Synthesis of tricyclic pyrano[2,3-*e*]isoindolin-3-ones as the core structure of stachybotrin A, B, and C†

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The substituted tricyclic pyrano[2,3-*e*]isoindolin-3-ones 2 and 3, as the core structure of stachybotrin A, B, and C (1a–c), have been regioselectively synthesized for the first time by a short route which involved Mannich reaction and Claisen rearrangement.

Stachybotrins A (**1a**) and B (**1b**),[1] two new aromatic alkaloids with antibacterial and antifungal activities, have been isolated from an aquatic isolate of a new species of the genus *Stachybotrys* (CS-710-1). Stachybotrin C (**1c**),[2] a novel neuritogenic compound, was isolated from the culture broth of *Stachybotrys parvispora* F4708. Stachybotrin C (**1c**) induced significant neurite outgrowths in PC12 cells and showed cell survival activity in the primary culture of cerebral cortical neurons. Since its protective effect on neuronal cell damage is pronounced, **1c** is supposed to work as a neurotrophic factor in cerebral neurons, and is expected to prevent hypoxic neuronal injury caused by ischemia.

Stachybotrins **1a–c** have a pyrano[2,3-*e*]isoindolin-3-one as the common core structure. The chroman has two stereogenic centers due to three different substituents and the relative stereochemistry was determined by analysis of NMR experiments as (2*S**, 3*S**) configuration.

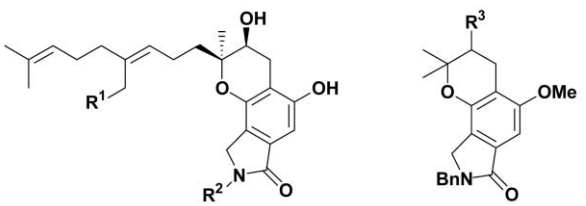


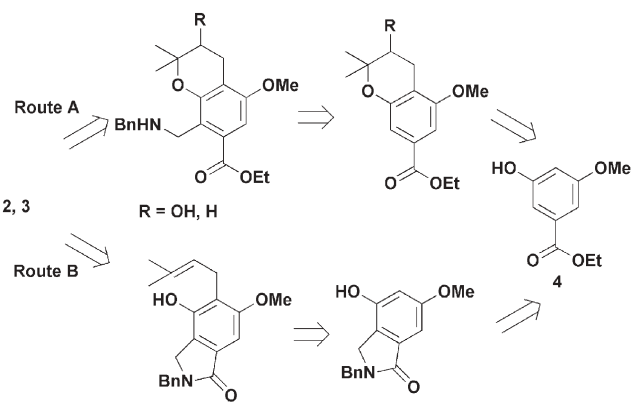
Fig.1

Stachybotrin A **1a** : R^1 = OH, R^2 = H **2** : R^3 = H
Stachybotrin B **1b** : R^1 = H, R^2 = H **3** : R^3 = OH
Stachybotrin C **1c** : R^1 = H, R^2 = $C_2H_4C_6H_4OH$

The most crucial problem in their synthesis is associated with the stereoselective creation of two asymmetric carbon centers in the chroman ring. Through our extensive study on the *ortho*-alkylation of phenols *via* a [2,3]sigmatropic rearrangement reaction under mild conditions,[3] we have previously reported their application to the stereoselective synthesis of 2,2-dialkylchroman and others.[4] This reaction forms a C–C bond at the *ortho* position of a phenol through a sulfonium intermediate. It is expected that this rearrangement is applicable to construction of the chiral chroman skeleton of stachybotrins. A further synthetic problem is how to regioselectively synthesize the tricyclic core structure, pyrano[2,3-*e*]isoindolin-3-one. Since regioselective alkylation to a polysubstituted phenolic nucleus is very difficult, although several approaches[5] have been developed, synthesis of the tricyclic pyranoisoindolinone is undoubtedly a challenging problem. Herein we report an efficient regioselective synthesis of the core structures **2** and **3** directed toward establishment of strategies for the total synthesis of the natural products.

