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Studies toward the total synthesis of naturally occurring pyranonaphthoquinones from *Ventilago harmandiana**

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Abstract: The enantioselective synthesis of a naturally occurring pyranonaphthoquinone isolated from a Thai endemic plant, *Ventilago harmandiana*, has been achieved. L-Rhamnose and gallic acid were used as the starting materials. A new *C*-1-glycosidation of L-rhamnal with trimethyl aluminum in the presence of a catalytic amount of ytterbium(III) triflate was developed. A new reagent, $PhSCF_2H/SnCl_4$, for the formylation of partially deactivated and hindered aromatic compounds has been introduced. Phenylthiophthalide was used efficiently as a cycloannulating agent in the Hauser cycloannulation reaction, employing slightly excess lithium *t*-butoxide as a base with a catalytic amount of lithium chloride. The synthetic route developed is applicable for the synthesis of other analogues with substituents at the aromatic and pyran rings.

Keywords: annulations; aromatic compounds; asymmetric synthesis; Hauser cycloannulation; phenylsulfanyldifluoromethane; pyranonaphthoquinone; stannic chloride; *Ventilago harmandiana*.

INTRODUCTION

The genus *Ventilago* (Rhamnaceae) is represented by about 40 species distributed throughout India and southern Asia [1] and seven of these *Ventilago calyculata* (= *V. denticulata*), *V. cristata*, *V. denticulata*, *V. harmandiana*, *V. malaccensis*, *V. ochrocarpa*, and *V. maingayi* were found in Thailand [2]. *V. harmandiana* Pierre, a climber known locally as "Khruea plok", is endemic to Thailand and found only in Panggna province in southern Thailand. In our extensive enthanobotanical survey, we found that the decoction of plants has been used traditionally for treating diabetes, wounds, chronic inflammation, psoriasis, and AIDS. As part of our ongoing project on the discovery of new lead structures for drug development from plants, we have chosen *V. harmandiana* for investigation on the basis of ethno-

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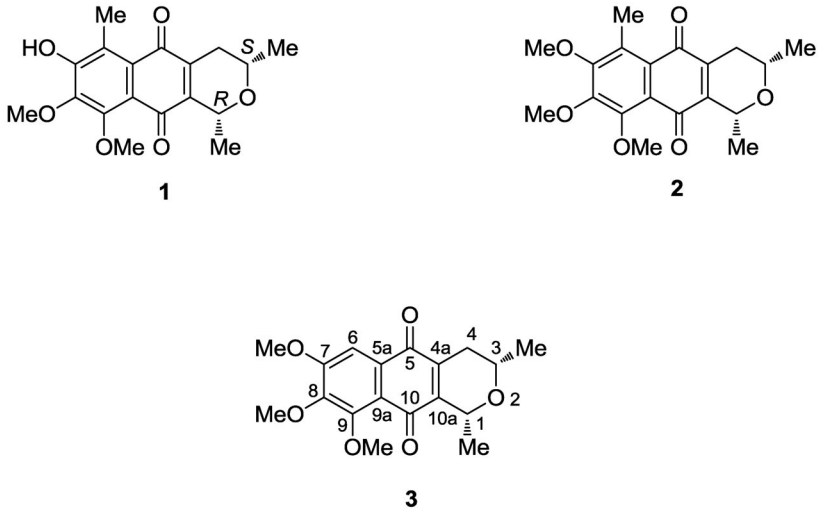
medical information. The methanol extract of the heart wood showed strong anti-inflammatory activity on the rat ears edema assay [3]. Several bioactive compounds were isolated, among them are novel pyranonaphthoquinones exemplified by the novel pyranonaphthoquinones **1**, **2**, and **3** (Scheme 1).



Scheme 1 Naturally occurring pyranonaphthoquinones.

