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A conceptually novel construction of the 6a-hydroxypterocarpan skeleton – synthesis of (±)-variabilin

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ABSTRACT

A new access to the 6a-hydroxypterocarpan variabilin was established. Key step of this concise total synthesis is a challenging cyclization of a haloketone via halogen–metal exchange and subsequent intramolecular addition to the carbonyl function.

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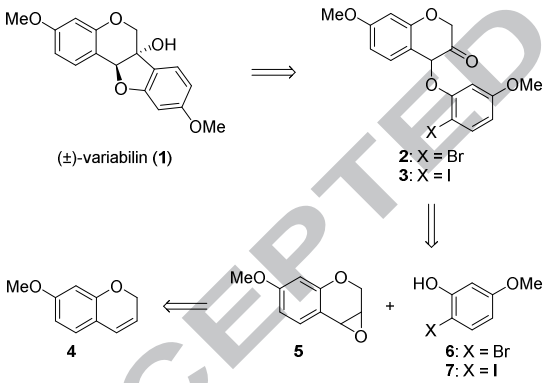
1. Introduction

The flavonoid variabilin (**1**), sometimes also referred to as homopisatin, is a typical representative of the wide variety of known natural phytoalexins bearing a 6a-hydroxypterocarpan skeleton.[1] Our interest to develop a new synthetic access to this compound was not only due to its antifungal activity,[2–4] but also encouraged by the occurrence of structurally more complex 6a-hydroxypterocarpans such as the glyceollins I-III, which exhibit impressing bioactivities.[1,5] Interestingly, both enantiomers of variabilin are found in nature. The (+)-enantiomer was extracted from *Dalbergia variabilis*, a tree or shrub from the pea family, while the (−)-enantiomer was isolated from *Sophora flavescens* and *Butea superba*.[6–9]

The first partial synthesis of (±)-**1** was described in 1964 starting from (−)-homopterocarpin by Bevan.[10] In 2001 Ferreira reported the enantioselective syntheses of both (+)- and (−)-variabilin utilizing a Sharpless asymmetric dihydroxylation with stoichiometric amounts of OsO_4 in 12 linear steps and 7.3% overall yield.[11] The synthesis of (−)-variabilin published in 2011 by Calter using an "interrupted" Feist–Bénary reaction takes 11 linear steps with 5.7% total yield.[12] Herein, we present our novel approach towards the 6a-hydroxypterocarpan skeleton.

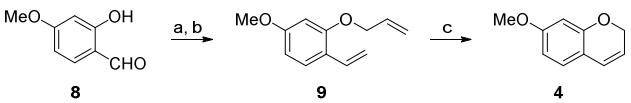
Our retrosynthetic analysis of variabilin (**1**) is outlined in Scheme 1. The natural product **1** is traced back to the ketones **2** or **3** by means of a halogen–metal exchange and subsequent intramolecular 1,2-addition to the carbonyl group. Ketones **2** and **3** ought to be accessible by oxidation of the corresponding secondary alcohols, which might be obtained by nucleophilic attack of halophenols **6** or **7** to epoxide **5**. Epoxidation of the known chromene **4**[13] would result in epoxide **5** in either racemic or enantioselective fashion.



Scheme 1. Retrosynthesis of variabilin (**1**).

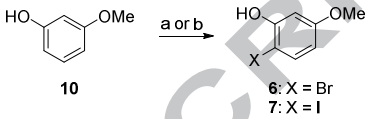
2. Results and discussions

As depicted in Scheme 2, chromene **4** was obtained from commercially available 2-hydroxy-4-methoxybenzaldehyde (**8**) with an improved yield of 89% over three steps. The published procedure[13] was optimized regarding the catalyst loading for the ring-closing metathesis (RCM) that was reduced from 2 mol % to 0.5 mol % Grubbs I catalyst. The product **4** was obtained as a light to dark green oil, which decomposed within a few weeks even if stored at −32 °C. To our delight, we were able to obtain **4** as a stable pale yellow oil by quenching the RCM with lead tetraacetate as described by Paquette and subsequent flash chromatography.[14]



