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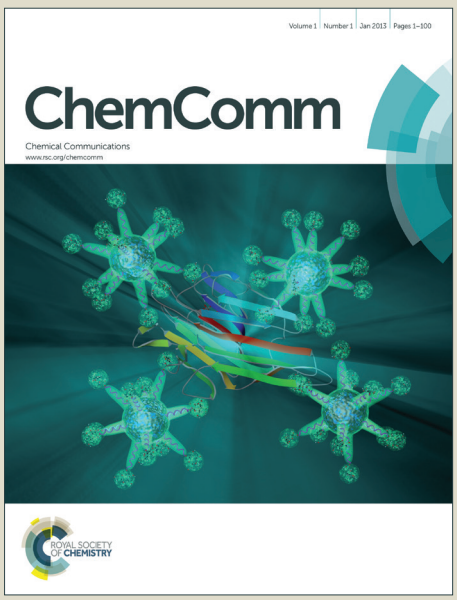


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# Total Synthesis of (-)-Deguelin via an Iterative Pyran-Ring Formation Strategy

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**Enantioselective synthesis of (-)-deguelin was accomplished via an iterative pyran-ring formation approach. The key features involve anionic addition of a chromene unit to aryloxyalkyl aldehyde for the double cyclization precursor and iterative pyran ring formations by Pd-catalyzed *O*-arylation and *C*-arylation, respectively.**

Deguelin (**1**) is a natural rotenoid isolated from several botanical sources[1] and has been considered as one of the most active natural pesticides and insecticides.[2] Deguelin has attracted much attention from biologists and chemists due to its promising anticancer and chemopreventive properties. It inhibits induction of ornithine decarboxylase, an enzyme associated with tumour progression.[3, 4] Fluorescently-labelled deguelin conjugates show strong cellular co-localization with mitochondria, the site of the electron-transport chain in human cells.[5] Recently, we reported that deguelin interfered with ATP binding to Heat Shock Protein 90 (HSP90), a protein associated with the stabilization and translocation of hypoxia inducible factor-1α (HIF-1α).[6-9] In addition, we identified a key skeleton (**2**) responsible for HSP90 inhibition and developed a number of pharmacologically and toxicologically improved deguelin analogues.[10, 11] More recently, we have disclosed the significant suppressing effects of these compounds in hypoxia-mediated retinal neovascularization and vascular leakage in the diabetic retina.[11]

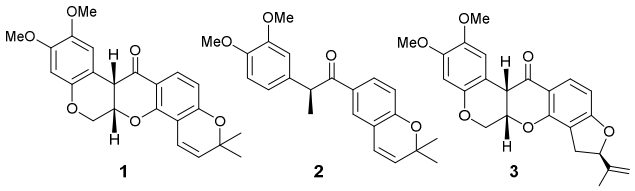
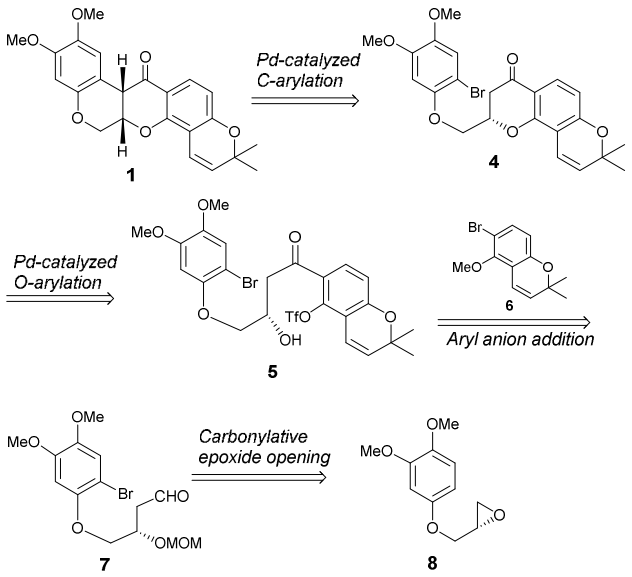



**Figure 1** Structures of (-)-deguelin (**1**), SH1280 (**2**) and rotenone (**3**)

Syntheses and synthetic studies of deguelin have been reported by several research groups.[12-18] Although racemic or formal syntheses of deguelin from rotenone (**3**) have been reported, the first asymmetric synthesis of (-)-deguelin was achieved in 2010 by Winssinger and coworkers. Recently, the Scheidt group reported the enantioselective total synthesis of (-)-deguelin and its enantiomer by employing a catalytic process. We have also made efforts to establish a concise and versatile synthetic strategy for (-)-deguelin. Herein, we describe the asymmetric total synthesis of (-)-deguelin based on iterative intramolecular Pd-catalyzed arylation of β-hydroxy ketone.