We proposed that the tricyclic structure could be constructed from 3,5-dihydroxybenzoic acid derivatives by alkylation at the *ortho* position to form the lactam ring and another alkylation at the *para* position to form the pyran ring. The retrosynthetic analysis can be shown as routes A and B in Scheme 1.

Route A includes the initial chroman formation followed by the lactam formation, and route B consists of the first formation of the lactam ring followed by the pyran formation. Initially we examined the regioselectivity of the alkylation of 3,5-dihydroxybenzoic acid derivative **4** by [2,3] sigmatropic rearrangement with isopentenyl sulfide (Scheme 2). Regioselective alkylation could not be realized and the desired product **5** (35%) was obtained along with regioisomer **6** (15%). We next examined the Claisen rearrangement of allyl ether **7** (Scheme 2).[6] Thermal treatment of allyl phenyl ether **7** provided *para*-allylated product **8** only in 7% yield along with a major amount of *ortho* product **9** in 87% yield. These results suggest that route A is not adequate to obtain **2** or **3** effectively.



Scheme 1

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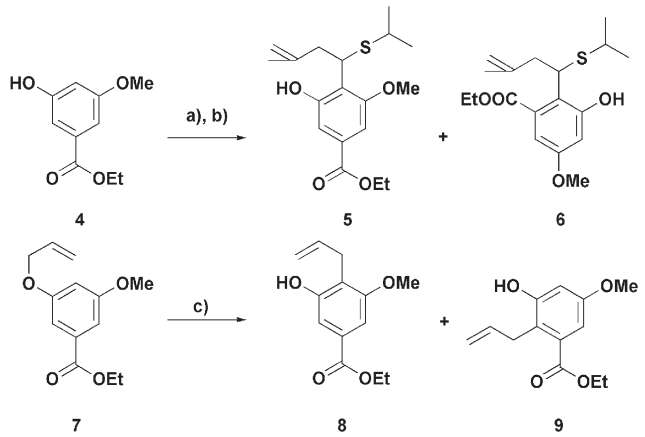


Scheme 2 (a) $CH_2{=}C(CH_3)CH_2CH_2SCH(CH_3)_2$, *s*-collidine, SO_2Cl_2, CH_2Cl_2, −50 °C, (b) Et_3N, CH_2Cl_2, −50 °C, **5**:35%, **6**:15%, (c) xylene, 140 °C, **8**:87%, **9**:7%

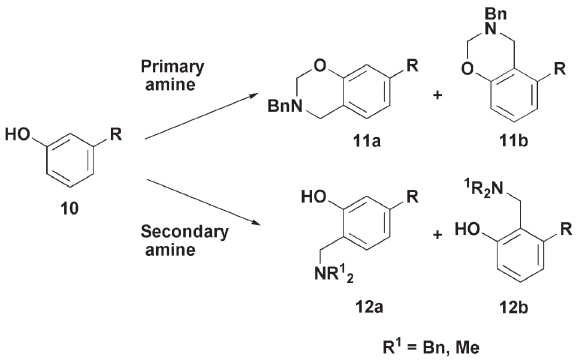
Then we examined route B. Although a wide variety of methodologies have been known for the preparation of indol compounds, a relatively small number of methods described the construction of isoindolinones.[7] Since the intramolecular condensation of aminomethyl group and ester group in *o*-(aminomethyl)benzoic acid derivative affords isoindolinone,[8] it is predicted that regioselective aminomethylation[9] at the *ortho* position of **4** can lead to the desired isoindolinone. As a promising method for aminomethylation, we chose the Mannich reaction of the phenolic compound. To the best of our knowledge, there have been no reports on the systematic investigation of the regioselectivity of the *meta*-substituted phenols. Therefore we examined the Mannich reaction of various phenols using some primary and secondary amines. The results are shown in Table 1.

