



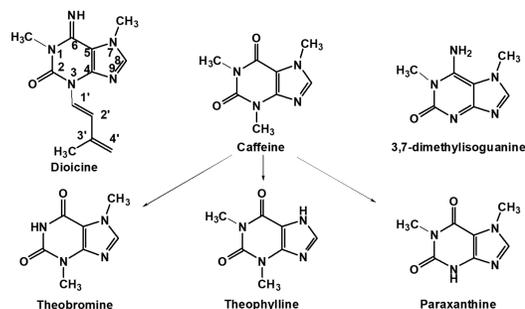
A Chan-Lam Route to Dioicene Analogs

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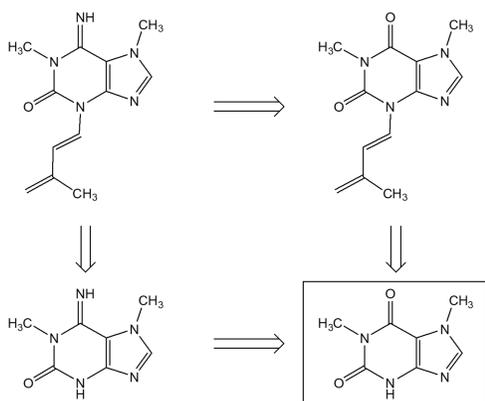
Kentucky Coffeetree

The Kentucky coffeetree, *Gymnocladus dioica* (L. Koch) is a deciduous dioecious tree native to the central US. The trees have large (up to 1 m) bipinnately compound leaves that produce a novel alkaloid, dioicene. It is a novel prenylated purine alkaloid. The dioicene can be acid hydrolyzed to 3,7-dimethylisoguanine and may be further hydrolyzable to 3,7-dimethylxanthine (paraxanthine). Paraxanthine is the major metabolite of caffeine in man. The main isomer that is obtained from the leaves is the *E*-isomer, only trace quantities of the *Z*-isomer are evident.



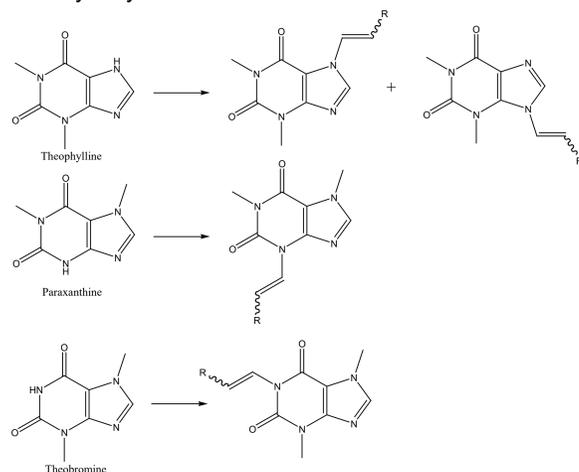
Retrosynthetic Analysis

Dioicene can be traced back to paraxanthine as a commercially available precursor. Only two transformations are required; replacement of a carbonyl oxygen by nitrogen and installation of the prenyl side chain. These may be performed in either order going through the dienyloxanthine or the dimethylisoguanine as shown below.



Xanthine Analogs

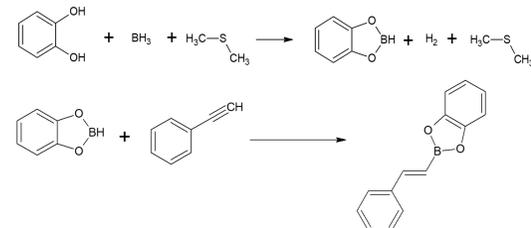
In addition to preparing dioicene, we wish to prepare a variety of analogs in order to identify structure-activity relationships and identify the pharmacophore. Thus we are looking at derivatives that place the labile N-vinyl side chain on any of the four nitrogens and to vary the structure of the side chain in a systematic way. Three dimethylxanthines are commercially available; theobromine, theophylline and paraxanthine. Of these the latter is the most expensive and so we chose to use the two former compounds as models since they vary in the nature of the aromatic N-H.



Forming the C-N bond from the NH bond can be done using either oxidative coupling (Chan-Lam) or by Buchwald Hartwig cross-coupling. The former requires vinylborates and Cu catalysis while the latter reverses polarity and uses vinyl iodides and Pd catalysis. Both vinyl iodides and boronates can be obtained through hydroboration of alkynes with catecholborane.

Hydroboration

To produce synthetic Dioicene, we first had to prepare our boronate for the reaction. This involves the preparation of catechol borane and the hydroboration of phenylacetylene.

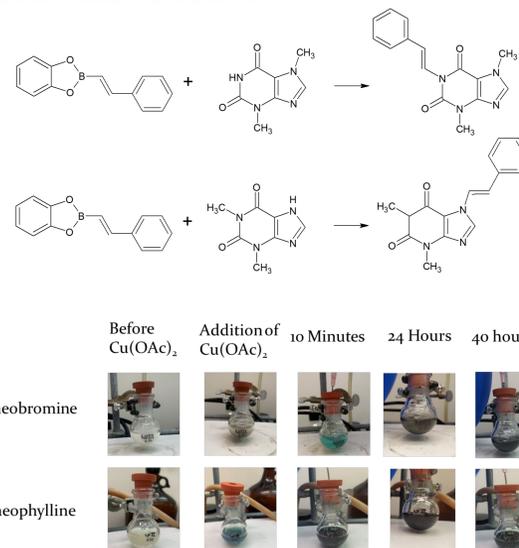


We performed the reaction using using borane-methyl sulfide and catechol, followed by addition of the alkyne in situ, affording the desired product in 49% distilled yield.



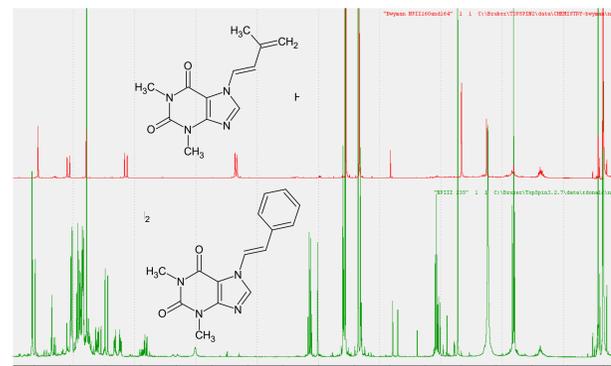
Chan-Lam

The first approach chosen to install side chains was the Chan-Lam reaction. Our reactions were carried out using analogs including theobromine and theophylline. These analogs are less expensive and were effective enough for the results we were looking to obtain. Likewise, we used the styryl boronate derived from phenylacetylene as an inexpensive model compound for the natural side chain of dioicene. Dry boronate, potassium carbonate, and xanthine were added to round bottom flasks, pumped, purged and placed under an oxygen balloon. DMF solvent was added and the mixture was stirred. Finally cupric acetate was added to initiate the reaction.



NMR Analysis

To analyze the product from our Chan-Lam reaction, we took an NMR and compared that to material obtained by a previous student. We can see the product but the yield is quite low and the isolated material has a good deal of solvent remaining.



Conclusion

The study was focused on the installation of side chains on xanthines with styryl as a model for the natural methylbutadienyl side chain. The Chan-Lam reaction is an inexpensive method for forming these analogs. However, the yields were very low and significant optimization is needed.

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