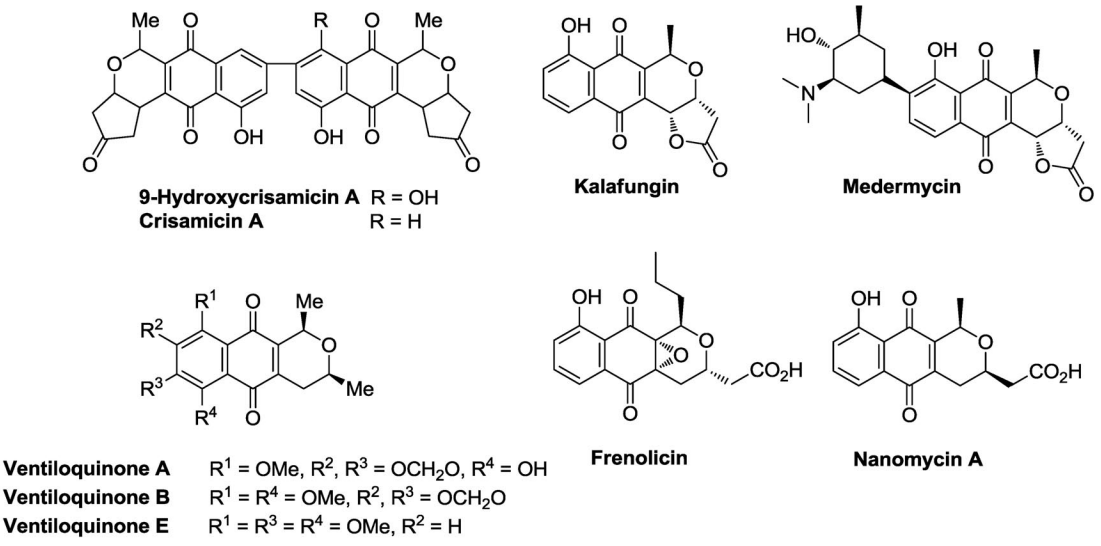
The structures of these compounds were established on the basis of spectroscopic information. Compound **1** formed a suitable crystal as a *p*-bromosulfonate derivative for a single X-ray diffraction analysis. Thus, the structure of compound **1** was confirmed and the absolute configurations of the two chiral carbons *C*-1 and *C*-3 on the pyran ring are determined as *R* and *S*, respectively. These results represent, for the first time, the absolute configurations of the chiral carbons in this class of compounds have been determined directly. The absolute configurations of chiral carbons *C*-1 and *C*-3 in compounds **2** and **3** are inferred as *R* and *S* by the comparison of their NMR spectral information and the optical rotation values with those of compound **1**.

Pyranonaphthoquinone derivatives are well known in the literature [4,5]. Many of them have been reported to be antibiotic, such as 9-hydroxycrisamicin A, crisamicin A [6], ventiloquinones A, B, and E [7], nanaomycin A, frenolicin, kalafungin, and medermycin [4,8] (Scheme 2).

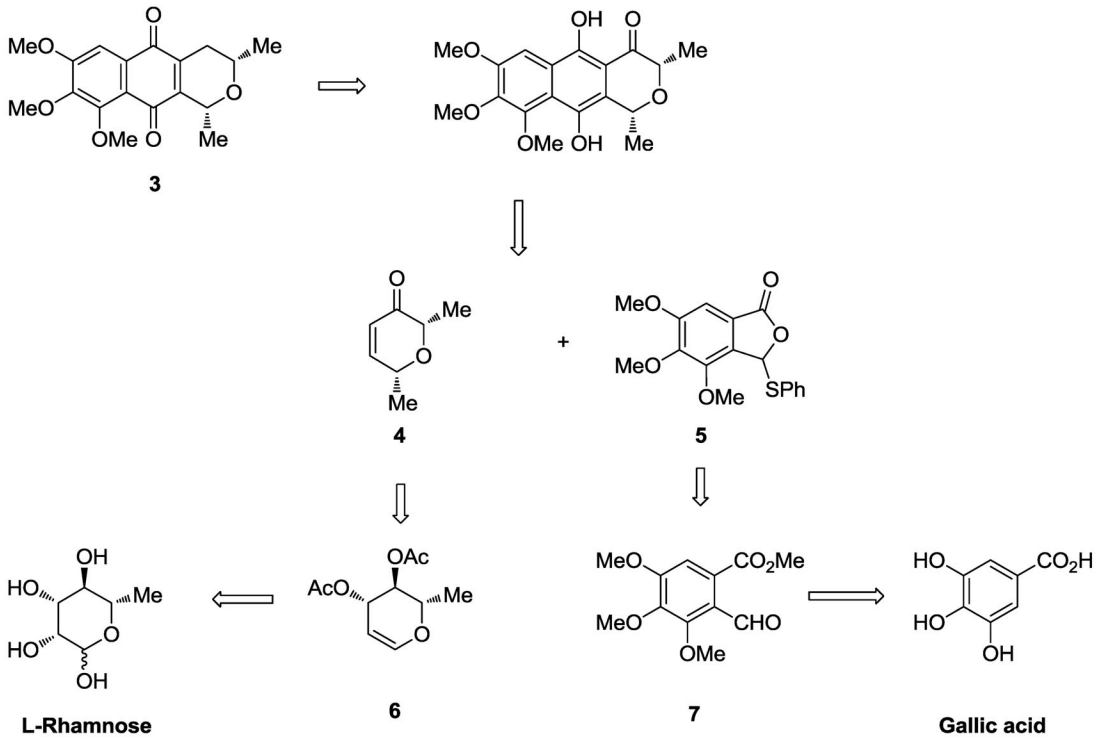
The novelty of our series of compounds is the substitution pattern in the aromatic ring A; for example, in compound **1** the aromatic ring was fully substituted.

