

EXTRACTIVES OF THAILAND CANNABIS: SYNTHESIS OF CANNIPRENE
AND ISOLATION OF NEW GERANYLATED AND PRENYLATED CHRYSOERIOLS

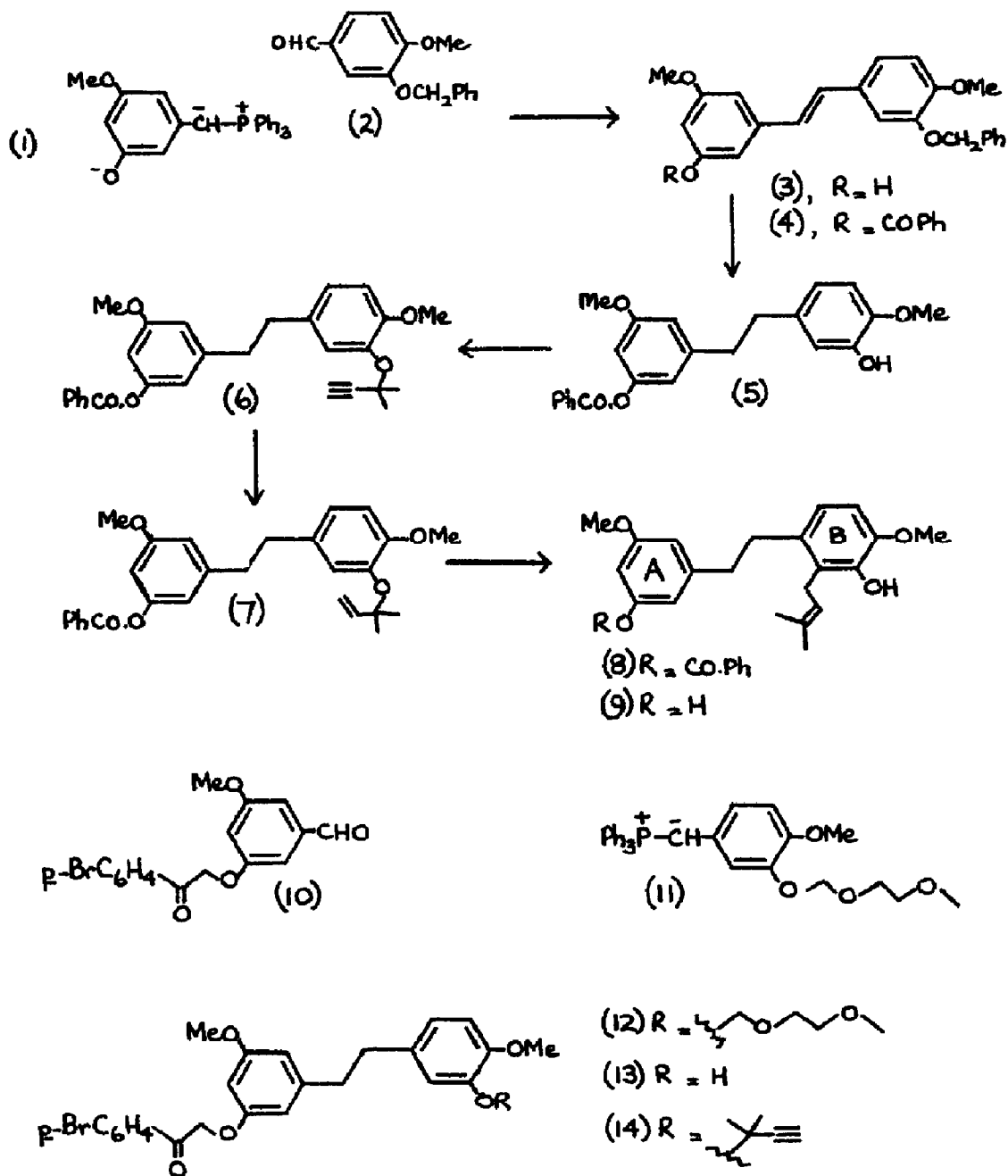
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Summary: Synthesis of canniprene (9), the major C-prenylated dihydrostilbene of cannabis, is reported. Two new geranylated (15) and prenylated (16) relatives of chrysoeriol have been isolated from Thailand-strain cannabis.

