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Cyanocuprate-Mediated Intramolecular Biaryl Couplings Applied to an Ellagitannin. Synthesis of (+)-O-Permethyltellimagrandin II

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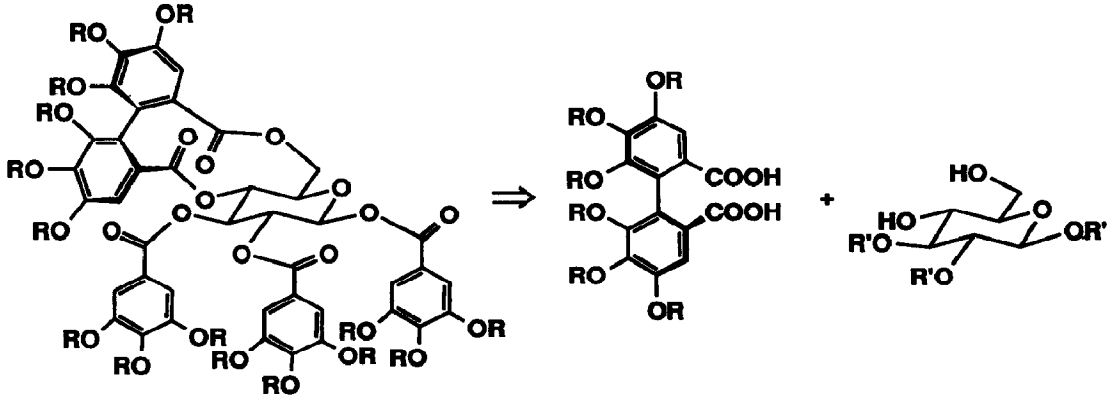
Summary. *Generation of an intramolecularly tethered, nonracemic diaryl cuprate followed by its oxidation with ground state oxygen at -78° leads to a biaryl precursor to an ellagitannin. Subsequent attachment of the appropriate glucose unit completes the synthesis of the title compound.*

Construction of axially chiral, nonracemic biaryls which proceed by way of cyanocuprate intermediates have recently been disclosed.[1] The key to controlling the directionality of these couplings lies in the proper choice of tether, which must (1) join the individual aryl subunits efficiently; (2) allow for cuprate generation and exert 100% stereocontrol in the reductive elimination step; and (3) undergo facile and high yield removal. With these considerations in mind, our attention turned to tellimagrandin II (**1a**),[2] one of several known ellagitannins.[3] As a group, these natural products display a variety of biological activities, most noteworthy being their inhibitory properties associated with both DNA topoisomerases I and II[4] as well as HIV reverse transcriptase.[5] We now describe a very short, highly efficient synthesis of (+)-tellimagrandin II in its O-permethylated form (*i.e.*, **1b**).[6]