This class of compounds has attracted intensive research effort in both synthetic and biological activities [9] owing to their novel structural features. Compound **3** has been chosen as an exploratory synthetic studies target assuming that the absolute configurations of the two chiral carbons are as *R* and *S*. Our synthetic studies would also confirm the absolute configuration of the two chiral carbons in this compound. The retrosynthetic analysis of compound **3** is as shown in Scheme 3. Our synthetic design will also be adaptable for the introduction of various substituents at the methylene carbon (*C*-4) of the pyran ring and substituents on the aromatic ring, e.g., at *C*-6 position.

The proposed key step is the Hauser cycloannulation reaction of the enone **4** and the phenylthiophthalide **5**. The L-rhamnose and gallic acids are chosen as the starting materials.



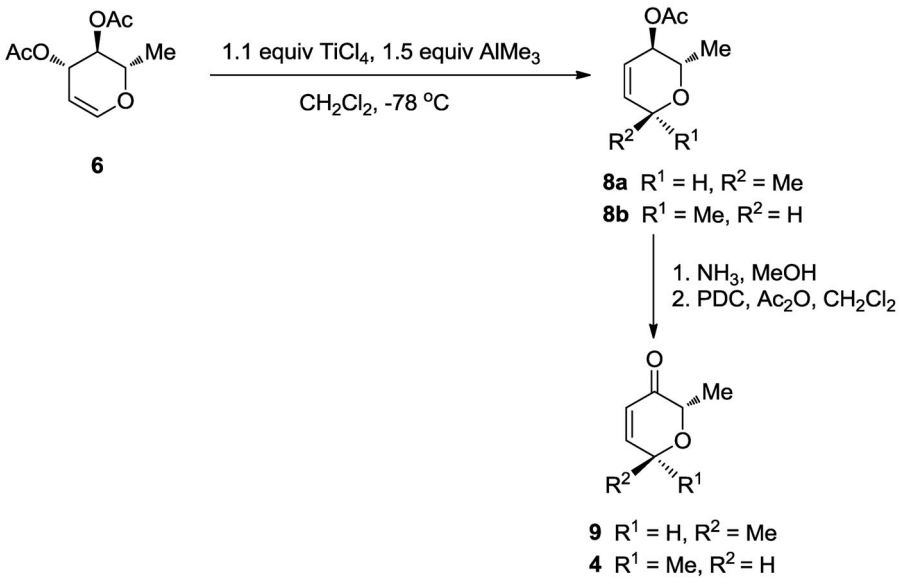
Scheme 2 Biologically active pyranonaphthoquinones.



Scheme 3 Retrosynthetic analysis of compound **3**.

SYNTHESIS OF ENONE 4

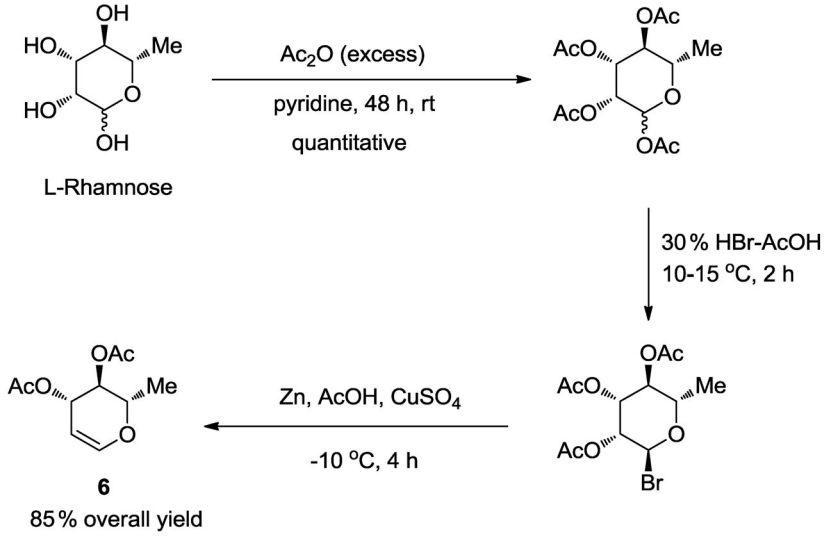
The synthesis of the enone **4** has been reported [10,11] as shown in Scheme 4.