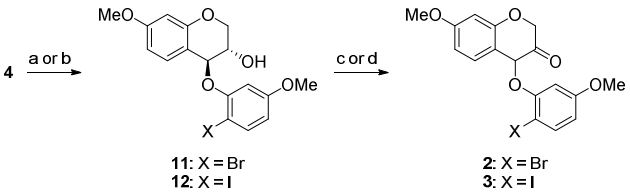
Scheme 2. Synthesis of chromene **4**. (a) Allyl bromide, K_2CO_3, acetone, reflux, 2 h; (b) $MePh_3PBr$, NaH, THF, RT, 2 h, 94% (two steps); (c) i) 0.5 mol % Grubbs I, DCM, RT, 18.5 h; ii) 0.9 mol % $Pb(OAc)_4$, RT, 24 h, 95%.

Bromophenol **6** was readily accessible by bromination of commercially available 3-methoxyphenol (**10**) with *N*-bromosuccinimide (NBS, Scheme 3). Utilizing the conditions of Snieckus yielded 79% of the desired regioisomer.[15] A common way to achieve the regioselective mono-iodination of **10** is application of stoichiometric amounts of silver trifluoroacetate or silver triflate with iodine to give **7** in 62–79% yield.[16–18] Gratifyingly, we could avoid the application of expensive silver salts using *N*-iodosuccinimide (NIS) in the presence of trifluoroacetic acid[19] (0.3 equiv.) to afford iodophenol **7** in 69% yield.



Scheme 3. Access to halophenols **6** and **7**. (a) NBS, DCM, RT, 1 h, 79% **6**; (b) NIS, TFA, DCM, RT, 50 min, 69% **7**.

With halophenols **6** and **7** in hand, we explored the epoxidation of chromene **4**. Epoxychromans with electron-donating substituent in the 7-position are known to be rather unstable.[20] Therefore, use of a neutral epoxidation agent like dimethyldioxirane (DMDO) is essential. Indeed, epoxide **5** proved to be prone to decomposition, which precluded its isolation. In consequence, a one-pot procedure of epoxidation and subsequent epoxide opening was established. Thus, addition of the nucleophiles **6** or **7** in the presence of triethylamine at low temperature to the intermediate epoxide **5** afforded alcohols **11** and **12** in good yields of 73% and 63% with diastereomeric ratios of 15:1 and 13:1, respectively (Scheme 4).[21,22] This stereochemical outcome could not be predicted, as quite contrary results are reported in the literature for similar reactions.[23–25]

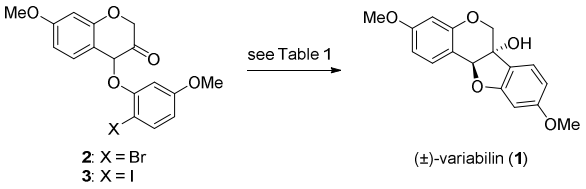


Scheme 4. Syntheses of cyclization precursors **2** and **3**. (a) i) DMDO (≈0.08 M in acetone), MeCN, −65 °C → −44 °C, 2.5 h; ii) **6**, Et_3N, −44 °C → RT, 16 h, 73% **11** (*dr* = 15:1); (b) i) DMDO (≈0.08 M in acetone), MeCN, −74 °C → −35 °C, 2.2 h; ii) **7**, Et_3N, −44 °C → RT, 18 h, 63% **12** (*dr* = 13:1); (c) Dess–Martin periodinane, DCM, RT, 6.5 h, 100% **2**; (d) Dess–Martin periodinane, DCM, RT, 23 h, 97% **3**.

Subsequent oxidation of the secondary alcohols to the corresponding ketones was achieved by the Dess–Martin periodinane.[26] A mild method was crucial for this transformation, as the ketones **2** and **3** proved to be highly sensitive towards traces of acid and temperatures above 25 °C. Apparently, these compounds tend to form *para*- or *ortho*-quinone methides leading to the isolation of the expelled halophenols **6** or **7**, respectively. In fact, products **2** and **3** could only be isolated by crystallization and subsequent washing with a small amount of diethyl ether.