**Scheme 1** Synthetic approach to (-)-deguelin

Our initial synthetic approach to (-)-deguelin (**1**) is illustrated in Scheme 1. We envisioned that double Pd-catalyzed arylation of β-hydroxy ketone **5** would yield the desired *cis*-fused bisbenzopyran system of **1** by transferring a chirality of the β-hydroxy moiety to the α-position of ketone. The final diastereoselective pyran ring formation was anticipated based on Pd-catalyzed α-arylation of ketone **4**. The first pyran ring formation would be possible via Pd-catalyzed *O*-arylation of β-hydroxy ketone **5**, which can be prepared from aldehyde **7** via a convergent procedure. Anionic addition of chromene **6** to aldehyde **7**, which is derived by a carbonylative epoxide opening of **8**, provides **5**. Chromene **6**, which was discussed

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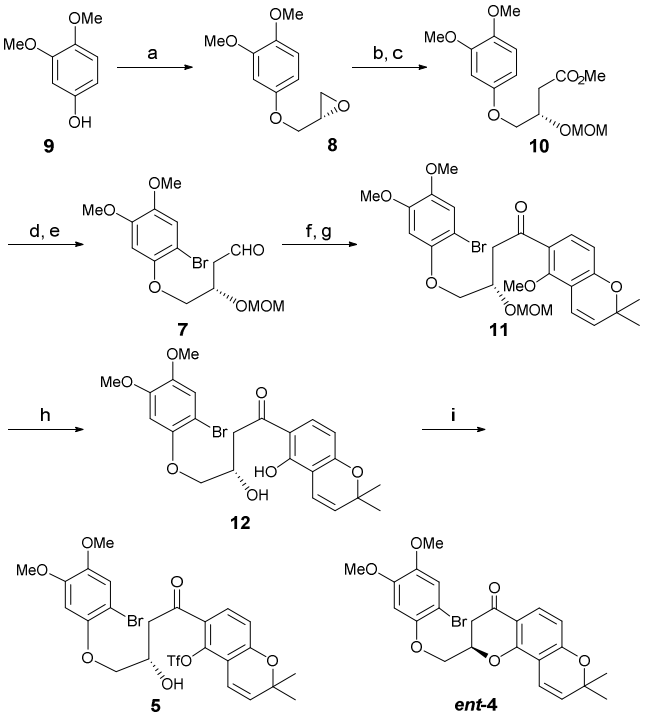
in a previous report by us,[10] is conveniently prepared via a sequence of chemoselective propargylation of 6-nitro-resorcinol and regioselective Claisen rearrangement of the resulting alkyl aryl ether.

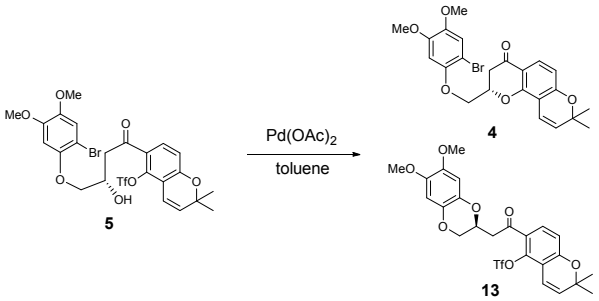
The synthesis was initiated by preparation of the double cyclization precursor **5** as depicted in Scheme 2. Treatment of 3,4-dimethoxyphenol **9** with (*S*)-glycidyl 3-nitrobenzenesulfonate produced epoxide **8** in 98% yield.[19, 20] Carbonylative ring opening of **8** with CO in the presence of $Co_2(CO)_8$ and MOM protection of the resulting β-hydroxy ester afforded **10** as a single product.[21] Regioselective bromination of ester **10** with NBS at -78 °C followed by ester reduction with DIBAL produced aldehyde **7**. Addition of aryl anion, prepared from **6** by *n*-BuLi treatment at -78 °C, to aldehyde **7** and Dess-Martin oxidation of the resulting alcohol afforded ketone **11** in 68% yield via 2 steps. Finally, selective MOM deprotection and demethylation of the benzopyran moiety were achieved by $BCl_3$ treatment of **11** at -78 °C to afford diol **12**. To prepare the double cyclization precursor **5**, phenol selective triflation of **12** was examined under a variety of reaction conditions. Treatment of **12** with $PhNTf_2$ in DMF in the presence of potassium carbonate provided the best result in terms of chemoselectivity and conversion yield to afford the desired mono-triflation product **5** in 61 % yield. The minor product was observed to be an ***ent*-4**, which was produced via initial triflation of the secondary alcohol of **12**, followed by intramolecular *O*-alkylation.




