2); 1.1–1.6 ppm (m, 2H, CH_2CH_2S).

(*R*)- and (*S*)-1-(3,5-Bis[methoxymethoxy]phenyl)-3-acetoxypentane (11a) and (11b):

To a suspension of freshly prepared Raney nickel (125 g) in ethanol (150 ml) containing anhydrous sodium carbonate (3 g) is added crude **9a** (10.47 g). The mixture is heated at reflux for 6 h, cooled, filtered, and concentrated in vacuo to give an oil. This material is dissolved in ether, washed with water and a saturated sodium chloride solution, dried with anhydrous magnesium sulfate, filtered, and evaporated to provide **10a** (yield: 6.4 g) as a pale yellow mobile oil identical (T.L.C., N.M.R.) to an authentic sample of racemic **10**[4].

In a similar fashion **9b** (12.0 g) gives **10b** (yield: 7.5 g).

Acetylation of **10a** and **10b**[4] is carried out with acetic anhydride and pyridine using 4-dimethylaminopyridine (0.1 eq) as catalyst at 25 °C for 5 h. After purification by column chromatography (20% ether/petroleum ether) **11a** and **11b** are obtained in overall yields of 51% and 48% from **3a** and **3b**, respectively, as pale yellow mobile oils, identical (T.L.C., N.M.R.) to an authentic sample of racemic **11**[4].

(*R*)- and (*S*)-3′-Acetoxyolivetol 2a and 2b:

Compounds **11a** and **11b** are deprotected following our procedure[4] to provide the corresponding olivetols **2a** and **2b** identical (T.L.C., N.M.R.) to an authentic sample of racemic 3′-acetoxyolivetol **(2)**[4].

(*R*)-and (*S*)-3′-Hydroxy-Δ^9-tetrahydrocannabinols (1a) and (1b):

Compounds **2a** and **2b** are condensed with (+)-*cis*-*p*-menth-2-ene-1,8-diol using our procedure[1] to give **1c** and **1d**, respectively, as a ~3:1 mixture of Δ^9- and Δ^8-isomers. Purification is effected by rapid column chromatography[6] (20% ethyl acetate/hexane) using a ratio of silica gel to compound of ~50:1. Fractions containing >80% Δ^9-isomer (G.L.C.) are pooled and rechromatographed under the same conditions. Purified **1c** and **1d** are saponified using potassium hydroxide[1] to furnish (*R*)-3′-hydroxy-Δ^9-tetrahydrocannabinol **(1a)** and (*S*)-3′-hydroxy-Δ^9-tetrahydrocannabinol **(1b)**, respectively, (ratio of Δ^9- to Δ^8-isomers ~9:1 by G.L.C.) as viscous oils that rapidly discolor in air, identical (T.L.C., N.M.R., G.L.C., M.S.) to an authentic sample of unresolved **1**[1].

1a: M.S.: *m/e* = 330.2197 (calc. 330.2195).

1b: M.S.: *m/e* = 330.2197 (calc. 330.2195).

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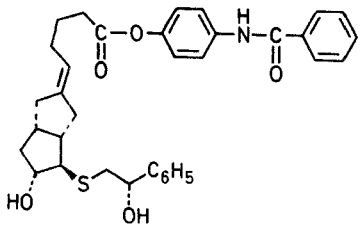
[1] G.R. Handrick et al., *J. Med. Chem.* **25**, 1447 (1982).
[2] J.L. Coke, W.Y. Rice, Jr., *J. Org. Chem.* **30**, 3420 (1965); J.L. Coke, R.S. Shue, *J. Org. Chem.* **38**, 2210 (1973).
[3] H. Sard, R.P. Duffley, R.K. Razdan, *Synth. Commun.* **13**, 813 (1983).
[4] R.P. Duffley et al., *Synthesis* **1980**, 733.
[5] For a similar transformation, see C.G. Pitt et al., *J. Org. Chem.* **44**, 677 (1979).
[6] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).
[7] C.J. Pouchert, J.R. Campbell, *The Aldrich Library of NMR Spectra*, Vol. 1, 145B.
[8] For other preparations of chiral 1,2-epoxybutanes, see:
A.T. Bottini, V. Dev, M. Stewart, *J. Org. Chem.* **28**, 156 (1963).
K. Mori et al., *Tetrahedron* **35**, 1601 (1979).
W.H. Pirkle, P.L. Rinaldi, *J. Org. Chem.* **43**, 3803 (1978).
B.T. Golding, P.J. Sellars, A.K. Wong, *J. Chem. Soc. Chem. Commun.* **1977**, 570.
B. Seuring, D. Seebach, *Helv. Chim. Acta* **60**, 1175 (1977).
G. Bettoni et al., *Tetrahedron* **36**, 409 (1980).
T. Nakajima, Y. Nakamoto, S. Suga, *Bull. Chem. Soc. Jpn.* **48**, 960 (1975), and references cited therein.

