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# The first stereoselective synthesis of the natural product, rotenone

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ABSTRACT

The total syntheses of rotenone and munduserone are reported in this paper. The synthesis of rotenone involves two key transformations, the first of which is a Pd π-allyl mediated cyclisation for the construction of the dihydrobenzofuran skeleton. The second is a 6-*endo*-hydroarylation which yields the chromene as a precursor to rotenone. The synthesis of rotenone was achieved in 17 steps from resorcinol and constitutes the first stereoselective synthesis of this complex natural product.



## 1. Introduction

In 2007, our group reported the first enantioselective synthesis of (*R*)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol **1** in 10 steps from resorcinol in an overall yield of 15.7%.[1] This was of importance as the 2-isopropenyl-2,3-dihydrobenzofuran moiety, possessing an asymmetric carbon at the 2-position, is found in a number of natural products.[2–4] Until this time, a stereoselective synthesis of this skeleton was yet to be achieved, other than by employing resolution methods.[5] The synthesis utilised as a key step a Trost Pd π-allyl mediated cyclisation in which (*E*)-4-(2,6-dihydroxyphenyl)-2-methyl-2-butenyl methyl carbonate **2** was treated with catalytic palladium in the presence of the commercially available *R,R′*-Trost ligand **3**, thereby affording (*R*)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol **1** in very good enantiomeric excess (Scheme 1).[1]

This asymmetric synthesis afforded the dihydrobenzofuran skeleton with the isopropenyl and phenolic substituents at the 2- and 4-positions, respectively, as found in the natural product rotenone **4** (Fig. 1).

Rotenone has been isolated from several leguminous plants of the *Derris* and *Lonchocarpus* species and exhibits significant pesticidal and insecticidal properties.[6a-b] It belongs to a class of compounds called the rotenoids which all possess the *cis*-fused tetrahydrochromeno[3,4-b]chromene nucleus (highlighted in blue). The class of rotenoids has also recently received renewed attention due to their anticancer properties.[7,8]

As rotenone contains three stereogenic centres, this complex pentacyclic molecule presents a challenging synthetic target. In fact, only a few total yet non-stereoselective syntheses have been reported,[9–11] and even when the enantiomerically pure form of rotenone was obtained, this was usually by resolution methods,[12] or as a result of a partial synthesis from an advanced organic intermediate, usually a product from the degradation of rotenone.[13–15] Therefore, a stereoselective synthesis of this natural product is yet to be achieved and remains a challenge.

The total synthesis of the related rotenoid, deguelin **5** has been reported by Sames and Pastine, using methodology that involves relatively mild reaction conditions.[16] A fundamental step in their approach involved a 6-*endo*-hydroarylation to afford the chromene scaffold which could subsequently be converted to deguelin. Intrigued by this concise and effective methodology, we envisaged being able to apply a similar protocol to the synthesis of rotenone (Scheme 2). We were confident that if we could synthesize the chiral dihydrobenzofuran with the appropriate aldehyde functionality i.e.**7**, we would be able to apply a similar synthetic protocol for the synthesis of rotenone.

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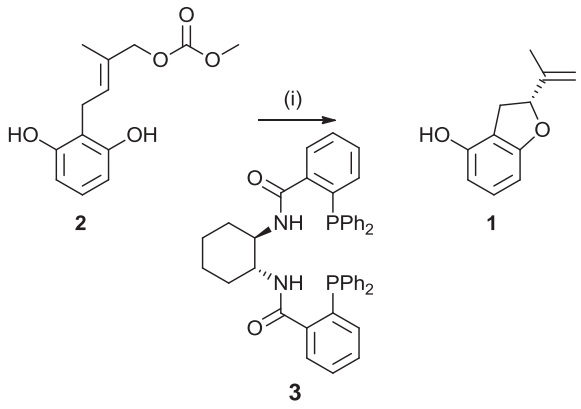
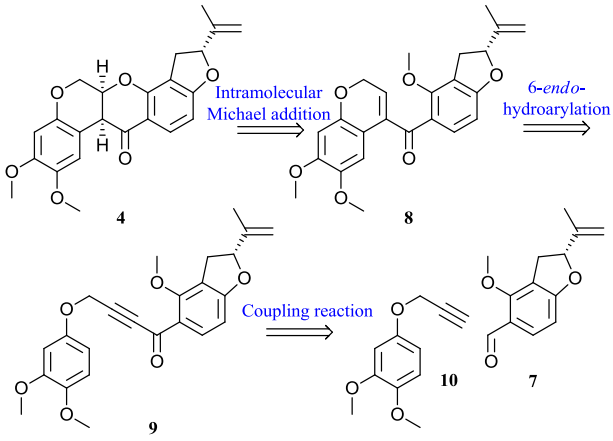



**Scheme 1.** Stereoselective synthesis of the dihydrobenzofuran moiety. Reagents and conditions: (i) 2 mol% $Pd(dba)_2$, 6 mol% *R*,*R*′-Trost ligand, 1 eq AcOH, $CH_2Cl_2$, rt, 18 h, 98%, 92% ee.




