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TOTAL SYNTHESIS OF (±)-ISOPETASOL, (±)-3-EPIISOPETASOL, AND (±)-WARBURGIADION

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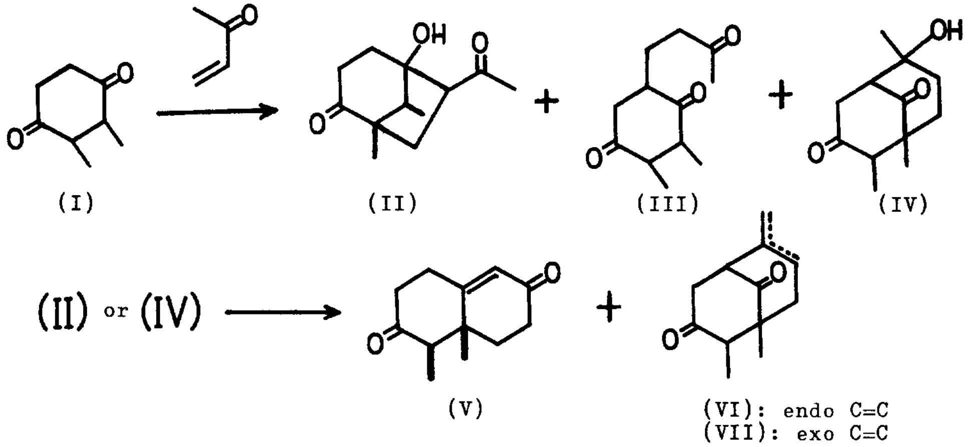
The eremophilane type sesquiterpenes are characeterised by a carbon framework which does not obey the well known isoprene rule. There are interesting aspects of the eremophilanes from a synthetic standpoint, namely the vicinal cis-dimethyl substituents on the hydronaphthalene framework.

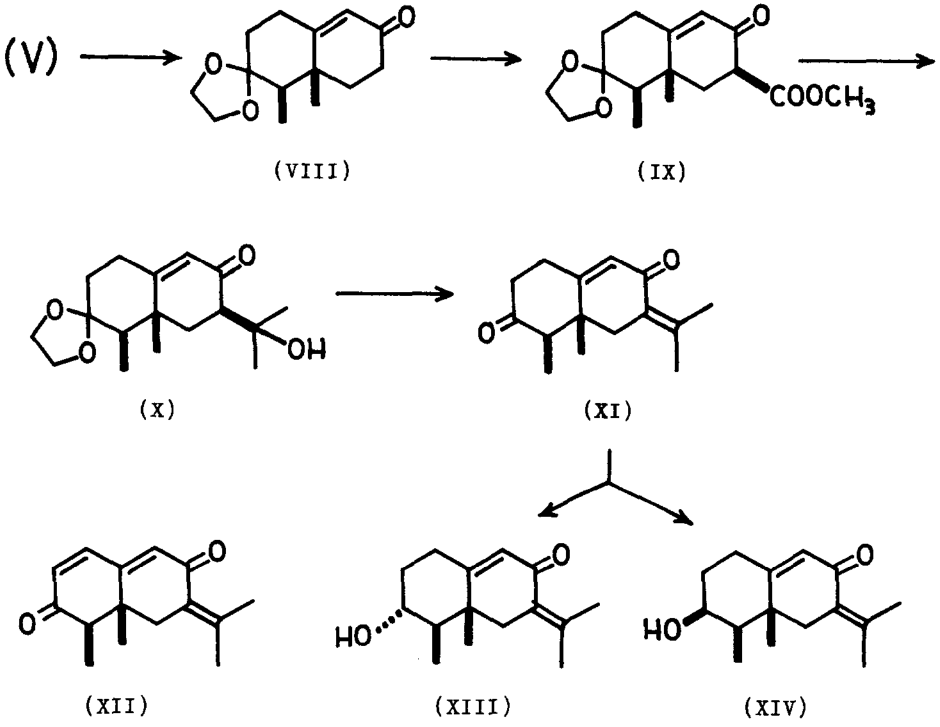
We will report the total synthesis of (±)-isopetasol, isolated from Petasites officinalis[1,2] and P. japonicus Maxim,[3] (compositae), and (±)-3-epiisopetasol, and (±)-warburgiadion, isolated from Warburgia ugandensis Sprague (canellaceae).