Considering the lability of the cyclization precursors **2** and **3**, conditions for their cyclization to (±)-variabilin (**1**) are very limited (Scheme 5). Halogen–metal exchange must proceed without nucleophilic addition to or enolate formation from the carbonyl group, which would make the cyclization impossible. Even after successful halogen–metal exchange, the

organometallic species might be protonated by intramolecular attack at the benzylic hydrogen via a five-membered ring transition state.



Scheme 5. Cyclization to (±)-variabilin (**1**).

In the 1990s, Mori used stannyl anions generated from $Me_3SiSnBu_3$ to achieve a halogen–metal exchange in the presence of a carbonyl group.[27–29] Unfortunately, these conditions only resulted in decomposition of the starting material. Another promising methodology, a palladium-catalyzed cyclization developed by Yamamoto,[30] was not successful either, probably due to the thermal lability of the substrates **2** and **3**. On the assumption that in all cases replacement of the halogen atom is too slow in competition to the side reactions mentioned above, we looked for appropriate reactions at lower temperature. In 1970 Corey described the utilization of di-*n*-butylcopperlithium to achieve an intramolecular addition of a vinyl iodide to a keto group in high yield – a methodology, which was successfully adapted by Posner some years later.[31,32] However, brominated substrate **2** was not dehalogenated under these conditions, and substrate **3** led to complete decomposition.

Inspired by the work of Chavan, we tested *n*- and *t*-BuLi under several conditions to perform the desired transformation (Table 1).[33] No halogen–metal exchange was observed using substrate **2** (entry 1), but iodoketone **3** was cyclized successfully at temperatures below −100 °C. Using 1.0 equiv. of *n*-BuLi at −108 °C gave rise to (±)-variabilin (**1**) in a good yield of 65% (entry 2), whereas *t*-BuLi resulted in a low yield of only 25% (entry 3). Application of the radical anion salt lithium di-*tert*-butylbiphenyl was another potential alternative, as lithiation may take place under less basic conditions. Indeed, the aryl anion was formed successfully, since phenol **10** was isolated in about 76% yield. Unfortunately, no cyclization product was formed, probably due to the competing homolytic cleavage of the benzylic C–O bond.[34]

Table 1. Selected conditions for cyclization to (±)-variabilin (**1**)

Entry	Substrate	Conditions	Yield [%]
1	**2**	1.1 equiv. *n*-BuLi, THF, −78 °C → RT, 26.5 h	0[a]
2	**3**	1.0 equiv. *n*-BuLi, THF, −108 °C → −2 °C, 6.25 h	65
3	**3**	2.2 equiv. *t*-BuLi, THF, −108 °C → 1 °C, 6.33 h	25

[a]Only **6** was isolated.

3. Summary and conclusion

In summary, we have developed a short total synthesis of (±)-variabilin (**1**), which provides an entirely new access to the 6a-hydroxypterocarpan skeleton. The natural product **1** was constructed in only three steps from the known 7-methoxychromene (**4**) in 40% overall yield and over six steps (35% overall yield) from the commercially available 2-hydroxy-4-methoxybenzaldehyde (**8**). The challenging key intramolecular nucleophilic addition to give the target molecule **1** was eventually achieved by chemoselective halogen–metal exchange using the iodoketone **3**. Current efforts are devoted to an enantioselective modification of this novel route.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/XXXXXXXXXX. These data include experimental procedures and analytical data of all compounds described in this article.

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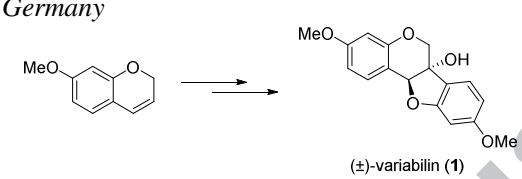

(±)-variabilin (**1**)