Synthesis of nitrogen analogues of bioactive lignans

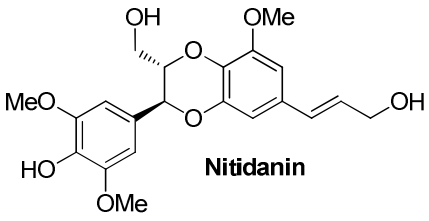
Eunkyung Jung, David Barker

University of Auckland, Auckland, New Zealand

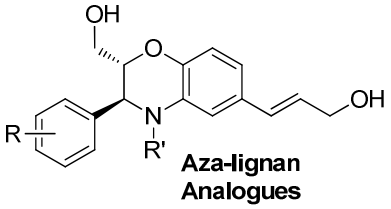
1,4-Benzodioxane neolignans are natural products that are a subclass within the lignan family that exhibit remarkable biological effects, including antimicrobial, hepaprotective and cytotoxic activities. In particular, 1,4-benzodioxane lignans with a 9-hydroxymethyl group such as silybin A, one of the components of silymarin (milk thistle extract), have shown inhibitory activity against hepatotoxicants. Nitidanin isolated from Santalum album is an antimalarial agent.

Previous work in our group has developed an enantioselective and flexible synthetic method to produce 1,4-benzodioxanes lignans such as eusiderin and isoamericanin. We now report our efforts to synthesise nitrogen analogues of 1,4-benzodioxane lignans. The synthetic strategy is to convert the 1,4-benzodioxane skeleton into a benzomorpholine. The added nitrogen will allow an additional site for substitution which could allow bio-conjugation and also increase solubility.

We report our synthetic approach towards aza-lignans involving Mitsunobu reaction of an enantiopure secondary alcohol and an amino protected phenol, giving chirally pure aryl ethers which are converted into a benzomorpholine aminol. The N-Boc and O-Bn aminol was then subjected to N-acyliminium aryl addition, under acid condition. Aryl nucleophiles that are found in natural products were added to give a range of aryl benzomorpholine. Functionalization of the aryl bromide in these aryl benzomorpholines allows addition of the side chain.



Nitidanin



Aza-lignan Analogues