R.F. Newton, S.M. Roberts, R.J.K. Taylor, *Synthesis* **1984** (6), 449–478:

The structure of compound **305** (p. 475) should be:



305 (EMD 46335)

H. Sard, R.P. Duffley, L.R. Robertson, R.K. Razdan, *Synthesis* **1984** (6), 506–509:

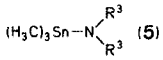
The fourth sentence in the paragraph above Scheme **A** (p. 507) should read:
This racemic compound could be preferentially enriched by a single recrystallization from ethanol as the (−)-dibenzoyl-L-tartrate salt **5a** (96% yield).

C.K. Ghosh, N. Tewari, A. Bhattacharya, *Synthesis* **1984** (7), 614–615:

Compounds **2a–d** should be named as 3-ethoxy-10-oxo-4,4a-dihydro-3*H*,10*H*-pyrano[4,3-*b*][1]benzopyrans.

Abstract 6925, *Synthesis* **1984** (7), 624:

The structure of reagent **5** should be:



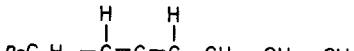
(5)

M. Sato, N. Katsumata, S. Ebine, *Synthesis* **1984** (8), 685:

The title compound should be named 4,5-Dihydrobenzocyclobutene-4,5-dione.

R.E. Doolittle, *Synthesis* **1984** (9), 730–732:

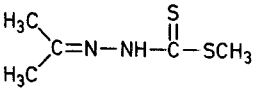
The structure of product **3** (p. 730) should be:



3

Y. Nakayama, Y. Sanemitsu, *Synthesis* **1984** (9), 771–772:

The structure of compound **6** (p. 772) should be:



6

I. Reichelt, H.-U. Reissig, *Synthesis* **1984** (9), 786–787:

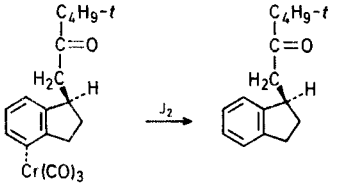
The title compounds **2** should be named as 3-oxo-2,3,4,5-tetrahydropyridazines

M. Tirant, T.D. Smith, *Synthesis* **1984** (10), 833–834

The names for products **2a** and **3a** should be bis[2-hydroxybenzylidenehydrazino] sulfide and 2-hydroxyethyl 2-hydroxybenzylidenehydrazino sulfide, respectively.

Abstract 6971, *Synthesis* **1984** (10), 892:

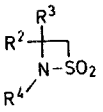
The structures of products **4** and **5** should be:



4 **5**

Abstract 6976, *Synthesis* **1984** (10), 894:

The structure of product **8** should be:



8

E.A. Mistryukov, I.K. Korshevetz, *Synthesis* **1984** (11), 947–949:

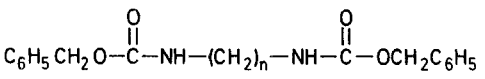
Compound **10** should be named as 1-(1-cyclohexenyl)-3-diethylaminopropyne.

Z. Arnold, V. Kral, G.V. Kryshtal, L.A. Yanovskaya, *Synthesis* **1984** (11), 974–976:

The title compounds **5** should be named as 3-substituted 2,2-diethoxycarbonyl-4-formyl-2,3-dihydrofurans.

G.J. Atwell, W.A. Denny, *Synthesis* **1984** (12), 1032–1033:

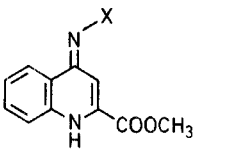
The structure of products **4a–f** (p. 1032) should be:



4a-f

R.G. McR. Wright, *Synthesis* **1984** (12), 1058–1061:

Formula **8** should be replaced by:



8 X = Cl–C6H4–O–SO2–

9 X = Cl3C–C(=O)–