SHORT COMMUNICATION

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First consecutive linear synthesis of hostmaniene, 5-formyl-2-(isopropyl-1'-ol)benzofuran and anadendroic acid using prenylated phenol

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Abstract: The paper describes a new pathway for the syntheses of three natural bioactive benzofuran type compounds, namely, hostmaniene, 5-formyl-2-(isopropyl-1'-ol)benzofuran and anadendroic acid. The key synthetic strategy involved prenylation of the carboxy-phenol **7** and followed by the [*5-exo-tet*]cyclization reaction to furnish the benzofuran ring synthon. Subsequently, performing sequences of reactions of epoxide ring opening, ester reduction and re-oxidation of the alcohol from the benzofuran ring synthon gave all the title compounds in reasonable yield. Their structures were confirmed by both spectroscopic data and chemical transformations.

Keywords: Hostmaniene; anadendroic acid; prenylated pheno; benzofuran.

1. Introduction

Prenylated phenols such as the compounds (**1**-**3**) constitute an interesting group of natural products, wide variety of biological activities of which have been described including anti-inflammatory, antifungal, anti-HIV and most frequently, antineoplactic properties.[1] Synthetically, prenylated phenols portray important structural motifs, which can be further manipulated towards the syntheses of other natural products containing benzofuran ring or their hydrolysis products as displayed by the title compounds, hostmaniene (**4**), 5-formyl-2-(isopropyl-1'-ol)benzofuran (**5**) and anadendroic acid (**6**) (Figure 1). Benzofuran containing natural products have been known for their

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activity against cancer, tuberculosis, malaria and cataracts.[2] As a consequence of the diverse biological activities of benzofuran type compounds, synthetic chemists have developed many effective methods for accessing the benzofuran ring skeleton.[3]

2. Background

Although benzofuran analogues of **6** fomannosin, fomannoxin and methoxyanodendroate have been characterized and synthesized, to our best knowledge, only one formal synthesis of anadendroic acid **6** has been reported.[4] Previously, synthesis of **6** included the reaction of phenol and isoprene dibromide for cyclization which was then underwent regioselective formylation and oxidation reactions to afford the compound **6** as reported by Kawase and co-workers.[5] Additionally, it was surprised that there is no report available in the literature for the syntheses of the compounds **4** and **5**.

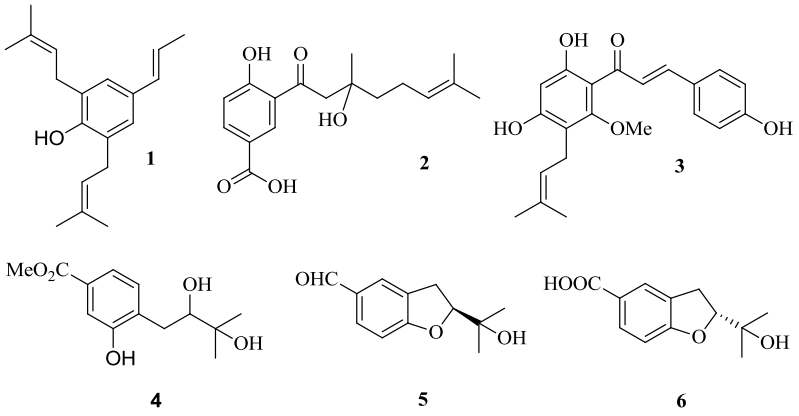


Figure 1. Structure of prenylated phenols (**1**-**3**) and the title compounds (**4**- **6**)

