Synthetic Studies towards Stachybotrin C

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Abstract: The preparation of racemic des-hydroxy stachybotrin C is described. Different approaches have been studied. Observations made in the course of the synthesis show the efficiency of the intermolecular cyclization between the diethyl acetal **19** and phenol **12** leading to the benzopyran moiety **17**.

Key words: natural products, pyrano-isoindolinone, spiro compounds, cyclization

Stachybotrin C (**1**; Figure 1), isolated from culture broths of *Stachybotrys parvispora* F4708, has been found to induce significant neurite outgrowth in PC12 cells at levels of 30 μg/mL and showed protecting effects against neuronal damage.[1] Because of its neuritogenic properties, stachybotrin C, like other small molecules, has been sought for the treatment of neurodegenerative diseases.[2] Stachybotrin C contains a unique pyrano-isoindolinone ring system with two stereogenic centers (of which only the relative stereochemistry is known) and is related to stachybotrins A and B, which were isolated from the fungus *Stachybotrys* sp.[3] Despite efforts described in 2006 by Inoue and co-workers, to our knowledge, no total synthesis has been reported to date.[4]

Being aware of the need to develop an efficient and flexible route to **1** and plausible analogues for medicinal chemistry purposes, we disclose in this paper our own efforts in this research area. First, we wanted to prepare pyrano-isoindolinone **2**, which was expected be a valuable precursor of **1**, relying on recent work on the gold-catalyzed intramolecular hydroarylation of alkynes and alkenes.[5] The cyclization could be preceded by the formation of an ether derivative, which, in turn, could be obtained by the combination of carbonate **4** with phenol **3** (Scheme 1). The advantage of this approach is that it enables the stereocenter at the α-position of the ether function to be controlled, and offers the possibility of developing an asymmetric synthesis of **1**.

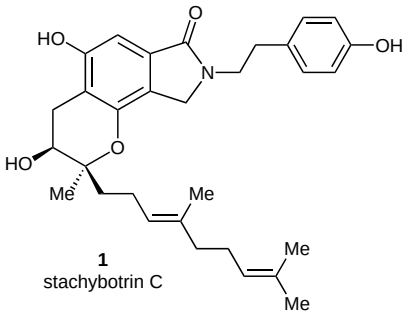
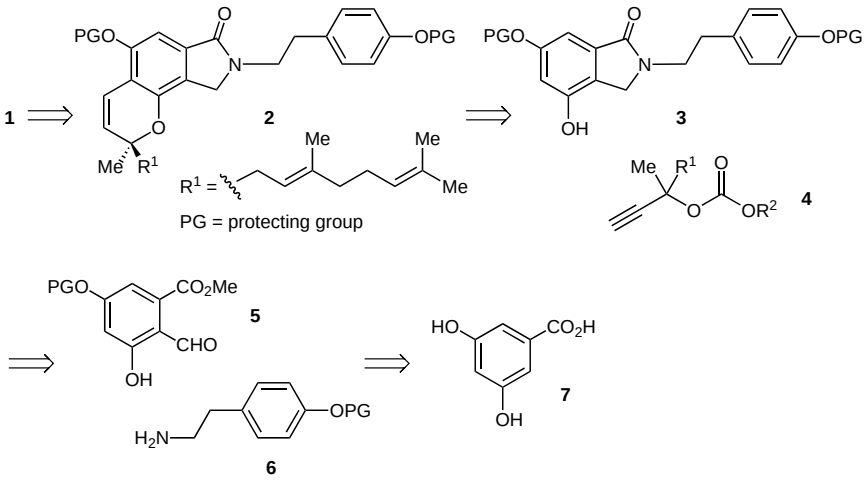


Figure 1 Structure of stachybotrin C

Our synthesis began with the preparation of the 2,3-dihydro-1*H*-isoindolinone derivative **12** from commercially



