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SYNTHESIS OF THE FIVE NATURAL CANNABIS SPIRANS

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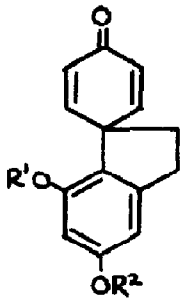
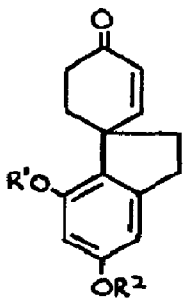
Summary: An efficient route to the O-protected spirenones (2c) and (2d) is described: from these, the five known natural spirans of cannabis, i.e. cannabispiradienone (1a), cannabispirenone-A (2a), cannabispirenone-B (2b), cannabispirone (3a) and cannabispiranol (4a), are synthesised.

Recent studies of Cannabis sativa leaf have brought to light an interesting new group of spiro-compounds which are apparently linked biogenetically to each other and to dihydrostilbenes and a dihydrophenanthrene found in the plant.[1] The spiro-compounds known are cannabispiradienone (1a)[1] cannabispirenone-A (dehydrocannabispiran) (2a),[2] cannabispirenone-B (2b)[3] cannabispirone (cannabispiran) (3a)[2] and cannabispiranol (4a).[4] Since these structures may influence the pharmacology of the botanical drug we have undertaken work in this area and now report the synthesis of all five natural



(1)



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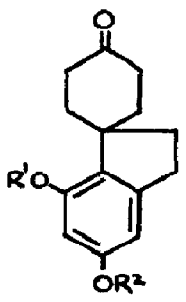

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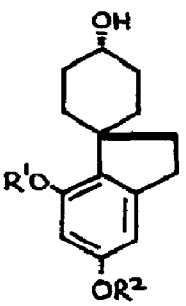
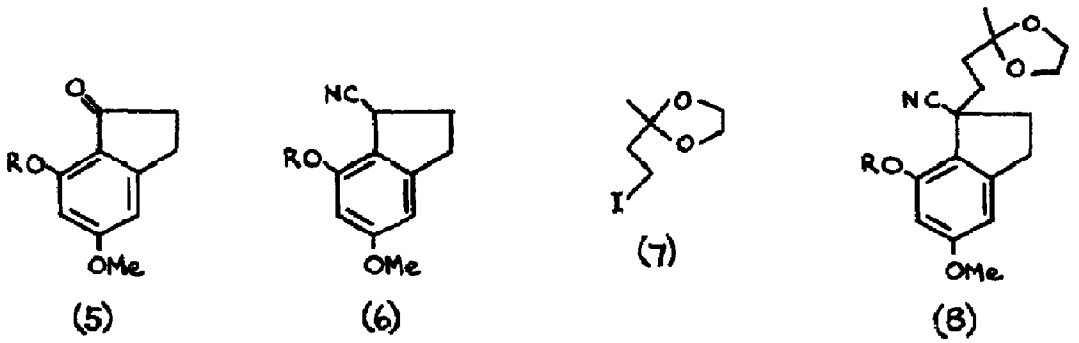


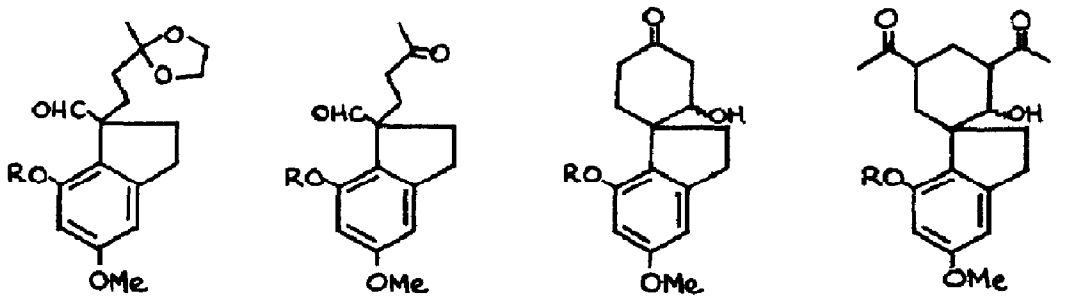
(4)

(a) $R' = H$, $R^2 = Me$ (c) $R' = R^2 = Me$

(b) $R' = Me$, $R^2 = H$ (d) $R' = MEM$, $R^2 = Me$



(5) (6) (7) (8)



(9) (10) (11) (12)

(a) R = Me ; (b) R = H ; (c) R = 

spirans. Our syntheses pivot on the dimethyl ether (2c) and the mixed methyl/methoxyethoxymethyl (MEM) ether (2d), the members of the natural sequence then being derived from these by further elaboration.

5,7-Dimethoxyindanone (5a)[5] (from polyphosphoric acid cyclisation of 3,5-dimethoxyphenylpropionic acid in 91% yield) was treated with toluene-p-sulphonylmethylisocyanide (TOSMIC)[6] (2 equiv.) and potassium t-butoxide (10 equiv.) in dimethoxyethane/t-butanol for 48 h at 20° to form the nitrile (6a), m.p. 94 - 95° (84%). The latter was treated with lithium diethylamide (1.1 equiv.)[7] in HMPA/THF at -78° for 2 h and then alkylated at -78° with the iodo-ketal (7)[8] (1.1 equiv.) for 1 h, followed by a further 1 h at 20°. This gave the nitrile (8a)(91%), m.p. 60 - 61°. Reduction with diisobutylaluminium hydride (DIBAL) in toluene at -78° formed the aldehyde (9a)(99%) (semicarbazone m.p. 219 - 220°). Treatment with 1M HCl in THF for 12 h at 20° deprotected the ketone (98%) and the resulting δ-keto-aldehyde was cyclised to O-methyl-cannabispirenone (2c), m.p. 94 - 96° from ether-hexane, (92%), on treatment with 10% KOH/MeOH at 20° for 20 h [overall yield from (5a) 68%]. Short reaction time (2 h) resulted in isolation of the aldol (11a), m.p. 125 - 127° (53%), which could be dehydrated to the enone (2c). An alternative sequence in which nitrile (6a) was reduced (DIBAL) to the corresponding aldehyde (98%),

which was then treated with potassium t-butoxide and methyl vinyl ketone at -10°, then 20° (8 h), gave (2c) and (11a) in poor yields along with some (12a) arising from double Michael addition.