Mannich reaction of 3-*tert*-butylphenol with benzylamine (entry 1) gave a "*para*" Mannich product (**11a**, R = *t*-Bu) in 95% yield with no *ortho* product. The regiochemistry of product was clearly established by NOE experiment. Similarly, *m*-cresol (entry 2) also provided only *para* Mannich product (**11a**, R = Me) in 89% yield. Reaction of ethyl 3-hydroxybenzoate (entry 3) with benzylamine did not take place without addition of acid catalyst because of lowered reactivity due to the lack of the electron density of the benzene ring, and acid-catalyzed reaction gave **11a** (R = COOEt) (45%) selectively. However, 3-bromophenol furnished both isomers of the Mannich products in the ratio of 1.6 : 1.

Then, we tried to use secondary amine for improving the regioselectivity. Contrary to our expectation, Mannich reaction of 3-bromophenol and dimethylamine (entry 5) provided a mixture of two regioisomers in the ratio of 1.2 : 1. When the reaction temperature was decreased at 0 °C (entry 6), regioselectivity was improved to 4 : 1. We next used dibenzylamine as a more sterically demanded amine, but Mannich reaction did not take place at 0 °C. The reaction proceeded only at reflux to give Mannich product in 26% yield as a sole product (entry 8).

In contrast to *m*-cresol, the treatment of 3-methoxyphenol with benzylamine (entry 9) gave both regioisomers in the ratio of 4.4 : 1. However, using dibenzylamine instead of benzylamine (entry 10), the *para* Mannich reaction proceeded selectively to give **12a** (R = OMe, R^1 = Bn) in 72% yield. These results suggested that the Mannich reaction took place preferentially, not always selectively,

Table 1 Mannich reaction of *m*-substituted phenols with primary and secondary amines.[a]

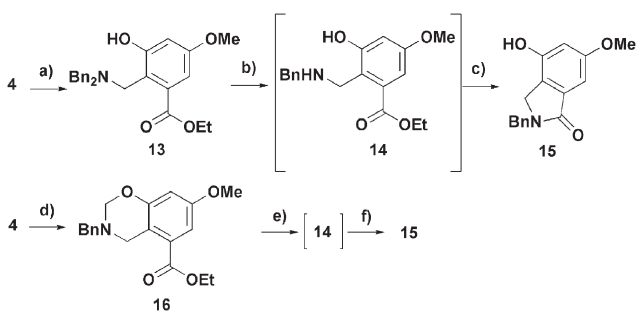


Entry	R	Amine	Temp./°C	Yield (%)	Ratio a/b
1	*t*-Bu	$BnNH_2$	Reflux	95	100 : 0
2	Me	$BnNH_2$	Reflux	89	100 : 0
3[b]	COOEt	$BnNH_2$	Reflux	45	100 : 0
4	Br	$BnNH_2$	Reflux	74	1.6 : 1
5		Me_2NH	Reflux	67	1.2 : 1
6		Me_2NH	0	42	4 :1
7		Bn_2NH	0	—	—
8[b]		Bn_2NH	Reflux	26	100 : 0
9	OMe	$BnNH_2$	Reflux	70	4.4 : 1
10		Bn_2NH	Reflux	72	100 : 0

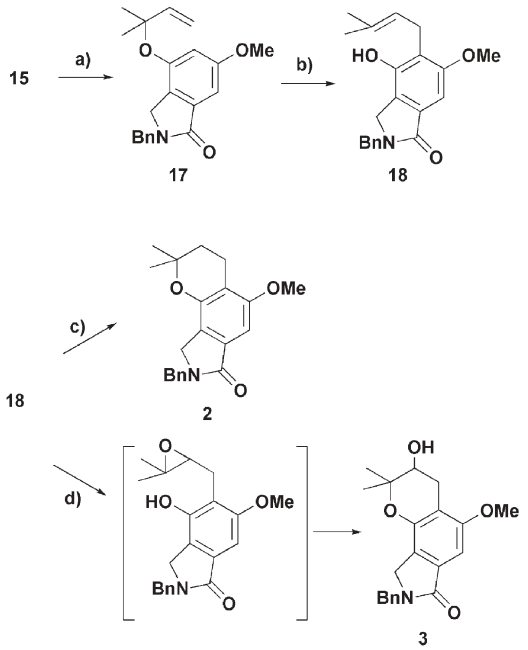
[a] Amine, aq. 38% HCHO, EtOH, 8 h. [b] Catalytic amount of conc. HCl was added.