Scheme 4 Previous synthesis of enones **9** and **4**.

The major drawback of the previously reported synthesis is the difficulty in obtaining the pure products. In our hands, we could not repeat the reported results, and the yields obtained were in the range of 30–50 %. Additionally, the product was very difficult to purify.

Our attempt to synthesize the starting glucal **6** from L-rhamnose was achieved in three steps in 85 % overall yield (Scheme 5). Alternative *C*-1 glycosidation using milder Lewis acid was explored

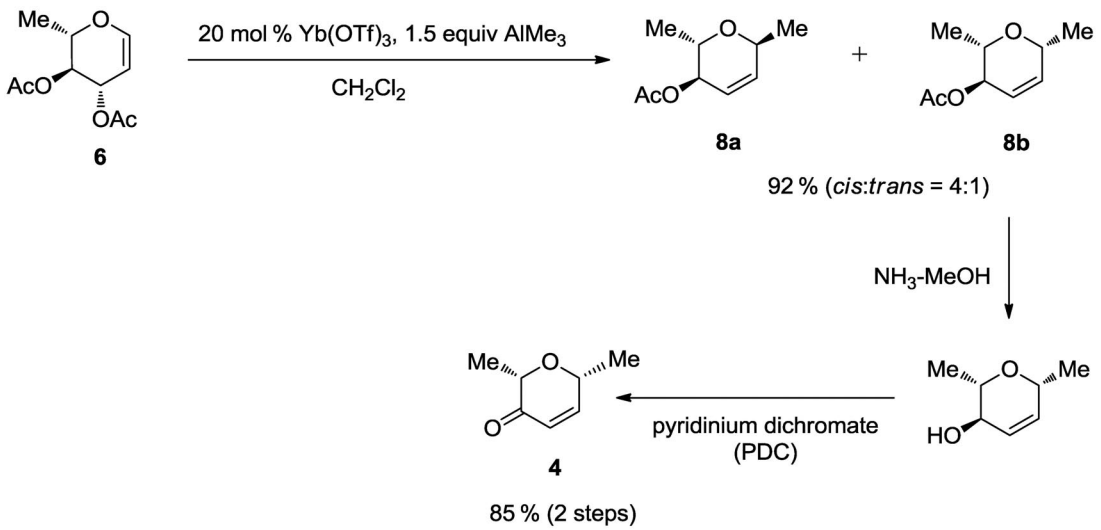


Scheme 5 Synthesis of rhamnal **6**.

[12]. The combination of metal triflates and trialkyl aluminum was extensively investigated. The Lewis acids screened included $In(OTf)_3$, $Sc(OTf)_3$, $Sm(OTf)_3$, $Hf(OTf)_4$, $Sn(OTf)_2$, $Bi(OTf)_3$, and $Yb(OTf)_3$ with trimethyl aluminum as the alkylating agent (Scheme 6). It was found that the use of 20 mol % of $Yb(OTf)_3$ with 1.5 equiv of $AlMe_3$ at 0 °C gave a mixture of **8a** and **8b** (1:4) in 92 % yield. It should be noted that this *C*-glycosidation procedure is also applicable for the *C*-1 alkylation of glucals that contained acid-sensitive protecting groups.

Scheme 6 Metal-catalyzed *C*-glycosidation of glucals.