**Scheme 2** (a) (*S*)-(+)-glycidyl-3-nitrobenzenesulfonate, $Cs_2CO_3$, DMF, 98%; (b) $Co_2(CO)_8$, CO, MeOH, 78%; (c) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, 96%; (d) NBS, THF, -78 °C, 100%; (e) DIBAL-H, THF, -78 °C, 90%; (f) **6**, *n*-BuLi, THF, -78 °C, 80%; (g) Dess-Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, 85%; (h) $BCl_3$, $CH_2Cl_2$, -78 °C, 67%; (i) $PhNTf_2$, $K_2CO_3$, DMF, 61%

Given two pathways for the first Pd-catalyzed *O*-arylation as shown in Table 1, we explored intramolecular Pd-catalyzed *O*-arylation under various conditions. Treatment of **5** with $Pd(OAc)_2$ and $Cs_2CO_3$ in the presence of Sphos or JohnPhos as a ligand in toluene at 70 °C produced the desired pyranone **4** as the only product. However, reaction of **5** with $Pd(OAc)_2$ and $K_3PO_4$ in the presence of DPPF under reflux provided the cyclization product **13** instead of **4** via *O*-arylation with aryl bromide. Cyclization under other reaction conditions resulted in the decomposition of the starting material or the production of side products with a trace amount of **4**.

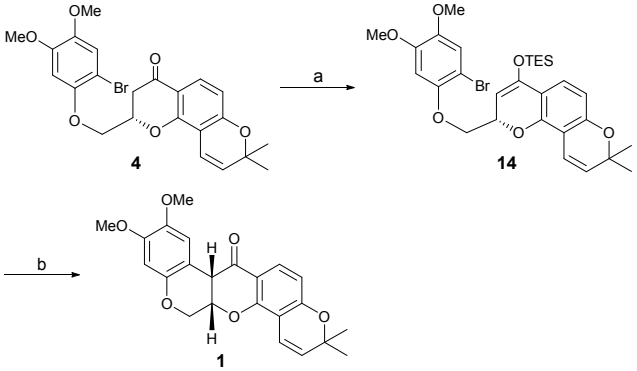
**Table 1** Pd-catalyzed intramolecular *O*-arylation




| Entry | Ligand[a] | Base | Temperature (°C) | Product (%) |
|---|---|---|---|---|
| 1 | DPPF | $K_3PO_4$ | reflux | **13** (46) |
| 2 | SPhos | $Cs_2CO_3$ | 70 | **4** (60) |
| 3 | JohnPhos | $Cs_2CO_3$ | 70 | **4** (<10) |

[a] DPPF: 1,1′-Bis(diphenylphosphino)ferrocene, JohnPhos: 2-(Di-*tert*-butylphosphino)biphenyl, SPhos: 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl

To complete the synthesis, attempts to achieve the direct α-arylation of aryl ketone **4** were not successful under various reaction conditions, including conditions in which $Pd(OAc)_2$, $Pd_2(dba)_3$ or $PdCl_2$ was used as a catalyst and DPPF, BINAP, DtBPF, P(*t*-Bu)$_3$, or *N*-heterocyclic carbene was used as a ligand. In particular, the basic reaction conditions appeared to consistently induce facile elimination to yield an α,β-unsaturated carbonyl moiety. Indeed, 4-chromanone has been reported to undergo ring opening to yield phenolate anions under basic conditions.[22, 23] Thus, we turned our attention to an Pd-catalyzed α-arylation of silyl enol ether possessing an aryl bromide moiety, as shown in Scheme 3, because the base-induced elimination would not occur in the absence of a carbonyl moiety.[24, 25] Subsequently, stable TES-enol ether **14** was prepared by reaction of **4** with TES-triflate in the presence of $Et_3N$. Enol ether **14** was treated with $Pd(OAc)_2$, P(*t*-Bu)$_3$, $Bu_3SnF$, and CsF in toluene at 70 °C and produced the desired (-)-deguelin (**1**) as an enantiomeric mixture (84 : 16)[26] in 27% yield, although this result was not satisfactory.