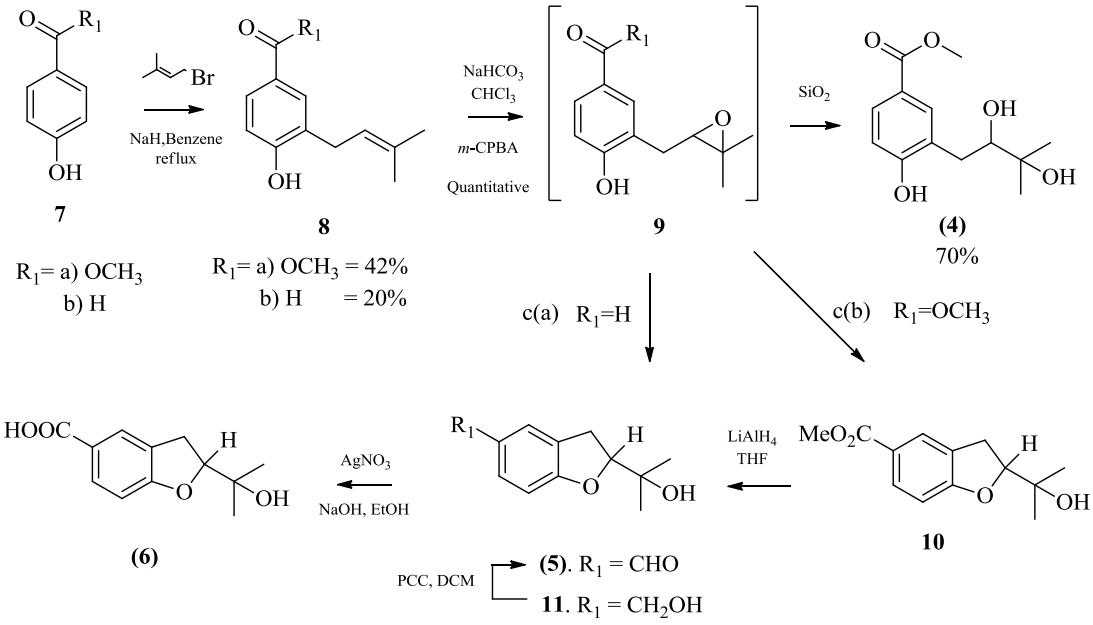
3. Experimental

All the chemicals and solvents employed in the synthesis were supplied by Merck (Germany) and Fluka (Germany), which were used without further purification. The melting points were measured on an automatics FP62 Mettler Toledo apparatus. The IR spectrums (KBr disc) were recorded on Varian 3100 Excalibur Series FT/IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Joel 400 MHz instrument. TMS (δ 0.00) and $CDCl_3$ (δ 77.0) were used as an internal standard and solvent, respectively, for ^{1}H and ^{13}C NMR spectroscopy measurements. *J* values were given in Hz. The multiplicities of the signals in the ^{1}H NMR spectra were abbreviated by s (singlet), d (doublet), t (triplet), q (quarted), m (multiplet), br (broad) and combinations thereof.

4. Present Study

In this communication, we report the first consecutive linear syntheses of all the title compounds via non-stereoselective cyclization employing prenylated phenolic epoxide **9** as an essential synthon (Scheme 1). Therefore upon refluxing of **7** with equimolar amount of 3,3-dimethylallybromide afforded the regioselective *meta*-prenylated adduct **8** along with *O*-alkylated compound as a side product.[6] Interestingly, during optimization of the prenylation reaction, hydroxybenzoate compound was found to give higher yield (42%) than the hydroxybenzaldehyde (20%) (Scheme 1). It was reasoned that the carboxylate functionality contribute to a more stabilized *meta*-benzylic anion which then led to a higher yield of aromatic substitution product. Subsequently, epoxidation of **8** using *m*-

CPBA led to the epoxide **9** as an oxidized product. Nevertheless, upon purification of **9** using column chromatography, oxirane hydrolysis was observed to give the product **4** in 70% yield. The acidic properties of the silica was believed to assist the hydrolysis of the oxirane ring of **9**.[7] This led to the first formal synthesis of hostmaniene **4** as the natural benzylated diol product.



Sheme 1. Synthetic route to title compounds of **4**, **5** and **6**

Isolation of **4** was first reported by Lago *et al* from DCM-MeOH extract of the leaves of *P.hostmannianum*.[8] The ^{1}H- and ^{13}C-NMR spectra of our synthetic hostmaniene **4** are identical to that of the corresponding natural product .[8] Consecutively, for the syntheses of **10**, the crude product **9** was subjected to base-promoted [5-*exo*-tet]-cyclization reaction by employing LiOH as a base to furnish the racemic benzofuran (**10**) in 63% yield.[9] However, it was reported that the cyclization of **9** under acidic condition using *p*-TSA produced a benzohydropyran ring as a major product through [6-*endo*-tet]-cyclization. Similar observations were also reported by others.[10] The structure of the product **10** was confirmed by ^{1}H-NMR data (Supporting information; S1), chiral HPLC (Supporting information; S3) and single x-ray analysis, (Figure 2).

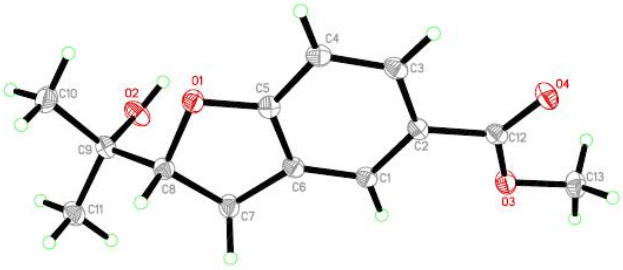


Figure 2. ORTEP crystal structure of compound methyl 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-5-carboxylate, **10**

Contrarily, different synthon of dimethylallyl hydroxybenzaldehye (**8b**) can only be cyclized using milder base such as TBAF. However, this led to a much inferior benzofuran (**5**) product (10%).

This observation was reasoned by the base-induced disproportionation of Cannizzaro type reaction. Disproportionation happened when strong base such as LiOH was employed in the reaction in the presence of carbaldehyde mioety.[11] By utilizing the aldehyde **8b** in the current strategy the first formal synthesis of the natural compound 5-formyl-2-(isopropyl-1'-ol)benzofuran, **5** was successfully furnished, which was first isolated during the screening of secondary fungal metabolite *H. annosum* as reported by Donnelly and co-workers[12].

Returning to previous synthetic route, reduction of the ester moiety of the compound **10** gave the alcohol **11** in a moderate yield (60%). Interesting to note that initial ester reduction of **10** to aldehyde **5** by employing DIBAL-*H* was unsuccessful. However, subsequent oxidation of **11** using PCC/silica in neat condition yielded the similar aldehyde **5**. Finally, further oxidation of **5** using silver oxide provided the natural compound anodendroic acid **6**. Its spectral data were identical with that of the natural compound[5]

5. Conclusion

In summary, we successfully demonstrated first practical consecutive linear synthesis of 3 different natural products hostmaniene (**4**), 5-formyl-2-(isopropyl-1'-ol)benzofuran (**5**) and anadendroic acid (**6**), using a common precursor. Finally, these results could reveal the biosynthetic pathway of the title compounds.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/OC

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