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A GENERAL SYNTHESIS OF SIDE CHAIN DERIVATIVES OF Δ^9-THC

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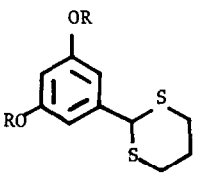
Abstract

The synthesis of (6aR, 10aR)-trans-3-[1',3'-dithian-2'-yl]-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-ol t-butyldimethylsilyl ether (4b) is reported. The use of this compound as a source of side chain derivatives of cannabinoids is illustrated by syntheses of 1'-,2'-,3'- and 4'-hydroxy-Δ^9-THC, and 3-carboxy-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-ol (6).

Side chain derivatives of cannabinoids, the biologically active principals of marihuana, are of current interest both because of the recent documentation that hydroxylation[1] and oxidative cleavage[2,3] of the n-pentyl side chain are significant metabolic processes and because of the variability of biological activity with side chain structure.[1,4] The synthesis of side chain derivatives has classically been achieved by preparation and condensation of the appropriately substituted resorcinol with a monoterpene such as p-mentha-2,8-dien-1-ol.[5] However,



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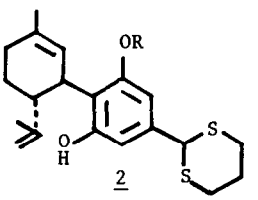

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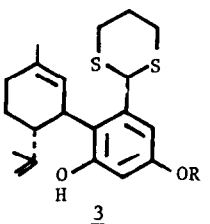

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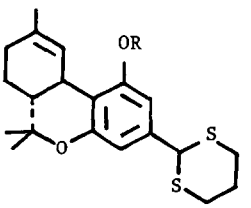

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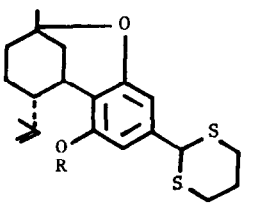

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a, R = H; b, R = t-BuMe$_2$Si

this approach is not compatible with many side chain functionalities[6], and each derivative requires an independent total synthesis with difficult chromatographic purifications.[5] Here we report a logistically superior approach involving the preparation of the 1,3-dithianyl derivative 4. This compound, by virtue of the diverse and well documented[7] chemistry of 1,3-dithian-2-yl carbanions, is a common precursor of a variety of side chain derivatized cannabinoids.

2-(3',5'Dihydroxyphenyl)-1,3-dithiane (1a) was prepared in 50-60% yield by trimethylsilylation then Vitride reduction of commercial methyl 3,5-dihydroxybenzoate to 3,5-dihydroxybenzyl alcohol,[8] Jones oxidation, and treatment of the resulting aldehyde[9] with propane-1,3-dithiol in the presence of $BF_3.Et_2O$. 1a was converted to the cannabidiol analog 2a by p-toluenesulfonic acid catalyzed condensation[5] with p-mentha-2,8-dien-1-ol in refluxing benzene and THF (10:1), the latter solvent being necessary because of the insolubility of 1a in non-polar solvents. Dehydration of the terpene to p-cymene was a major side reaction under these conditions, but was compensated for by slow addition of 3 mole equivs. of the terpene to 1a. Chromatography of the reaction products afforded 2a (20-25%), an isomer 3a (35-40%), and a compound derived from 2 moles of the terpene and one mole of 1a (10-15%). Treatment of 2a with $BF_3.Et_2O$ (1 v/v%) in CH_2Cl_2 at -15° gave the Δ^9-THC analog 4a (60%) containing ~20% of the isomer 5a.