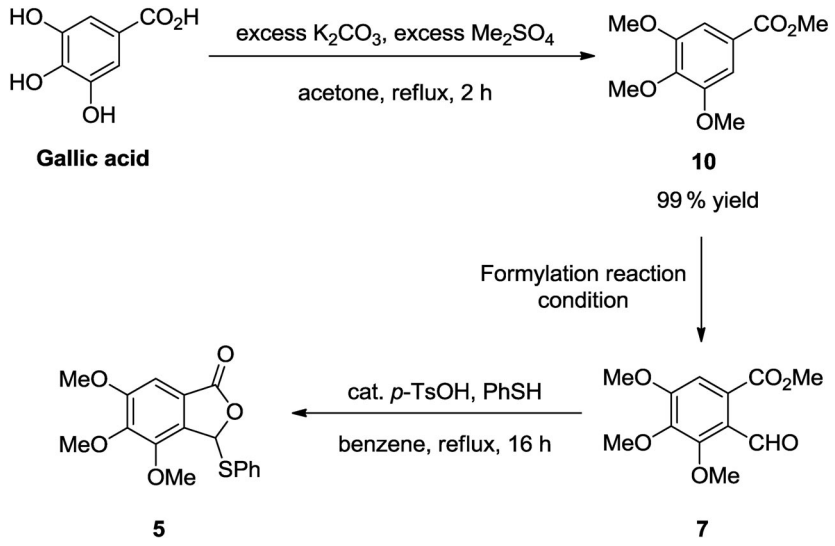
The diastereomers could be easily separated by column chromatography over silica gel with ethyl acetate/hexanes as an eluent. The stereochemistries of *trans*-**8a** and *cis*-**8b** were established on the basis of their NMR spectra and the nuclear Overhauser effect (NOE) experiments. The *cis*-**8b** was transformed to the required enone **4** in two steps. Upon hydrolysis with methanolic ammonia follow by oxidation with pyridium dichromate in methylene chloride at ambient temperature, the *cis*-**8b** was transformed to the required enone **4** in 85 % yield (two steps from *cis*-**8b**, Scheme 7).



Scheme 7 Synthesis of enone **4**.

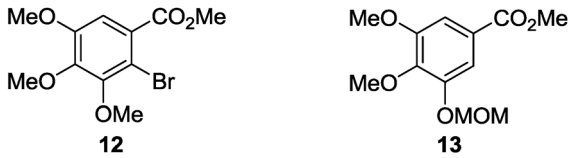
SYNTHESIS OF PHENYLTHIOPHTHALIDE 5

Having achieved the synthesis of the requisite optically pure enone **4** in high yield, we then turned our attention to the synthesis of the phenylthiophthalide **5**. The synthetic route is as shown in Scheme 8.



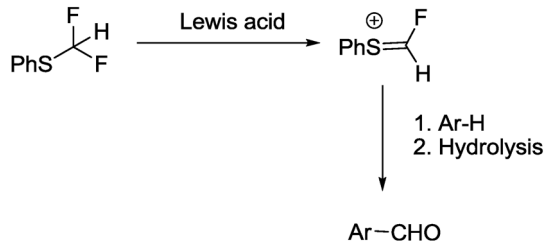
Scheme 8 Synthesis of phenylthiophthalide **5**.

The requisite methyl trimethoxygallate **10** was synthesized in quantitative yield by the exhaustive methylation with excess dimethyl sulfate and potassium carbonate in refluxing acetone for 2 h. The formylation step turned out to be very problematic. Compound **10** was very resistant to usual formylation reaction conditions. Two main approaches were explored: the metallation reaction and Friedel–Crafts-type formylation. The metallation of compound **10** with *n*-BuLi with and without HMPA, *s*-BuLi, *i*-PrMgCl, TMPMgCl-LiCl with CuCN·2LiCl [13,14], then trapping with dimethylformamide (DMF) or Weinreb formamide [15] failed to give the expected formylated product **7** in any appreciable yields (yields isolated were in the range of 0 to 10 %). The use of the derivatives **12** and **13** in the metallation reaction also failed to give the expected formylated product.