**Scheme 3** (a) TESOTf, $Et_3N$, $CH_2Cl_2$, 95%; (b) $Pd(OAc)_2$, P(*t*-Bu)$_3$, $Bu_3SnF$, CsF, toluene, 70 °C, 27% (e.r. = 84 : 16)

After further attempts to successfully cyclize **4**, we decided to replace aryl bromide **4** with aryl iodide **15**, which was anticipated to

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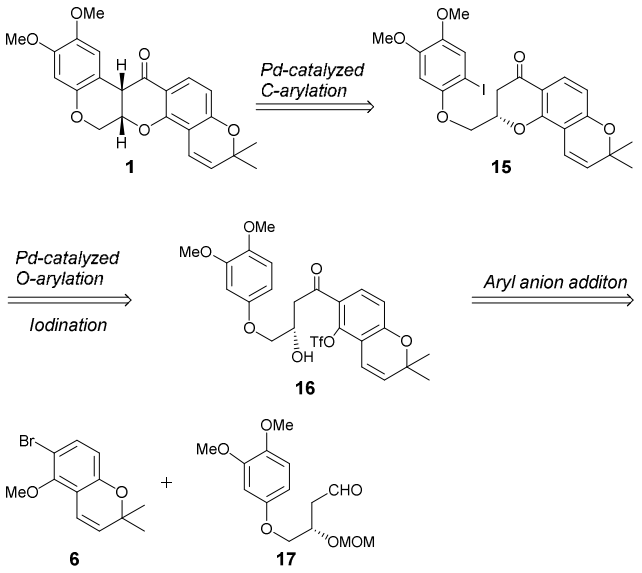
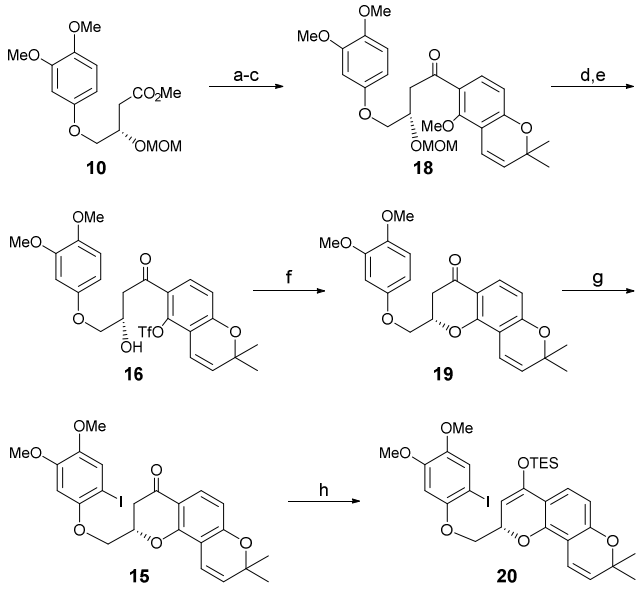
undergo more facile oxidative addition with the Pd-catalyst. We ultimately expected that the more reactive oxidative addition would result in a higher conversion yield and lower racemization during the *C*-arylation. As shown in Scheme 4, late-stage iodide substitution was performed because we were concerned that the labile aryl iodide moiety would not be tolerable during the *O*-arylation and preparation of the second arylation precursor **16**.




**Scheme 4** Revised synthetic approach to (-)-deguelin

As outlined in Scheme 5, the revised synthesis commenced with the preparation of the advance intermediate **16**, which would later be iodinated after the first arylation to afford the second Pd-catalyzed arylation precursor **15**. DIBAL reduction of ester **10** and coupling of the resulting aldehyde with the chromene unit **6** followed by Ley oxidation afforded ketone **18**. Global deprotection of **18** and chemoselective triflation of the resulting diol produced mono-triflate **16** as a first arylation precursor. Chemoselective triflation was again extensively examined under a variety of reaction conditions. Finally, $PhNTf_2$ treatment of diol in DMF in the presence of potassium carbonate provided the desired mono-triflate **16** in 72% yield, which was higher than the yield obtained for **5**.

The Pd-catalyzed *O*-arylation of **16** toward tetrahydropyanone **19** was greatly improved, as shown in Scheme 5, under the reaction conditions described for aryl bromide **4**. At this stage, preparation of intermediate **19** by a different strategy and its direct cyclization to (-)-deguelin was independently reported by Scheidt's group,[18] although the conversion yield was still not satisfactory. Thus, we executed our own strategy to complete the synthesis of deguelin in expecting improved results in terms of enantioselectivity and conversion yield. We attempted the regioselective iodination of **19** without affecting another aromatic system, which was coupled before iodination relative to the halogenation substrate **10** shown in Scheme 2. We optimized the iodination conditions to obtain the desired iodination product **15** in a moderate yield.[27-29] The ketone **15** was quantitatively converted to silyl enol ether **20**, which could be purified by chromatography.