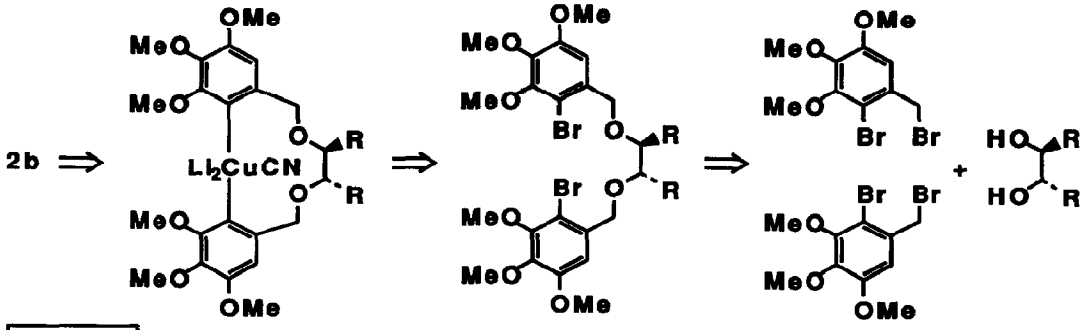


1a, R = H (tellimagrandin II)
1b, R = Me

2a, R = H
2b, R = Me

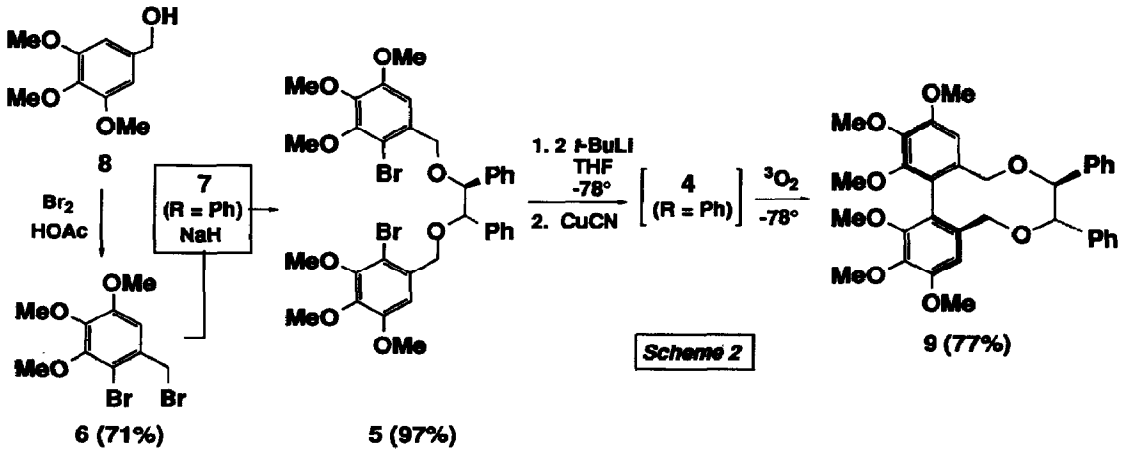
3a, R' = H
3b, R' = galloyl

The required S-biaryl diacid **2b** was anticipated to derive from the oxidation of diarylcuprate **4**, this organometallic being prepared (*vide infra*)[7] from an aryl bromide precursor **5**. Cuprate forerunner **5**, in turn, should result from a straightforward double displacement on benzylic bromide **6** using a readily available, stereopure diol **7**.



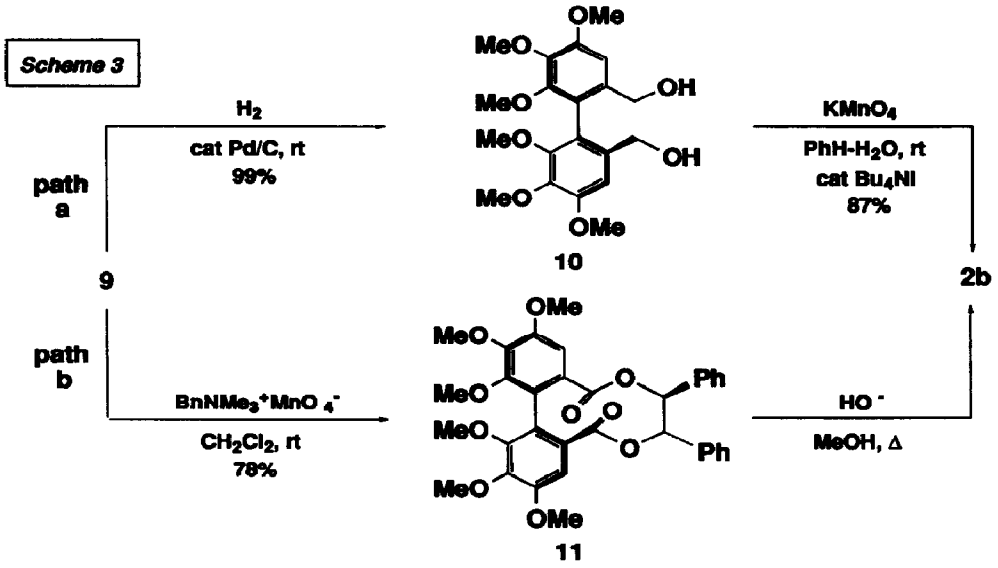
Scheme 1

Starting with commercially available alcohol **8**, treatment with Br_2/HOAc leads to dibromide **6** in 71% yield (Scheme 2). Prior exposure of S,S-stilbene diol **7** (R = Ph)[8] to 2 equivalents of NaH in THF followed by introduction of **6** affords the tethered product **5** (97%, R = Ph). Dilithiation of **5** using 1 equivalent of *t*-BuLi per aryl bromide in THF at -78° sets the stage for addition of CuCN (1 equiv), presumably leading to the higher order species **4** (R = Ph). After stirring at this temperature for 30 minutes, dry molecular oxygen is vigorously bubbled through the solution for 1 hour.[9] The resulting dark mixture is then worked up in the usual way to give **9** in 77% isolated yield, which by 500 MHz NMR analysis is a single diastereomer. Performing this coupling at 0° leads to a 93:7 ratio of isomers.