Scheme 1 Retrosynthetic approach

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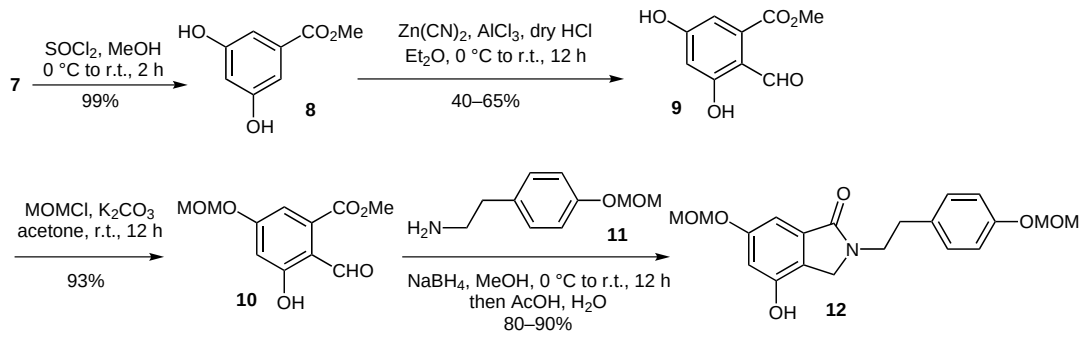
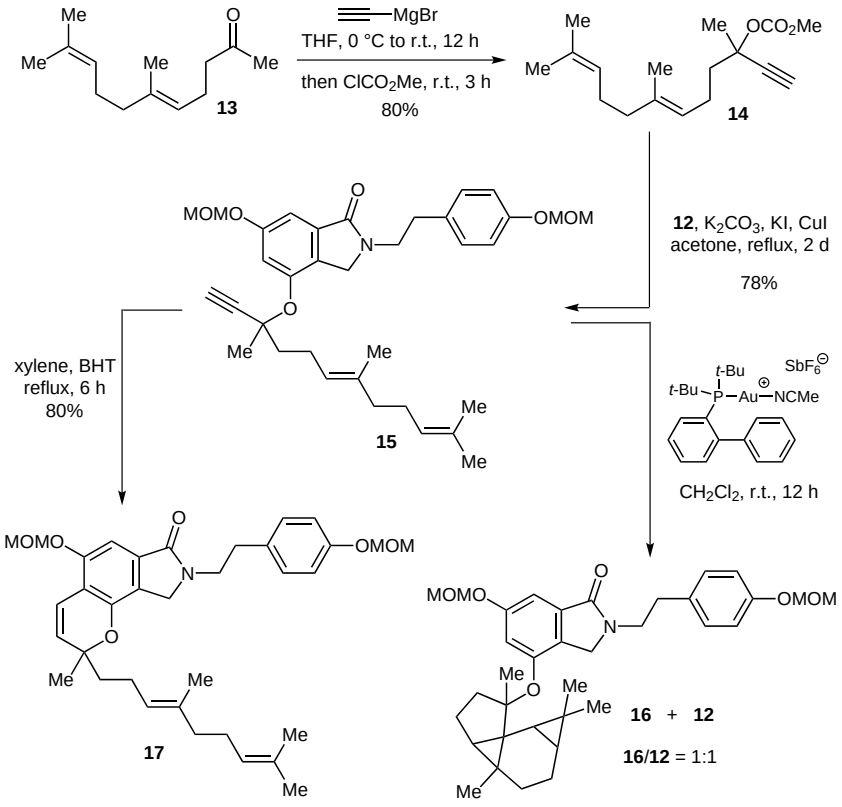


Scheme 2 Preparation of the 2,3-dihydro-1*H*-isoindolinone derivative **12**

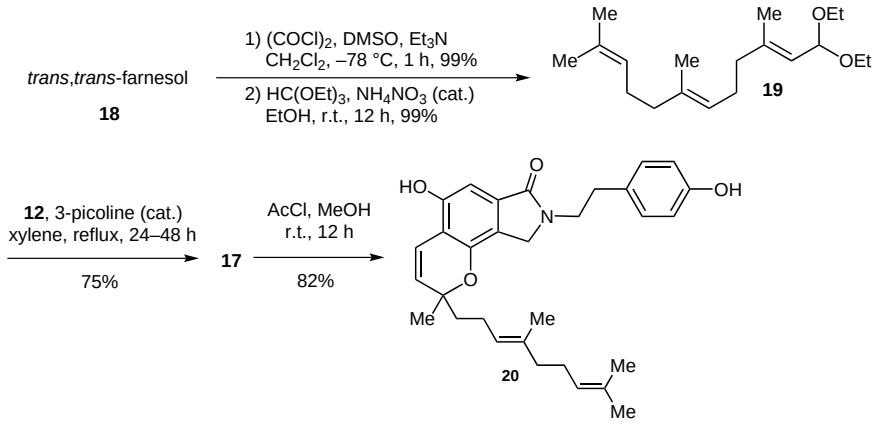
available 3,5-dihydroxybenzoic acid (**7**) in a short sequence of reactions (Scheme 2). Salicylaldehyde **10** was prepared according to the literature in three steps[6] and then converted into the expected amide **12** after a selective reductive amination and amide formation with O-protected tyramine **11**.[7]

Scheme 3 summarizes the synthesis of the advanced pyrano-isoindolinone intermediate **17**, which was obtained after thermal intramolecular cyclization. Thus, alkylation of readily available (*E*)-geranylacetone **13** (prepared from geraniol in three steps)[7] with ethynylmagnesium bromide in tetrahydrofuran (THF) proceeded smoothly to afford carbonate **14** after quenching the reaction mixture with a slight excess of methyl chloroformate. Coupling optimization studies on phenol **12** with propargylic carbonate **14** led to the production of ether **15**, which was obtained in good yield by mixing **12** with **14** (2 equiv) in the presence of K_2CO_3 (2 equiv), KI (2 equiv), and CuI (0.2 equiv) upon reflux for 24 hours, followed by an addition of one more equivalent of carbonate **14** and additional stirring under reflux for 24 hours to complete the reaction.