Better results were obtained when 1a was converted to its mono-t-butyldimethylsilyl ether prior to condensation with p-mentha-2,8-dien-1-ol. Monosilylation was accomplished by either (a) treatment with 1.1 mol. equiv. of t-$BuMe_2SiCl$/imidazole in DMF[10] (60% yield) or (b) bis-silylation, then monodesilylation by titration with 20% n-Bu_4NF in THF[10] (74% yield). Condensation of the monosilyl ether with p-mentha-2,8-dien-1-ol in CH_2Cl_2 at -15° for 4 hr in the presence of $BF_3.Et_2O/MgSO_4$, according to Razdan et al.[11], afforded the cannabidiol analog 2b in 50% yield (based on 42% recovered starting material). Treatment of 2b with 1% $BF_3.Et_2O$ in CH_2Cl_2 at -20° for 48 hr gave a 1:3 mixture of 5b and 4b (54-66% yield), which could be separated by elution from florisil (1-4% ether in petroleum ether). The structure of 4b was confirmed by conversion to the dithian-2-yl carbanion with t-butyl lithium at -70°, alkylation with n-butyl bromide, reductive cleavage of the propane-1,3-dithiol residue with $Na/NH_3/Et_2O$,[12] and desilylation with fluoride ion.[10] The product (42%) was identical (^{1}H-NMR, MS, GLC, TLC) with an authentic sample of Δ^9-THC. In particular, the chemical shift of the 10a proton (3.20 δ) ruled out a cis ring juncture. Raney Ni could not be used to effect reductive cleavage of the propane-1,3-dithiol residue without concommitant reduction of the 9,10 double bond. Despite some precedent,[13,14] reductive desulfurization with $LiAlH_4$ in the presence of zinc and cupric chlorides failed, as did Wolff-Kischner conditions.

The utility of 4b is illustrated by its conversion to five previously unsynthesized compounds of pharmacological interest (CHART). 1'-Hydroxy-Δ^9-THC, a likely but as yet undetected metabolite of Δ^9-THC, was obtained as an easily separable mixture of diastereoisomers, epimeric at C-1 (Rfs, 0.58, 0.66, SiO_2, 25% acetone in CH_2Cl_2). No separations of the diasteroisomers of the metabolites 2'-3'-, or 4'-hydroxy-Δ^9-THC were observed.