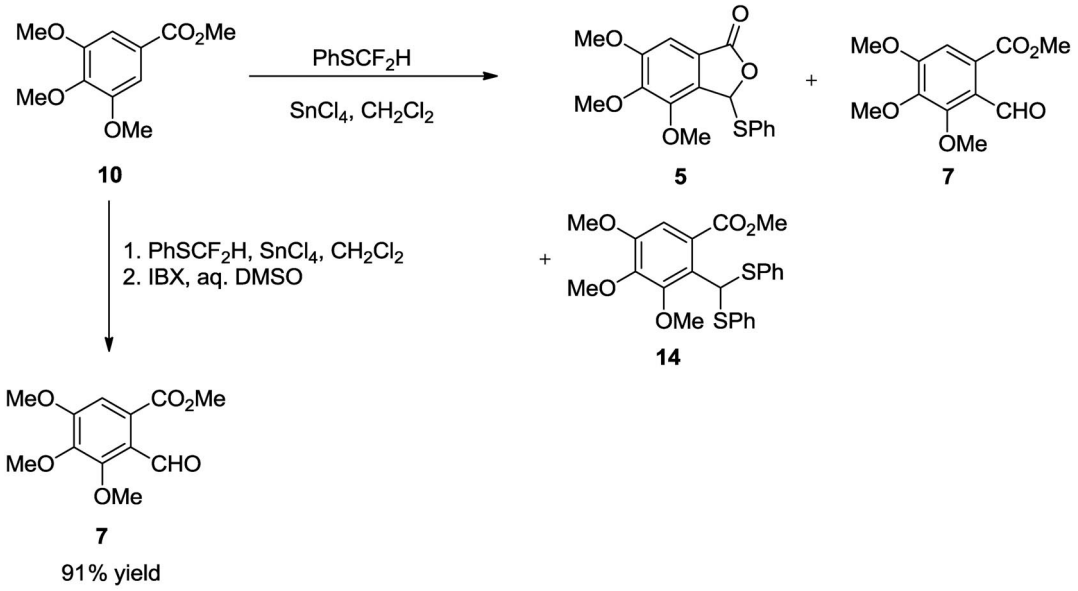
For Friedel–Crafts-type formylation approach, various traditional formylating agents were investigated. The Vilsmeier–Haack reaction conditions with DMF and PPCl [16] or $POCl_3$ [17] as Lewis acids at room temperature or 60 °C gave the formylated product **7** in 20–32 % yields. Employing the Gross formylation reaction [18,19] in dichloromethoxymethane with $TiCl_4$ or $SnCl_4$ gave the formylated product **7** in 30–70 % yield. The yield was very erratic, and the product was difficult to purify.

In connection with our on-going research in utilizing difluoromethylene group as the synthetic building block [20,21], we envisioned that phenylsulfanyldifluoromethane might be a good source of the carbocation stabilized by the fluorine atom. Formylation with aromatic compounds followed by hydrolysis will give the corresponding aromatic aldehydes (Scheme 9).



Scheme 9 Proposed formylation with phenylsulfanyldifluoromethane.

The initial experiment of this reaction with 2 equiv of $SnCl_4$ as the Lewis acid in methylene chloride at room temperature gave three products **7**, **14**, and **5** in 39, 21, and 21 % yields, respectively (Scheme 10).



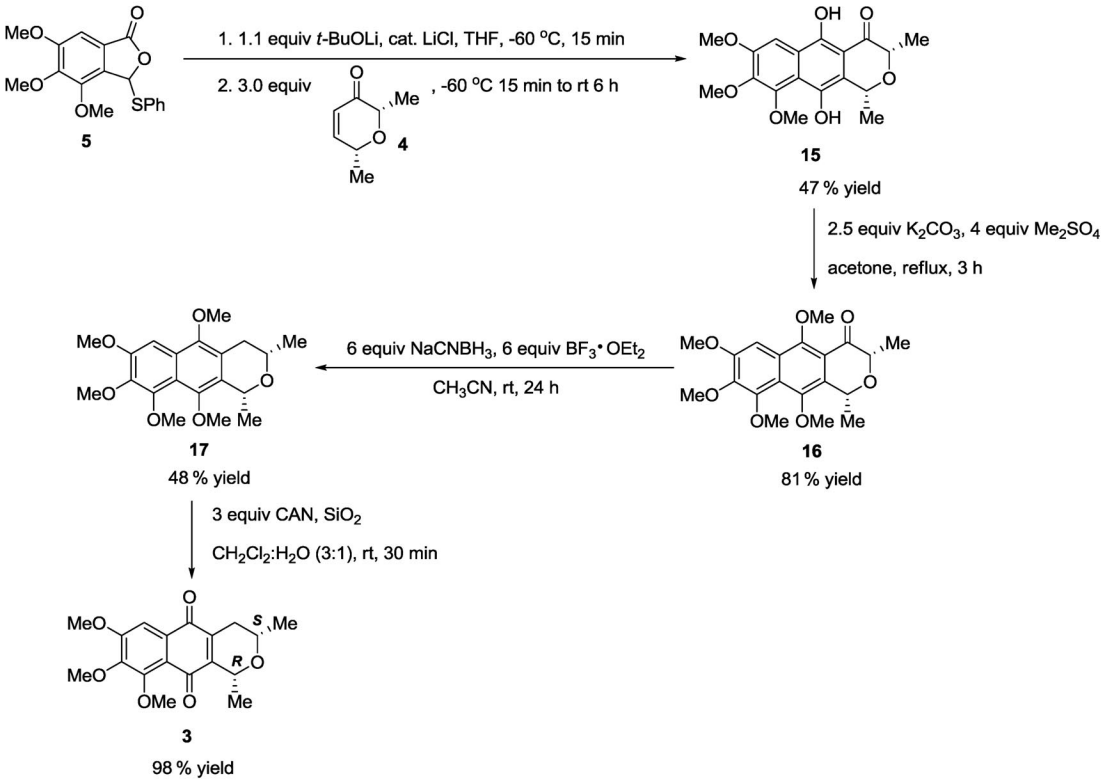
Scheme 10 The formylation of **10** with $PhSCF_2H$ and $SnCl_4$ in CH_2Cl_2.

