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Stereoselective synthesis of peracetylated (-)-gloeosporiol *via* acid catalysed intramolecular etherification

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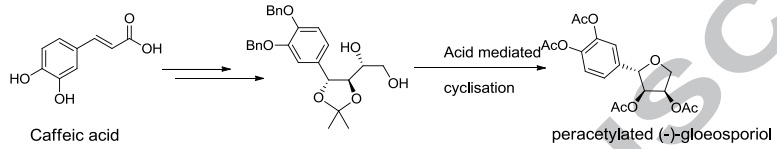

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Stereoselective synthesis of peracetylated (-)-gloeosporiol *via* acid catalysed intramolecular etherification

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ABSTRACT

A simple and an efficient strategy have been developed for the stereoselective synthesis of peracetylated (-)-gloeosporiol by acid catalysed cyclisation from the commercially available starting materials.

Introduction:

Natural *C*-nucleosides and their synthetic analogs constitute an important class of organic compounds and shows significant therapeutic properties such as antiviral, antitumor and anticancer activities[1]. Several naturally occurring ribofuranosyl *C*-nucleosides, such as showdomycin, pseudouridine, pyrazomycin and formycin are showing interesting antibiotic and antitumor activities.[2-5] Among the *C*-nucleosides, the aryl-nucleosides have attracted more attention in studying DNA-DNA and DNA-protein interactions.[6] The *C*-aryl-nucleosides which have been designed are incorporated as base surrogates into DNA to study base stacking interactions,[7] to enable new base pairing modes,[8,9] and also to find out the reaction mechanisms of DNA-polymerases[10] and DNA-repair enzymes.[11] The interesting biological activity of these *C*-nucleosides has prompted organic chemists to design and synthesize non-natural *C*-nucleosides to study the structure-activity relationships.

Especially 2-aryl tetrahydrofuran system is present in some important biologically active compounds of both natural & synthetic origin. For example altholactone **1,** isoaltholactone **2,** 1-deoxy-1-phenyl-b-D-ribo furanose **3,** 1-deoxy-1'-(3,4-dihydroxyphenyl)-b-D-ribofuranose **4,** magnones **5,** virgatusin **6,** goniothalesdiol **7** and gloeosporiol **8** belongs to this unique class. In specific, the 3,4-dihydroxy tetrahydrofuran with C-2 aryl group may be an important factor for the interesting activity of above compounds.[12]

In 2006 Collado *et al.*[13b] isolated tetrahydrofuran ring contain natural product (-)-gloeosporiol **8** as a peracetylated derivative **9** from a culture of the fungus *Colletotrichum gloeosporioides* which shows great radical scavenging activity. To the best of our knowledge so far a couple of synthesis for this molecule is reported in the literature[13], where they carried resolution to get the optically active isomer.

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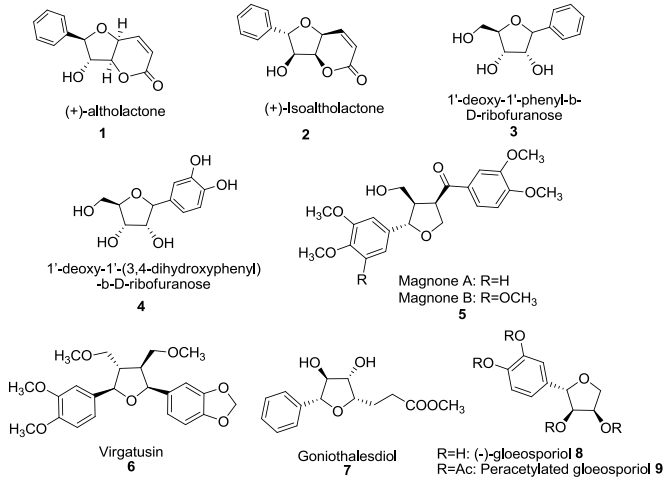
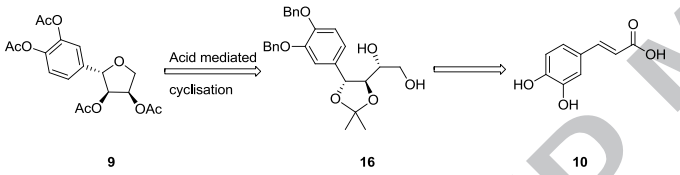


Figure.1 Some aryl C-nucleosides

With these considerations, as well as in continuation of our interest in the synthesis of natural and natural product like molecules, herein we disclose a flexible synthetic route to peracetylated (-)-gloeosporiol **9** which involves the construction of tetrahydrofuran ring using acid mediated cyclisation.