**Scheme 5** (a) DIBAL-H, THF, -78 °C; (b) **6**, *n*-BuLi, THF, -78 °C; (c) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, 84% for 3 steps; (d) $BCl_3$, $CH_2Cl_2$, -78 °C, 64%; (e) $PhNTf_2$, $K_2CO_3$, DMF, 72% (f) Sphos, $Pd(OAc)_2$, $Cs_2CO_3$, toluene, 70 °C, 100%; (g) NIS, TFA, MeCN, rt, 64%; (h) TESOTf, $Et_3N$, $CH_2Cl_2$, rt, 100%

With the desired silyl enol ether **20**, we investigated Pd-catalyzed *C*-arylation to obtain the enantiomerically enriched (-)-deguelin (**1**). Generally, $AsPh_3$ was superior to other ligands, including P(*t*-Bu)$_3$ in terms of conversion yield and stereoselectivity. Presumably $AsPh_3$ stabilizes the Pd-substrate-stannane complex ultimately leading to increase of the yield and stereoselectivity.[30, 31] As shown in Table 2, CsF (1.4 equiv.) was essential as a fluoride source to produce the cyclization product. Interestingly, reaction in a solvent containing toluene and THF (10 : 1) while gradually raising the temperature resulted in effective arylation although partial racemization was observed in the polar solvent, presumably via initial elimination of the phenoxy group.[18] Noticeably, the use of benzene considerably enhanced both the enantioselectivity and conversion yield. In this particular case, the reaction was completed with minimal racemization. Consequently, the final cyclization was completed in 72% conversion yield with an 80 : 20 enantiomeric ratio. A decrease in reaction time for *C*-arylation increased the enantiomeric ratio up to 90 : 10 although the conversion yield was reduced to 30%. Clearly, the significantly improved result was likely due to the facile arylation of the iodinated precursor as well as the optimized reaction conditions, including the solvent and ligand type.

In summary, the complete synthesis of (-)-deguelin was achieved through 12 steps with 10.5% overall yield. The key features of our synthesis include the efficient preparation of the double cyclization precursor via highly convergent assembly of two aromatic systems and facile construction of the *cis*-fused bisbenzopyran skeleton via Pd-catalyzed *O* and *C*-arylation. In addition, the key architecture of the intermediate involves carbonylative epoxide ring opening catalyzed by cobalt. Our iterative intramolecular arylation strategy appears to widely applicable in rotenoid synthesis.

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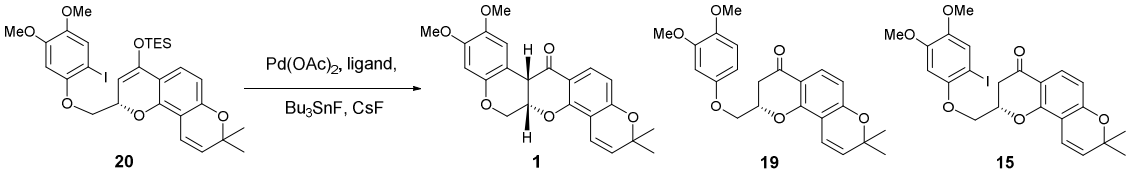
**Table 2** Pd-catalyzed intramolecular *C*-arylation




| Entry | Ligand | $Bu_3SnF$ (equiv.) | CsF (equiv.) | Solvent | Reaction time (h) | Temperature (℃) | Results | er |
|---|---|---|---|---|---|---|---|---|
| 1 | P(*t*-Bu)$_3$ | 1.4 | 1.4 | toluene | O/N[a] | 70 | <10% of **1** | |
| 2 | | 3 | 3 | | | | Degradation | |
| 3 | $AsPh_3$ | 1.4 | 1.4 | | | | **1** (20~40%) | 68 : 32 |
| 4 | | 3 | 3 | | 4 | | Degradation | |
| 5 | | 1.4 | 0 | | O/N | | No reaction | |
| 6 | | 1.4 | 1.4 | THF, DMF, MeCN or $Et_2O$ | | 60 | **15** | |
| 7 | | | | Toluene : THF (10 : 1) | | | **1** (60%) | 45 : 55 |
| 8 | | | | m-xylene | | | **1** (23%) | 65 : 35 |
| **9** | | | | **benzene** | **1** | | **1 (30%)** | **90 : 10** |
| **10** | | | | **benzene** | **3.5** | | **1 (72%)** | **80 : 20** |
| 11 | | | | DCE | O/N | | **19** | |

[a]O/N: over night

## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for all new compounds along with copies of $^1H$, $^{13}C$ NMR and HPLC spectra. See DOI: 10.1039/c000000x/

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