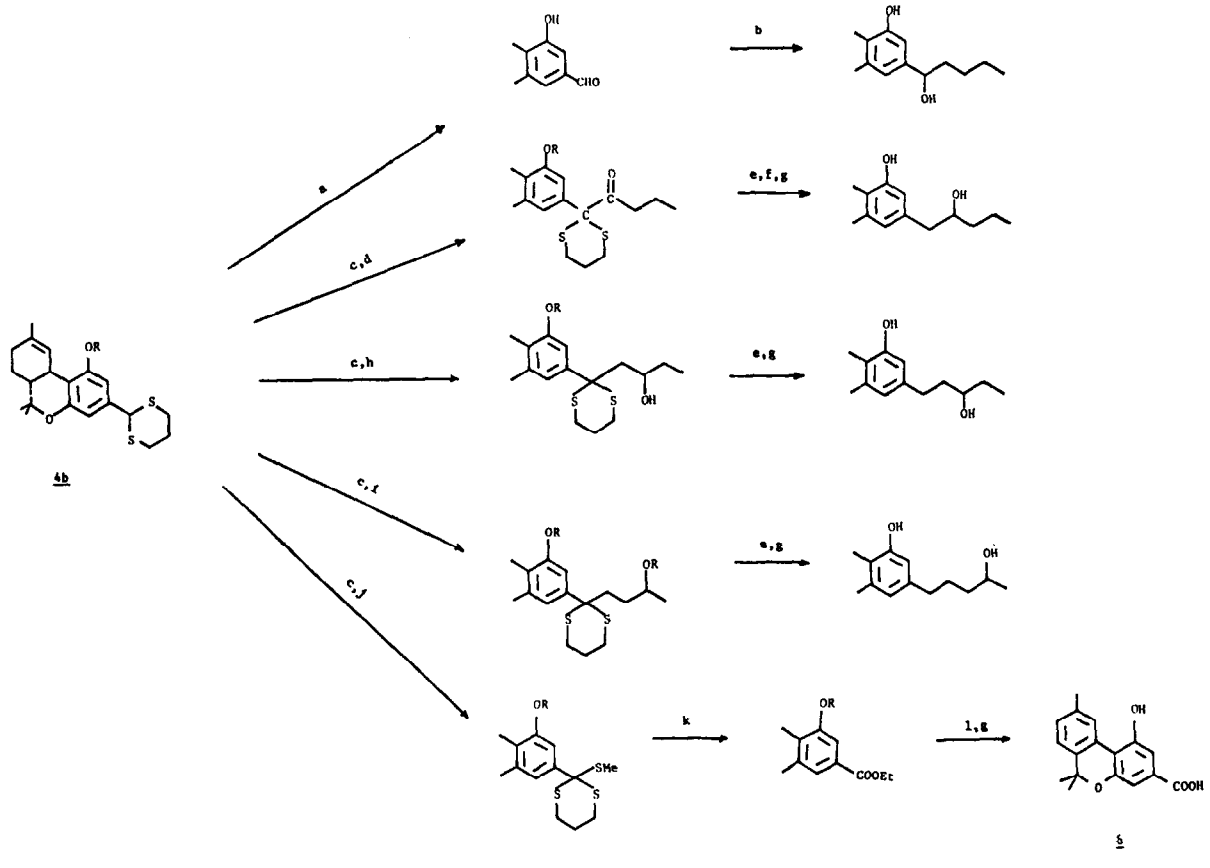

CHART: Syntheses of Side Chain Metabolites of Δ^9-THC (a = $HgO/BF_3.Et_2O$; b = n-BuLi; c = t-BuLi; d = C_3H_7COCl; e = Na/NH_3; f = $LiAlH_4$; g = Me_4NF; h = 1,2-epoxybutane; i = $BrCH_2CH_2CHMeOSiMe_2Bu$-t; j = MeSSMe; k = $HgCl_2/HgO$; l = S).

Side chain derivatives of cannabidiol obviously are accessible from 2, while the preparation of the reported[3] metabolite 6 illustrates the application to cannabinol derivatives.

Acknowledgement

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References

1. For a recent review, see S. Agurell, M. Binder, K. Fonseka, J. E. Lindgren, K. Leander, B. Martin, J. M. Nilsson, M. Nordqvist, A. Ohlsson, and M. Widman, in "Marihuana: Chemistry, Biochemistry, and Cellular Effects", G. G. Nahas, Ed., Springer-Verlag, New York, N. Y., 1976, pp 141-157.
2. B. R. Martin, D. J. Harvey, and W. D. M. Paton, J. Pharm. Pharmacol., 28, 773 (1976)
3. Z. Ben-Zvi, J. R. Bergen, S. Burstein, P. K. Sehgal, and C. Varanelli, In "Pharmacology of Marihuana," M. C. Braude and S. Szara, Ed., Raven Press, New York, N.Y., 1976, p.71.
4. For a review, see R. Mechoulam and H. Edery, in "Marihuana, Chemistry, Pharmacology, Metabolism and Clinical Effects," R. Mechoulam, Ed., Academic Press, New York, N.Y., 1973, pp 101-136.
5. (a) R. Mechoulam in Ref 4, pp 31-59; (b) R. Mechoulam, N. K. McCallum, and S. Burstein, Chem. Rev., 76, 75 (1976); (c) R. K. Razdan., Prog. Org, Chem., 8, 79 (1973).
6. For example, see K. E. Fahrenholtz, J. Org. Chem., 37, 2204 (1972).
7. D. Seebach and E. J. Corey, J. Org. Chem., 40, 231 (1975), and references therein.
8. J. E. Lightowler and H. J. Rylance, J. Pharm, Pharmacol., 15, 633 (1963).
9. E. Späth and K. Kromp, Chem. Ber., 74, 1424 (1941).
10. E. J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 94, 6190 (1972).
11. R. K. Razdan, H. C. Dalzell, and G. R. Handrick, J. Amer. Chem. Soc., 96, 5860 (1974).
12. R. E. Ireland, T. I. Wrigley, and W. G. Young, J. Amer. Chem. Soc., 80, 4604 (1958).
13. (a) T. Mukaiyama, Int. J. Sulfur Chem., B, 7, 173 (1972); (b) P. A. Stadler and P. Stültz, in "Reagents for Organic Systhesis," M. Fieser and L. F. Fieser, J. Wiley and Sons, New York, N.Y., Vol 5, p 161.
14. V. Georgian, R. Harrisson, and N. Gubisch, J. Amer. Chem. Soc., 81 5834 (1959).