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RHODIUM CATALYSED [2+2+2] CYCLOADDITIONS- AN EFFICIENT REGIOSPECIFIC ROUTE TO CALOMELANOLACTONE

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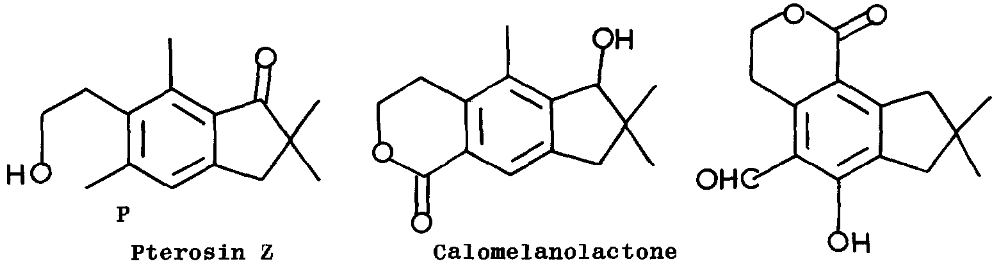
Abstract: A short regiospecific synthesis of calomelanolactone has been devised in which the key step is a [2+2+2] cycloaddition.

The illudalane class of sesquiterpenes[1] includes the pterosins[2], il-ludalic acid[3] and calomelanolactone[4] (Scheme1).



Pterosin Z

Calomelanolactone

Illudalic acid

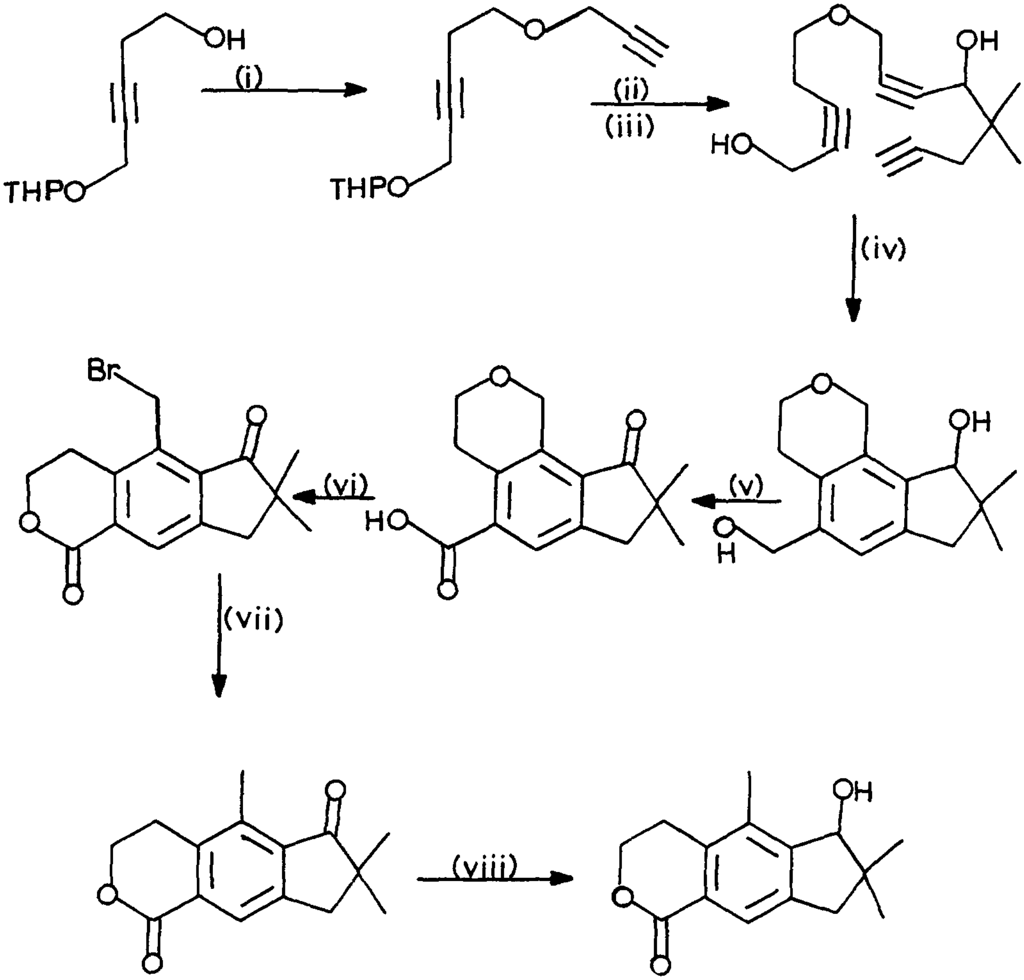
Scheme1

A major obstacle to the synthesis of these compounds is the problem of regioselective construction of the penta- and hexa- substituted aromatic rings. To date synthetic approaches have relied heavily on classical electrophilic substitution reactions with their inherent problems of regio-control[5].

We now report a short efficient route to calomelanolactone using an intra-molecular rhodium catalysed [2+2+2] cycloaddition[6] as the key step (Scheme2). The methodology is clearly applicable to the other illudalane sesquiterpenes.

The mono protected diol (1) was first converted to it's proparygl ether by conventional means. Condensation of the lithium acetylide of (2) with 2,2-dimethyl-4-pentynal at -78°C in THF then give after removal of the protecting group, the tri-acetylene (3) in (92%) overall yield. The key step in the scheme is intramolecular trimerisation of the tri-acetylene (3). Hence treatment of a 0.1M solution of (3) with 2 mol% Wilkinsons catalyst in ethanol at 25°C for 12hr under a nitrogen atmosphere gave the tricyclic aromatic compound (4, 86%). The conditions are exceedingly mild and the cyclisation is completely regiospecific.

Oxidation with Jones reagent followed by regiospecific ring opening of the cyclic benzylic ether (5)[8] gave the bromolactone (6, 75%, m.p.175°C). Reduction with tri-butyl tin hydride gave an oxidation product of calomelanolactone (54% from 4) whose physical data matched those given by Bardonille[4]. Sodium borohydride reduction of (7) gave calomelanolactone in (83%) yield. The route is short, efficient and regio-specific and could easily be modified to give other illudalanes



Reagents (i) NaOH, propargyl bromide, THF, 60°C, (ii) Bu^{n}Li, then 2,2-dimethyl-4-pentynal, (iii)MeOH, PTSA, (iv) 2 mol % $RhCl(PPh_3)_3$, EtOH, 12h 25°C, (v)Jones Reagent, (vi) BBr_3, CH_2Cl_2, 3h 35°, (vii)Bu_3SnH, AIBN, benzene. (viii) sodium borohydride.

Scheme 2

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