Synthesis of the mixed-ether spiran (2d) utilised the finding that the 7-methoxy of the indanone (5a) could be selectively demethylated by BCl_3 in CH_2Cl_2 at 0°, then 20° (2h), to give monomethyl ether (5b)(96%), converted into the 7-MEM ether (5c) m.p. 48 - 49.5° (88%). Synthesis of (2d) from the latter then followed the above route, all yields being > 85% except for formation of the nitrile (6c) where purification difficulties reduced it to 51%. Selective dealkylation of the mixed-ether spirenone (2d) with BCl_3 (2 equiv.) in CH_2Cl_2 at -78° (1 h) gave (±)-cannabispirenone-A (2a) m.p. 172 - 173° (69%) identical (nmr, uv, tlc, glc) with the natural compound,[1,2] the major spiran of Thailand cannabis. There was no depression in mixed m.p. between the synthetic specimen and a naturally derived specimen m.p. 173 - 174°. Catalytic hydrogenation (Pd/C) of (2a) gave cannabispirone (3a) m.p. 181 - 182° (99%) and sodium borohydride reduction of the latter gave natural ß-cannabispiranol (4a),[4] m.p. 190 - 192° together with the unnatural α-epimer. Both (3a) and (4a) were identical with specimens from the plant.

Partial demethylation of the dimethyl ether (2c) (2 equiv. BBr_3/CH_2Cl_2, -78°, then 10° → 0° for 2 h) gave (±)-cannabispirenone-B (2b)(32%), m.p. 238 - 242° (decomp.) with ir, nmr and ms data in agreement with those recorded.[3,9] On the other hand, demethylation of (2a) with lithium t-butylthiolate[10] (2 h, 70° in HMPA) gave (±)-cannabispirenone-A (2a) in 85% yield and opened the way to synthesis of cannabispiradienone. Dehydrogenation (3 equiv. DDQ in dioxan, refluxed in N_2 for 48 h) of the dimethoxyenone (2c) gave the dimethoxydienone (1c) m.p. 118 - 120° (91%). Treatment with lithium t-butylthiolate as above then brought about selective 7-demethylation to give cannabispiradienone (1a) (82%), m.p. 174 - 176° (decomp.), identical spectroscopically (and mixed m.p.) with the natural product.[1,11] This completes the synthesis of all the known spirans of cannabis.[12]

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References

1. L. Crombie, W.M.L. Crombie and S.V. Jamieson, Tetrahedron Letters, 1979, 661.

2. F.S. El-Feraly, M.A. Elsohly, E.G. Boeren, C.E. Turner, T. Ottersen and A. Aasen, Tetrahedron, 1977, 33, 2373. C.A.L. Bercht, J.P.C.M. van Dongen, W. Heerma, R.J.J. Ch. Lousberg and F.J.E.M. Küpers, Tetrahedron, 1976, 32, 2939.

3. J.J. Kettenes-van den Bosch and C.A. Salemink, Recueil, J. Royal Netherlands Chem. Soc., 1978, 97, 221. J.J. Kettenes-van den Bosch, Thesis, Utrecht, December 1978.

4. E.G. Boeren, M.A. Elsohly, C.E. Turner and C.A. Salemink, Experientia 1977, 33, 848.

5. Conversion of (5a) into the aldehyde corresponding to nitrile (6a) by Darzens, Wittig and dimethylsulphoxonium methylide approaches were frustrated, apparently by enolisation of the ketone.

6. O.H. Oldenziel, D. van Leusen and A.M. van Leusen, J. Org. Chem., 1977, 42, 3114. J.R. Bull and A. Tuinman, Tetrahedron, 1975, 31, 2151.

7. Use of sodium hydride/DMSO as the base lowered the yield to 40%.

8. B.M. Trost and R.A. Kunz, J. Amer. Chem. Soc., 1975, 97, 7152.

9. There are differences in the aromatic proton resonances of cannabispirenone-A and -B: differentiation is particularly clear in the ir near 800-900, 1300-1350 and 1600 cm^{-1}: spectra (KBr) for natural (chiral) and synthetic (±)-specimens are closely similar. In the ms the base peak of the former is at m/e 189 and the latter at 216 and 173: no m.p. is given[3] for natural -B, nor is a rotation recorded.

10. G. Büchi, D. Spitzner, S. Pagliaunga and G.N. Wogan, Life Sciences, 1973, 13, 1143.

11. Our work on an alternative route using internal oxidative coupling of a suitably substituted dihydrostilbene will be reported later. Some experiments along these lines have been reported recently (F.S. El-Feraly, Y.M. Chan, M.A. El-Sohly and C.E. Turner, Experienta, 1979, 35, 1131).

12. A 4'-acetate of β-cannabispiranol ('acetyl cannabispirol') has been found in Japanese cannabis and can be made from (4a) by partial acetylation (Y. Shoyama and I. Nishioka, Chem. Pharm. Bull., 1978, 26, 3641).

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