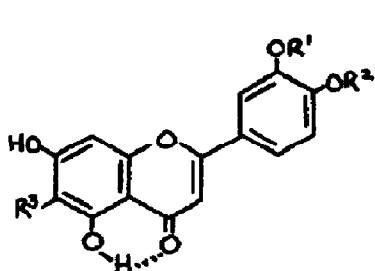
Among natural products of Cannabis sativa leaf which may influence the pharmacology of the drug, the recently discovered canniprene, a prenylated dihydrostilbene (9),¹ is of interest since its occurrence in high Δ^1 -THC-type Thailand cannabis (1.49 g/Kg in 6 week old plants by glc assay) shows it to be an appreciable component relative to Δ^1 -THC itself (cannabinoids 2.5 g/Kg, 92% Δ^1 -THC; cannabinoid acids 4.3 g/Kg, 88% Δ^1 -THC acid). We report the first synthesis of canniprene, making the compound accessible for biological work and labelling studies.

Wittig reagent (1) was prepared by treating the phenolic phosphonium salt with butyl lithium (2 mol) in THF and condensed with the benzyl-protected aldehyde (2) to give the stilbene (3) as a mixture of geometrical isomers in 73% yield. Benzoylation produced the crystalline trans-stilbene (4) m.p. 120 - 122° (71%). Catalytic hydrogenation over palladium then effected both hydrogenation and hydrogenolysis of (4) giving the partially de-protected dihydrostilbene (5) (97%). The latter, on refluxing in dry acetone with 3-chloro-3-methylbutyne, potassium carbonate, potassium iodide and 18-crown-6 for 24 h gave the dimethylpropargyl ether (6) (24%)² This ether was semi-hydrogenated over Lindlar catalyst and the dimethylallyl ether (7) was rearranged thermally at 150° to give the benzoyl derivative (8), the combined steps proceeding in 50% overall yield. Hydrolysis then yielded canniprene (9) (90%), m.p. and mixed m.p. 111.5° - 112.5°, identical in all respects with the natural material (tlc, ir, nmr).

In a different blocking-deblocking arrangement a cis-/trans-stilbene was prepared (61%) using the p-bromophenacyl protected aldehyde (10) and the methoxyethoxymethyl (MEM) protected Wittig reagent (11). Catalytic hydrogenation (10% Pd/C in ethyl acetate at 20°) however not only hydrogenated the



stilbene but unexpectedly caused substantial cleavage of the MEM grouping so that (13), m.p. 118 - 120.5°, could be isolated directly in 26% yield along with (12). Since formation of the dimethylpropargyl ether (14) proceeded poorly under a variety of conditions (e.g. 11% using the KI/K₂CO₃ procedure above), and in most cases some complicating cleavage of the p-bromophenacyl ester occurred, this protecting system was abandoned.



- (15) $R^1 = \text{Me}, R^2 = \text{H}, R^3 =$
- (16) $R^1 = \text{Me}, R^2 = \text{H}, R^3 =$
- (17) $R^1 = \text{Me}, R^2 = R^3 = \text{H}$
- (18) $R^2 = \text{Me}, R^1 = R^3 = \text{H}$

Continued investigation of the acidic fraction of Thailand cannabis from which canniprene was isolated, has led to the discovery of two new flavones, one geranylated (15), and the other prenylated (16), in ring A. The geranylated flavone (6 mg/Kg) $M^+ 436.1862$, $C_{26}H_{28}O_6$, formed pale yellow needles m.p. $185 - 186^\circ$, $\nu_{\text{max}} 1653 \text{ cm}^{-1}$. It had λ_{max} (MeOH) 242i ($\epsilon 18,750$), 276 (19,350), 344 (24,550 nm) and uv-shift studies, (NaOMe; AlCl_3 ; $\text{AlCl}_3 + \text{HCl}$; NaOAc; NaOAc + H_3BO_3) showed the presence of a chelated carbonyl, absence of two adjacent free hydroxyls, and close resemblances to chrysoeriol (17) and diosmetin (18).³ ^1Hmr data (d_6 acetone, d_6 DMSO and d_4 methanol) show ring-B to possess ortho-coupled protons, one being further meta-coupled to a single proton,⁴ thus leaving only the relative orientation of the OH and OMe in doubt. This was settled by recourse to ^{13}Cmr spectra:⁵ C-2' resonated at $\delta 111.3$ and C-5' at 116.6 [compare chrysoeriol (17) C-2' 110.2, C-5' 115.8 diosmetin (18) C-2' 113.1, C-5' 112.1 and similar models].⁶ ^1H and ^{13}Cmr as well as ms data confirm a geranyl side-chain attached to phloroglucinol ring A. It is placed at C-6 since C-8 (OR-doublet) resonates at $\delta 94.0$ (models show C-8: 94-95; C-6: 98-99),⁶ leading to the complete structure (15).