at the *para* position to the *meta* substituent of a phenol although a clear relationship could not be found between the regioselectivity and bulkiness or electron-donating ability of *meta* substitution.

Therefore we expected that the Mannich reaction could be applied to synthesis of the isoindolinone. Phenolic ester **4** was treated with dibenzylamine and formaldehyde to give only *para* Manich product **13**. One benzyl group of **13** was removed by hydrogenolysis with Pd/C in 4.4% formic acid–ethanol to lead to **14**, followed by treatment with NaH to give desired isoindolinone **15** regioselectively. Although **15** was obtained selectively, the overall yield was not satisfactory. If the Mannich reaction of **4** were to take place regioselectively with primary amine, another synthetic route would be realized. Fortunately, the desired Mannich reaction of **4** using benzylamine proceeded to give the desired **16** exclusively. Oxazine **16** was converted to **14** by acid



Scheme 3 (a) Bn_2NH, *aq*. 38% HCHO, EtOH, reflux, 58%, (b) 10% Pd/C, 4.4% formic acid–EtOH, quant., (c) NaH, THF, 75%, (d) $BnNH_2$, EtOH, reflux, 93%, (e) HCl, EtOH, reflux, (f) NaOEt, EtOH, reflux, 58% (2 steps from **16**).



Scheme 4 (a) $Pd(PPh_3)_4$, THF/DMF(1 : 1), $^{i}BuOCOOC(CH_3)_2CH{=}CH_2$, 65%, (b) xylene, 140 °C, 86%, (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 84%, (d) $VO(acac)_2$, TBHP, TFA, 65%

hydrolysis followed by treatment with NaOEt *in situ* to give isoindolinone **15** in good yield.

With the isoindolinone **15** in hand, *ortho*-alkylation by Claisen rearrangement was investigated to make **2** and **3** (Scheme 4). Recently a synthetic method for tertiary allyl phenyl ether has been explored by employing mixed carbonate with π-allylpalladium species.[10] Thus, reaction of isoindolinone **15** with 1,1-dimethyl-2-propenyl isobutyl carbonate in the presence of tetrakis(triphenylphosphine)palladium in THF and DMF gave the allyl phenyl ether **17** (65%) as a single product. Thermal Claisen rearrangement of **17** furnished prenylated isoindolinone **18** (86%). Addition of $BF_3{\cdot}OEt_2$ to **18** in dichloromethane at 0 °C afforded the desired compound **2**.

Finally, we studied cyclization to 3-chromanol (**3**). Although *m*-CPBA has been frequently employed for the epoxidation of *o*-allylphenols, carefully controlled experimental conditions such as low temperature and, more importantly, buffered reaction medium, are required in order to prevent further cyclization to dihydrofuran and dihydropyran derivatives.[11] On the other hand, the $VO(acac)_2$–TBHP–TFA system is simple and mild, and chroman-3-ol is successfully prepared.[12] The cyclization *via* epoxidation with this system gave the desired compound **3** (65%).

In summary, we achieved the synthesis of pyrano[2,3-*e*]isoindolin-3-ones, **2** and **3**, as the core structure of stachybotrins **1a–c**. The synthetic highlights are a regioselective Mannich reaction for construction of isoindolinone and Claisen rearrangement for prenylation at the selected position. Further work toward total synthesis of **1a–c** is currently under way.

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