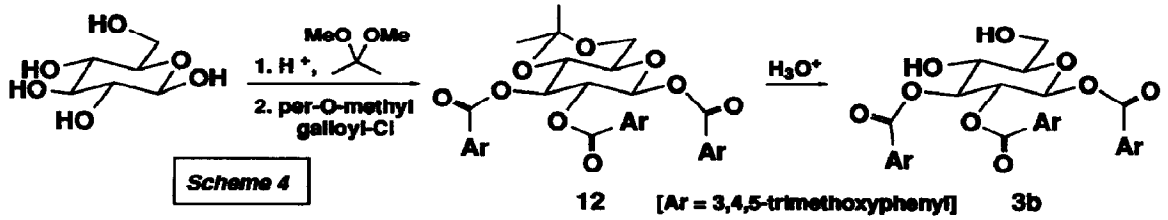


Scheme 2

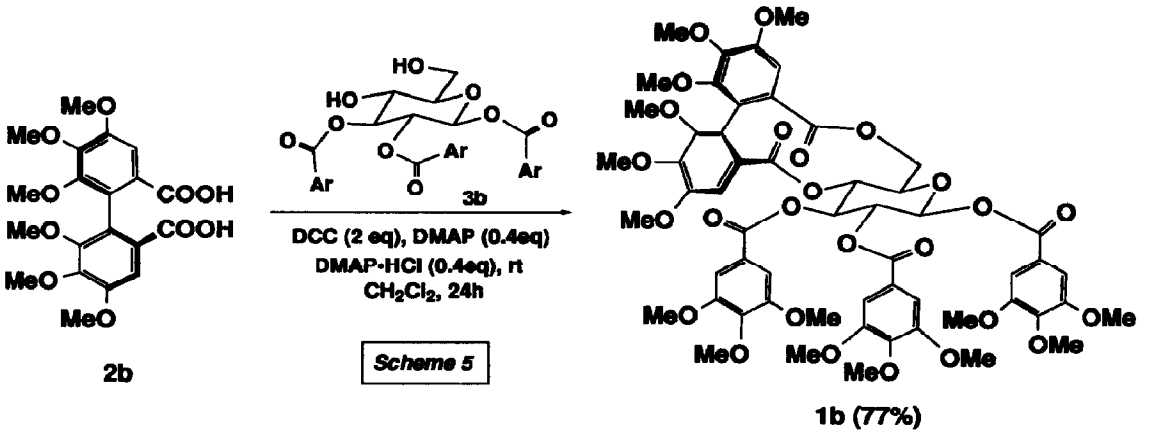
Removal of the tether could be accomplished in virtually quantitative yield *via* catalytic hydrogeneration over Pd/C in MeOH to afford diol **10** (Scheme 3).[10] Double benzylic oxidation with $KMnO_4$ in benzene provided the known diacid **2b**.[6b,11] While **9** could also be oxidized in good yield to diolide **11** using Schäfers' soluble permanganate,[12] this reaction took over one week to consume educt with several equivalents of reagent being added along the way. Nonetheless, the strength of this latter sequence lies in the opportunity to recover the original tether intact (quantitatively). Given the availability of tether **7**, R = Ph, however, path (a) in Scheme 3 is the preferred route.



The synthesis concludes with the attachment of glucose derivative **3b** to diacid **2b**. The sugar **3b** derives originally from β-D-glucose, which in its 4,6-acetonide protected form, reacts with galloyl chloride to give triester **12**. Mild aqueous acid hydrolysis arrives at **3b**. Coupling of **3b** with **2b** under the influence of DCC and DMAP[13] afforded the desired tellimagrandin II derivative **1b** in 42% isolated yield. The yield could be dramatically improved to 77% using the Keck modification[14] of this Steglich esterification; that is, by simply adding an equal quantity of DMAP•HCl under otherwise identical conditions (Scheme 5).



In conclusion, a 6 step synthesis of (+)-tellimagrandin II in per-O-methylated form has been developed. The route (*via* path a in Scheme 3), which proceeds in 35% overall yield and produces material of high optical purity, demonstrates our intramolecular biaryl coupling strategy. Further examples of this methodology will be reported in due course.



Scheme 5

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