Because it is well established that gold complexes possess high affinity for C–C triple bonds and activate many nucleophilic additions to this kind of unsaturated bond,[8] we thought to use this methodology to form the pyran ring. Unfortunately, in the presence of a catalytic amount of a cationic gold(I) complex,[5a] no formation of the expected pyran was observed. The desired hydroarylation reaction failed and only a mixture of phenol **12** and a polycyclized derivative **16** in a ratio 1:1 was obtained.[9] This problem was, however, solved by performing the reaction under thermal conditions; thus, heating **15** in xylene at reflux provided the pyrano-isoindolinone intermediate **17** in good yield.



Scheme 3 Intramolecular cyclization



Scheme 4 Intermolecular cyclization

Encouraged by this result, we decided to focus on a straightforward approach involving an intermolecular cyclization, as rationalized by North and co-workers.[10] After conversion of *trans*,*trans*-farnesol **18** into diethyl acetal **19** in two efficient steps, heating the latter in xylene under reflux with phenol **12** and a catalytic amount of 3-picoline led, after two days, to the pyrano-isoindolinone derivative **17** in 75% yield (Scheme 4).[11] The MOM protecting group was cleanly removed by exposure of **17** to HCl (generated in situ by adding AcCl to methanol), affording **20** in good yield.[12]

In conclusion, the preparation of pyrano-isoindolinone derivative **20** (30% overall yield in 11 steps) from 3,5-dihydroxybenzoic acid (**7**) has been achieved. Compound **20** can be considered as an analogue of stachybotrin C and its biological activity will be evaluated later. Whereas the approach involving intramolecular gold-catalyzed hydroarylation reaction of alkyne failed, intermolecular cyclization to form the benzopyran moiety proved to be effective. To date, despite our continuous efforts, conversion of intermediate **17** or compound **20** into racemic stachybotrin C has been unsuccessful. A revised strategy is in progress and will be reported in due course.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) For the preparation of **11** and **13**, see the Supporting Information.

(8) For a significant and recent review on gold-catalyzed additions to C–C multiple bonds, see: Huang, H.; Zhou, Y.; Liu, H. *Beilstein J. Org. Chem.* **2011**, *7*, 897.

(9) The gold-catalyzed biscyclopropanation of dienynes has been already reported, see: Nieto-Oberhuber, C.; López, S.; Paz Muñoz, M.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem.–Eur. J.* **2006**, *12*, 1694.

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(11) To a solution of **12** (500 mg, 1.34 mmol, 1.0 equiv) in anhydrous *o*-xylene (8 mL), **19** (790 mg, 2.68 mmol, 2.0 equiv) and 3-picoline (33 μL, 0.34 mmol, 0.25 equiv) were added. The reaction mixture was heated to reflux for 48 h, then the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2–EtOAc, 9:1→4:1) to afford **17** (775 mg, 75%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.56 (s, 3 H), 1.59 (s, 3 H), 1.66–1.76 (m, 5 H), 1.92–1.97 (m, 2 H), 2.01–2.15 (m, 4 H), 2.92 (t, *J* = 7.5 Hz, 2 H), 3.47 (s, 3 H), 3.48 (s, 3 H), 3.74–3.84 (m, 2 H), 4.16 (s, 2 H), 5.05–5.14 (m, 2 H), 5.15 (s, 2 H), 5.22 (s, 2 H), 5.61 (d, *J* = 10.2 Hz, 1 H), 6.76 (d, *J* = 10.2 Hz, 1 H), 6.96 (d, *J* = 8.7 Hz, 2 H), 7.07 (s, 1 H), 7.16 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 17.7, 22.5, 25.7, 26.6, 34.0, 39.6, 41.2, 44.3, 47.7, 55.9, 56.3, 78.9, 94.5, 95.0, 101.2, 113.6, 116.4, 117.5, 121.4, 123.6, 124.2, 129.4, 129.7, 131.4, 132.1, 133.9, 135.5, 148.2, 153.2, 155.9, 168.3. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{45}NO_6Na$: 598.3139; found: 598.3139.

(12) To a solution of **17** (200 mg, 0.35 mmol, 1.0 equiv) in anhydrous MeOH (4 mL) was added at 0 °C, acetyl chloride (100 μL, 1.39 mmol, 4.0 equiv). The solution was stirred at room temperature for 20 h then concentrated under reduced

pressure and the residue was purified by column chromatography on silica gel (PE–EtOAc, 1:1) to afford **20** (140 mg, 82%) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.56 (s, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.66–1.76 (m, 2 H), 1.92–1.97 (m, 2 H), 2.01–2.15 (m, 4 H), 2.85 (t, *J* = 7.5 Hz, 2 H), 3.70–3.84 (m, 2 H), 4.17 (s, 2 H), 5.05–5.14 (m, 2 H), 5.55 (d, *J* = 10.2 Hz, 1 H), 6.76–6.79 (m, 3 H), 6.96–7.01 (m, 3 H), 7.46 (br s, 1 H), 8.40 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 17.7, 22.5, 25.7, 26.6, 26.6, 33.8, 39.6, 41.2, 44.4, 47.9, 79.0, 102.4, 112.2, 115.6, 117.5, 119.6, 123.7, 124.2, 129.0, 129.7, 130.2, 131.4, 133.2, 135.6, 148.4, 152.7, 154.6, 169.0. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{37}NO_4Na$: 510.2620; found: 510.2621.