**Scheme 2.** Retrosynthetic strategy for the preparation of rotenone.

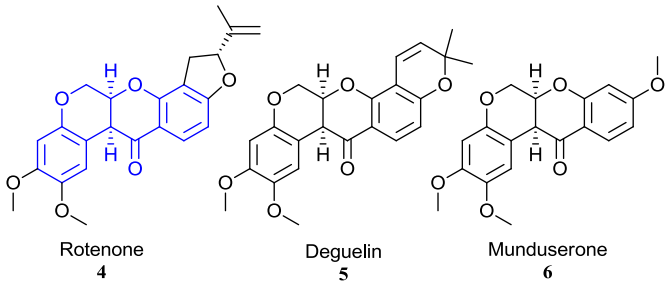



**Fig. 1.** The rotenoids rotenone, deguelin and munduserone.

Thus, as shown in the retrosynthesis in Scheme 2 it was envisaged that the final transformation in the synthesis of rotenone would be an intramolecular Michael addition of the chromene moiety **8**, itself a product of the crucial 6-*endo*-hydroarylation of **9**, obtained by means of a coupling reaction of **10** and the formylated dihydrobenzofuran **7**.

This paper reports the development of the methodology for the synthesis of the simpler rotenoid, munduserone followed by the synthesis of the more complex natural product, rotenone.

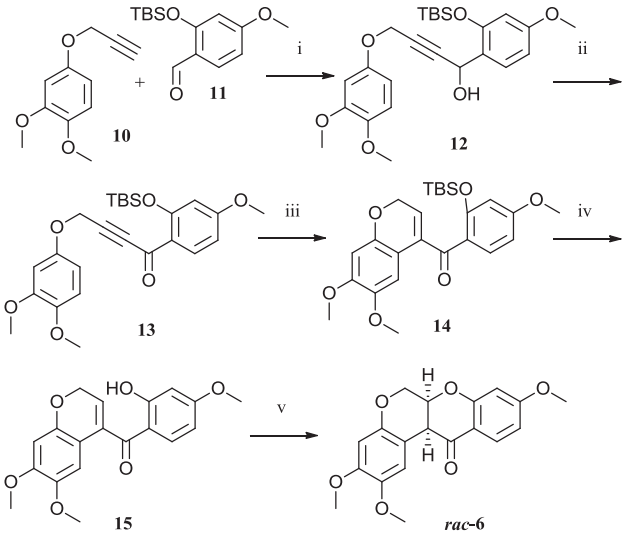
## 2. Results and discussion

### 2.1. Synthesis of munduserone

Coupling of the propargyl ether **10** and the substituted benzaldehyde **11**, afforded the desired alcohol **12** (Scheme 3). Oxidation to the alkynone **13**, followed by the 6-*endo*-hydroarylation reaction, yielded the required chromene moiety **14**, albeit in a poor yield. This was attributed to the use of a bulkier TBS protecting group, in contrast to the methyl group employed in the synthesis by Pastine.[16] Nevertheless, the silyl protecting group was cleaved and a final base-catalysed intramolecular oxy-Michael addition of **15** furnished (±)-munduserone in five steps and a satisfactory overall yield of 23%.

### 2.2. Synthesis of rotenone

Satisfied with the results, we commenced with the synthesis of rotenone (Scheme 4). The dihydrobenzofuran moiety **1** was synthesised from commercially available resorcinol **16**, according to the reported methodology,[1] and was obtained in enantiomeric excess as high as 94.8% but is scale-dependant. A mild, magnesium-mediated formylation was employed to selectively install the formyl functionality in the position *ortho* to the phenol **1**, furnishing **17** in a 75% yield.[17] With the formyl group in place, a protecting group could be introduced. The use of the TBS-protecting group for the phenol **1** was considered to be too bulky and thus, we resorted to a methyl protecting group as this had been successfully employed in the synthesis of deguelin by Sames and Pastine.[16] This resulted in the formation of **7** in good yield.[16] The choice of base was key for the next step as the use of LDA over *n*BuLi to generate the anion of **10** saw an improvement in the yield from 40% to 76% for the coupling reaction with **7** to furnish **18**. Following an oxidation reaction on **18**, the key 6-*endo*-hydroarylation reaction furnished the chromene moiety **20**. Interestingly, the reaction proceeded to completion in less time and in a higher yield than in the synthesis of munduserone in the model study. As was rationalised, this was by virtue of the fact that in utilising TBS groups in the synthesis of munduserone, the alkyne was sterically congested, thus obstructing initial coordination of the platinum catalyst to the alkyne. However, in using a less bulky methyl protecting group, the alkyne was accessible for coordination to the metal catalyst, thereby rendering it susceptible to attack by the nucleophile which,




**Scheme 3.** Synthesis of munduserone. *Reagents and conditions*: (i) a: **10**, *n*BuLi, THF, −78 °C, 30 min, b: **11**, 1 h, rt, 81%; (ii) $MnO_2$, $CH_2Cl_2$, rt, 18 h, 84%; (iii) $PtCl_2$, toluene, 70 °C, 18 h, 46%; (iv) HF, MeCN, rt, 1.5 h, 87%; (v) NaOAc, EtOH, 90 °C, 2 h, 92%.