Further optimization using 1.5 equiv of $PhSCF_2H$, 2 equiv of $SnCl_4$ in CH_2Cl_2 for 2 h at room temperature, followed by oxidative work-up with 3 equiv of IBX in H_2O:DMSO (1:3) [22] at room temperature for 5 h gave the required aromatic aldehyde **7** in 91 % yield.

HAUSER CYCLOANNULATION REACTION: SYNTHESIS OF PYRANONAPHTHOQUINONE 3

Having overcome the major problem in the formylation step, our next effort was the preparation of the phenylthiophthalide **5**. The reaction of the aromatic aldehyde **7** using 1 equiv of thiophenol with catalytic amount of *p*-toluenesulfonic acid in refluxing benzene for 16 h gave the phenylthiophthalide **5** in 96 % yield. The crucial Hauser cycloannulation reaction was accomplished, after a considerable experimentation, by reacting the phenylthiophthalide **5** and enone **4** using 1.1 equiv of *t*-BuOLi, 10 mol % of LiCl in tetrahydrofuran (THF) at –60 °C for 15 min [23,24]. The tricyclic product **15** was isolated in

47 % yield. The use of excess *t*-BuOLi led to extensive isomerization of the chiral carbons in the pyran ring. Removal of the carbonyl group to form the methylene carbon *C*-4 in the pyran ring was accomplished by first protecting the two phenolic hydroxyl groups using dimethyl sulfate with potassium carbonate in refluxing acetone, resulting in compound **16** in 81 % yield. The reduction of the benzylic ketone *C*-1 was accomplished by using 6 equiv of sodium cyanoborohydride and 6 equiv of $BF_3{\cdot}OEt_2$ in acetonitrile at room temperature for 24 h. The product, compound **17**, was isolated in 48 % yield. The final product pyranonaphthoquinone **3** was obtained in 98 % yield by the oxidation of **17** with 3 equiv of ceric ammonium nitrate on silica gel in CH_2Cl_2:H_2O (3:1) [25] at room temperature for 30 min. The final product exhibits the NMR spectrum identical to those of the natural product and displays optical rotation value of $[\alpha]_D$ +317, the natural compound possessing the optical rotation value of $[\alpha]_D$ +335. These results also confirm the absolute configuration of the two chiral carbons *C*-1 and *C*-3 in the pyran ring as *R* and *S*, respectively (Scheme 11).



Scheme 11 Synthesis of the naturally occurring pyranonaphthoquinone **3**.

CONCLUSION

The naturally occurring pyranonaphthoquinone was synthesized by using L-rhamnose and gallic acid as the starting materials. A new synthesis of optically pure enone **4** from L-rhamnal mediated by catalytic ytterbium(III)triflate-trimethyl aluminum was developed. A new reagent $PhSCF_2H/SnCl_4$ for the formylation of partly deactivated and hindered aromatic compound was introduced. The scope of this reaction is being explored. The Hauser cycloannulation reaction could be efficiently carried out using a slight excess of lithium *t*-butoxide on silica gel with a catalytic amount of lithium chloride at low temperature. Phenylthiophthalide has been demonstrated to be an efficient Hauser cycloannulating agent.

The synthetic route is also amenable to the introduction of other functional groups at *C*-4 and *C*-6 carbons of the pyranonaphthoquinones.

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