Except for the presence of prenyl signals in place of geranyl, the second flavone, $M^+ 368.1282$, $C_{21}H_{20}O_6$, pale yellow needles (0.8 mg/Kg), m.p. $230 - 231^\circ$ has ir, uv, ^1Hmr (d_6 acetone and d_6 DMSO) and ms data which exactly parallel those of (15):⁷ it is clearly the lower prenylogue (16).

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References

1. L. Crombie and W.M.L. Crombie, Tetrahedron Letters, 1978, 4711; J.J. Kettenes-vanden Bosch, Thesis, Utrecht, December 1978.
2. The limited yield in the O-alkylation reaction appears to be due to steric effects. See R.D.H. Murray, M.M. Ballantine and K.P. Mathai, Tetrahedron, 1971, 27, 1247 and J. Hlubucek, E. Ritchie and W.C. Taylor, Aust.J. Chem., 1971, 24, 2355 for this approach to C-prenylation.

3. T.J. Mabry, K.R. Markham and M.B. Thomas, "The Systematic Identification of Flavanoids", Springer Verlag, New York, 1970.
 4. Three solvent systems were required to extract complete data: the doublet of the 6'-meta- and ortho-coupled proton is best seen in CD₃OD.
 5. ¹³Cmr (DMSO): 182.4s (C-4), 164.1s (C-2), 162.7s (C-9), 159.1s (C-7), 155.8s (C-5), 151.5s (C-3'), 148.8s (C-4'), 134.7s (C-3"), 131.1s (C-7"), 124.8d (C-6"), 122.9d (C-2"), 122.5s (C-1'), 121.0d (C-6'), 116.6d (C-5'), 111.8s (C-6), 111.3d (C-2'), 104.2s (C-10), 103.9d (C-3), 94.0 (C-8), 56.8q (OCH₃), 39.8t (C-4"), 26.9t (C-5"), 25.9q (C-8"), 21.6t (C-1"), 18.1q (C-9"), 16.6q (C-10").
 6. Inter alia H. Wagner, V.M. Chari and J. Sonnenbichler, Tetrahedron Letters, 1976, 1799; V.M. Chari, S. Ahmad and B.-G. Österdahl, Z. Naturforsch., 1978, 33b, 1547.
 7. For geranyl-flavone (15), ¹Hmr (d₆ acetone): δ 13.33s, 1H (D₂O exch.), (chelated OH); ~9.5 - 8.0 br, 2H (D₂O exch.), (2OH); 7.65 - 7.55 m, 2H, (2' and 6'H); 7.01d, J 8.3 Hz, 1H, (5'H); 6.71s, 1H and 6.63s, 1H, (3 and 8H); 5.31t, J 7 Hz, 1H (2"H); 5.08t, J 7 Hz, 1H, (6"H); 4.00s, 3H, (OMe); 3.38d, J 7.3 Hz, 2H, (1"-H's); ~1.95 m (obscured by acetone) (4" and 5"H); 1.81s, 3H (10" Me); 1.61s, 3H and 1.56s, 3H (8" and 9" Me).
- For prenyl-flavone (16), ¹Hmr (d₆ acetone): δ 13.28s, 1H (D₂O exch.), (chelated OH); ~9.5 - 8.0 br, 2H (D₂O exch.) (2OH); 7.65 - 7.55 m, 2H, (2' and 6'H); 7.00d, J 8 Hz, 1H (5'H); 6.68s, 1H and 6.62s, 1H (3 and 8H); 5.28t, J 7 Hz, 1H (2"H); 3.99s, 3H (OMe); 3.36d, J 7 Hz, 2H (1"-H's); 1.79s, 3H and 1.65s, 3H, (4" and 5" Me).

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