Scheme 1: Retro synthetic analysis

Our retro synthetic analysis of the target molecule is outlined in Scheme **1.** As indicated we envisaged that peracetyl derivative of (-)-gloeosporiol **9** could be synthesized by acid mediated cyclisation of compound **16.** The requisite poly hydroxy aryl derivative inturn, can be accessed from commercially available caffeic acid **10** by simple transformations.

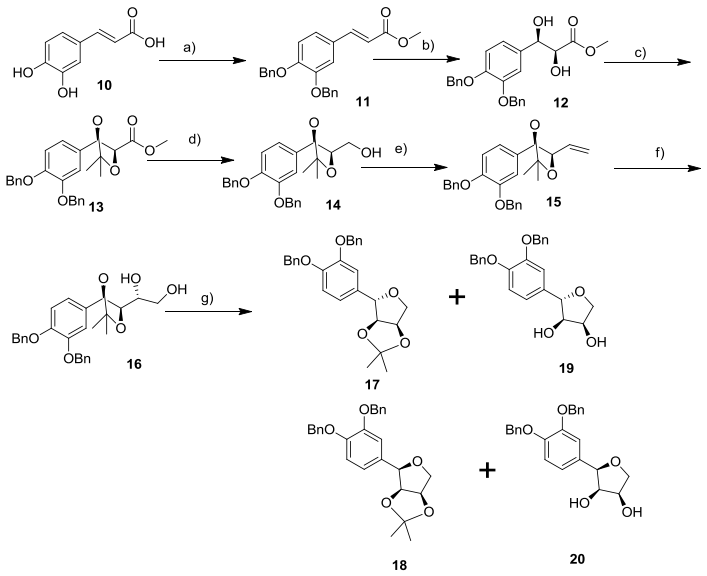
Our synthetic endeavor commenced with simple esterification of the acid group in caffeic acid **10** and protection of the two phenoxy groups as benzyl ethers using benzyl bromide & K_2CO_3 to get compound **11** in 95% yield. The compound **11** was subjected to asymmetric dihydroxylation[14] with AD-mix-β & methane sulfonamide to get selectively the β-dihydroxy compound **12**. Subsequently, the resulting two hydroxy groups were protected as acetonide by treatment with acetone & 2,2-dimethoxypropane in presence of catalytic amount of acid to give compound **13** in 90% yield. The ester functionality in compound **13** was easily reduced with lithium aluminium hydride (LAH) to afford the compound **14** in good yield. The primary alcohol in compound **14** was oxidized under Swern conditions to give aldehyde. The crude aldehyde was then directly used for Wittig reaction to give compound **15**. The olefin compound **15** was subjected to catalytic dihydroxylation with OsO_4 and gave exclusively *anti* diol compound **16.**

Table 1: Cyclisation studies on compound **16** with different Lewis acids.

S.No.	Lewis acid (LA) (10 mol%)	Ratio[a] 17/18	Ratio[a] 19/20	Yield %
1	$Sc(OTf)_3$	4:1	--	90
2	$Yb(OTf)_3$	4:1	--	90
3	$BF_3.Et_2O$	4:1	--	78
4	TMSOTf	4:1	--	80
5	TFA	--	4:1	85
6	$SnCl_4.5H_2O$	--	4:1	90
7	$CuCl_2.2H_2O$	--	--	0
8	*p*-TSA	--	--	0

