



Significance: Isolated from the shrub *Piper arborens*, the piperarborenines display in vitro cytotoxicity against cancer cell lines (P-388, HT-29 and A549). The piperarborenines feature a central cyclobutane core appended with both aromatic and imide groups.

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Comment: Key to the synthesis of the proposed structure of piperarborenine D was the sequential C–H-activated arylation of a cyclobutane core (**E** → **G** and **H** → **J**). However, it was found that the true identity of piperarborenine D was that of a head-to-head [2+2] cycloaddition.