The bicyclic key intermediate (V) was prepared by the Robinson annelation reaction of 2,3-dimethylcyclohexane-1,4-dione (I) with methyl vinyl ketone in the presence of sodium ethoxide at -20° for 98 hr. The reaction products were chromatographed to give three intermediates; 7-acetyl-5,8-dimethyl-4-oxo-bicyclo-[3.2.1]octane-1-ol (II), m.p. 145-146° [i.r. cm^{-1}: 3400 (OH), 1705 and 1690 (C=O); n.m.r. δ: 0.82 (d, J=7.5 Hz; 3H), 1.03 (s; 3H), 2.24 (s; 3H), and 3.35 (s; 1H)], 2,3-dimethyl-6-(3'-oxobutyl)cyclohexane-1,4-dione (III), m.p. 92-94° [i.r. cm^{-1}: 1710 (C=O); n.m.r. δ: 1.15 (d, J=7.0 Hz; 6H), 2.12 (s; 3H)], and 4,5,8-trimethyl-3,9-dioxo-bicyclo[3.3.1]nonane-8-ol (IV), m.p. 163-165° [i.r. cm^{-1}: 3420 (OH), 1710 (C=O); n.m.r. δ: 1.11 (s; 3H), 1.14 (d, J=7.5 Hz; 3H), 1.37 (s; 3H), and 2.12 (s; 1H)]. Treatment of (II) and (IV) with p-toluene sulfonic acid in refluxing benzene for 20 hr gave the enone (V), m.p. 101-103° (63% yield) [i.r. cm^{-1}: 1710 and 1680 (C=O), 1630 (C=C); n.m.r. δ: 1.04 (d, J=7.5 Hz; C_4-CH_3), 1.07 (s; C_5-CH_3), and 5.87 (s; C_9-H)] which may possess cis-dimethyl, together with a mixture of olefines (VI) and (VII) (10-15% yield), respectively.



Enone (V) and a mole of ethylene glycol in benzene containing a catalytic amounts of p-toluene sulfonic acid were refluxed for 20 hr and a mono-ketal (VIII), m.p. 80-83° was obtained. Reaction of (VIII) with dimethylcarbonate in the presence of sodium hydride in abs. dioxane gave an enone ester (IX), m.p. 158-160°, in quantitative yield. The methoxycarbonyl substituent possess equatorial (7β) orientation, which showed at δ 3.50 (C_7-H; dd, J=6.3 and 11.3 Hz) in their n.m.r. spectrum. Treatment of (IX) with an excess of ethereal methyl lithium in the presence of sodium hydride afforded enone alcohol (X), m.p. 91-92°. Dehydration and deketalisation of (X) by treatment with 1% hydrochloric acid in refluxing methanol produced a keto-isopropyridene derivative (XI), m.p. 110-112° [i.r. cm^{-1}: 1720 and 1680 (C=O), 1640 and 1630 (C=C); n.m.r. δ: 0.96 (s; C_5-CH_3), 1.08 (d, J=7.5 Hz; C_4-CH_3), 1.85 and 2.13 (s; $=\!<^{CH_3}_{CH_3}$), and 5.92 (s; C_9-H)]. The n.m.r. data of our synthetic (XI) was in agreement with that for natural isopetasone as reported by Brooks and Draffan[4] and Kurihara *et al.*[5] Brooks and Draffan[4] have reported the conversion of natural isopetasone into (+)-warburgiadion (XII), isolated from the heatwood of *Warburgia ugandensis* Sprague (Canellaceae), by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone in dioxane. Therefore, our synthesis of (XI) constitutes a formal total synthesis of (±)-warburgiadion.

Reduction of (XI) with sodium borohydride gave (±)-isopetasol (XIII), m.p. 105-106° [i.r. cm^{-1}: 3450 (OH), 1670 (C=O), and 1635 (C=C); u.v. nm: λ_{max}^{EtOH} 247 (ε 12,000) and 279 (ε 7,200); n.m.r. δ: 0.98 (s; C_5-CH_3), 1.10 (d, J=7.5 Hz; C_4-CH_3), 1.85 and 2.10 (s; $=\!<^{CH_3}_{CH_3}$), 3.58 (m, W1/2=25 Hz; C_3-H), and 5.78 (s; C_9-H)] and (±)-3-epiisopetasol (XIV), m.p. 109-110° [i.r. cm^{-1}: 3450 (OH), 1660 (C=O), 1630 and 1610 (C=C); u.v. nm: λ_{max}^{EtOH} 248 (ε 11,200) and 279 (ε 7,000); n.m.r. δ: 1.13 (d, J=7.5 Hz; C_4-CH_3), 1.18 (s; C_5-CH_3), 1.85 and 2.10 (s; $= ^{CH_3}_{CH_3}$), 3.95 (m; C_3-H), and 5.80 (s; C_9-H)] in the ratio of 1:5. I.r., u.v., n.m.r. spectra and gas and thin-layer chromatographic data confirmed the identity of the synthetic compound (XIII) with natural (+)-isopetasol which was isolated from *Petasites japonicus* Maxim by Naya and his coworkers.[3] The stereoformula of the alcohol (XIV) was also confirmed to be (±)-3-epiisopetasol by it's physico-chemical data.



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