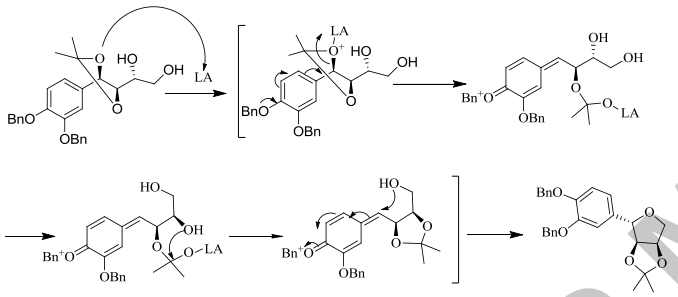
[a] Ratios was calculated based on the isolated yields

Next, our plan was to construct the 2-aryltetrahydrofuran ring from diol **16**. For this purpose compound **16** was subjected to different acids. This reaction afforded two sets of cyclised products **17 & 18** and **19 & 20** as summarized in table 1. The major product during cyclisation is the *trans* isomer, where the phenyl group is *trans* to acetonide as in **17** and in diol **19.** In most of the cases the acetonide is intact, but in the case of TFA and $SnCl_4.5H_2O$ catalyzed reaction the deprotection of acetonide occurred and gave the diol compounds **19** and **20**. In all the above cases the yields of the products are in the range of 78-90%.



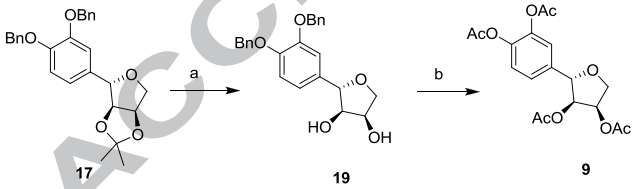
Scheme 2. Conditions: a) (i) H_2SO_4, dry MeOH, rt, 12 h; (ii) K_2CO_3, BnBr, acetone, 56 °C, 15 h, 95% (over 2 steps) ; b) AD-mix-β, methane sulfonamide in *t*-BuOH-H_2O, rt, 12 h, 90%; c) 2,2-dimethoxy propane, acetone, $BF_3.OEt_2$, 2 h, 90%; d) LAH, THF, 0 °C, 1 h, 85%; e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 3h; (ii) $Ph_3P{=}CH_2$, THF, 0 °C, 4h, 80% (over 2 steps) ; f) OsO_4, NMO, acetone:H_2O (4:1), 0 °C, 3 h 80%; g) Acid, CH_2Cl_2, 0 °C, 30min.

The mechanism for the formation of products **17** and **18** involves shifting of acetonide followed by cyclisation in presence of acid (Scheme 3). The benzylic C-O bond was cleaved in presence of acid giving rise to stable benzylic carbocation which undergoes cyclisation with the free primary hydroxy group leading to tetrahydrofuran system having trans configuration as major.



Scheme 3. Plausible Reaction Pathway.

The deprotection of the compound **17** with 1N HCl in MeOH afforded the compound **19.** Stirring of the compound **19** with PtO_2 in MeOH under hydrogen for 2 h and treatment of the crude with Ac_2O and pyridine gave the compound **9.** The spectral data of compound **9** was in good agreement with reported values (Scheme 4).[13b]



Scheme 4. Conditions: a) 1N HCl, MeOH, 0 °C, 30 min. b) (i) PtO_2, MeOH, H_2 (30 psi), 2 h; (ii) Ac_2O, Pyridine, 0 °C (98% over 2 steps).

Conclusions:

In summary, an efficient and novel synthetic pathway has been developed to synthesize peracetylated derivative of (-)-gloeosporiol **9** from commercially available caffeic acid using acid catalysed cyclisation which involves the migration of the acetonide group and this reaction was studied in presence of different acids. This pathway was shown to be applicable for the synthesis of many compounds containing tetrahydrofuran moiety.

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Highlights

- An efficient stereoselective synthesis of peracetylated (-)-gloeosporiol.
- Cyclisation and acetonide migration occurs in a single step under acid condition.
- This strategy can be used in the synthesis of many compounds contains tetrahydrofuran ring.