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Synthesis of 3-methoxy-9-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[7]annulen-4-ol, a potent antineoplastic benzosuberene derivative for anti-cancer chemotherapy

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ABSTRACT

Benzosuberene **8** is a tubulin polymerization inhibitor that possesses remarkable potency against a variety of cancer cell lines. Herein, an efficient synthetic route for **8** is described featuring a Claisen rearrangement/RCM sequence and a late stage Suzuki coupling as the key steps. By adopting this strategy **8** was synthesized in eight steps in 18% overall yield starting from known compound **18**.

Microtubules are cytoskeletal polymers of tubulin αβ heterodimers that are essential in several cellular functions such as cell division and morphogenesis.[1] The functional assembly–disassembly cycle of αβ tubulin units includes activation by GTP binding at the β-subunit, polymerization into microtubules, GTP hydrolysis, depolymerization of GDP-tubulin, followed by replacement with GTP. Compounds that interfere with the polymerization/depolymerization dynamics of tubulin represent an important class of antineoplastic agents. Four major classes of microtubule active agents have been identified in terms of four different binding sites within β-tubulin.[2] The vinca alkaloids (e.g., vincristine, vinblastine, vindesine, and vinorelbine), peptide inhibitors (e.g., dolastatins) and maytansines bind to two overlapping sites on β-tubulin and induce microtubule depolymerization. The taxoids paclitaxel (Taxol) and docetaxel (Taxotere), as well as the epothilones, bind to β-tubulin and induce microtubule polymerization. The fourth class of agents, typified by the natural products such as colchicine (**1**) and podophyllotoxin (**2**) (Fig. 1), bind at the α-β-subunit intradimer interface and include the combretastatins, which also promote tubulin depolymerization. Combretastatins, as exemplified by combretastatin A4 (**3**) and its phosphorylated prodrug CA4P (**4**), represent a class of drugs that are in clinical trials as antitumor agents.[3,4] A large array of compounds have been reported that bind to the colchicine binding site such as chalcone **5**,[5] benzofurans (**6**, **7**)[6] and benzosuberene **8**[7] (Fig. 1). There is a great interest in this class of compounds for cancer chemotherapy based on the observation that agents that bind to the colchicine binding site act as vascular disrupting agents and block the blood supply to the tumor vasculature, in addition to their cytotoxic effects.[8,9]

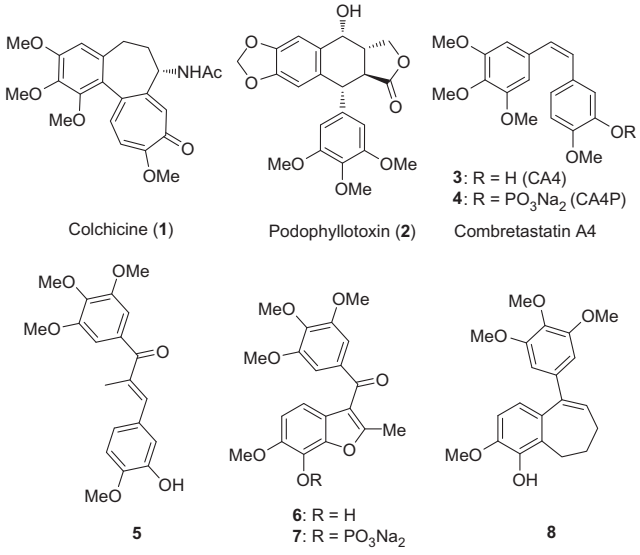

Figure 1. Selected compounds that bind to the colchicine binding site of β-tubulin.

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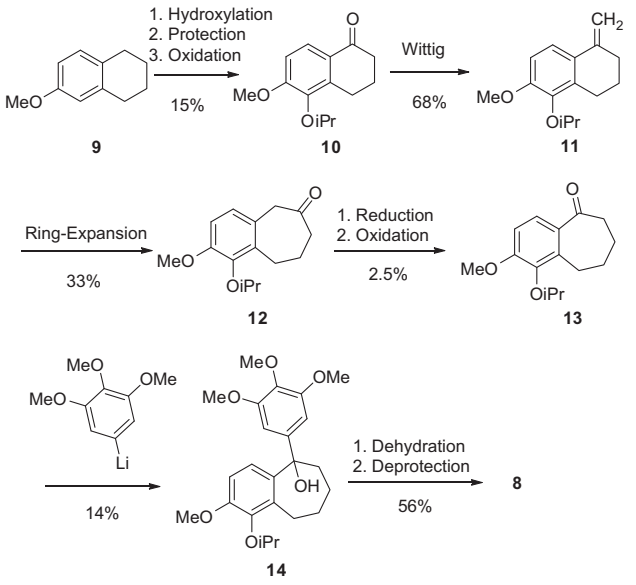
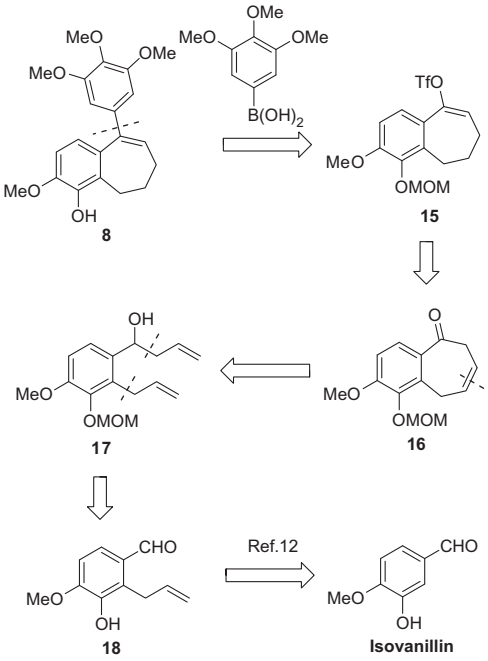
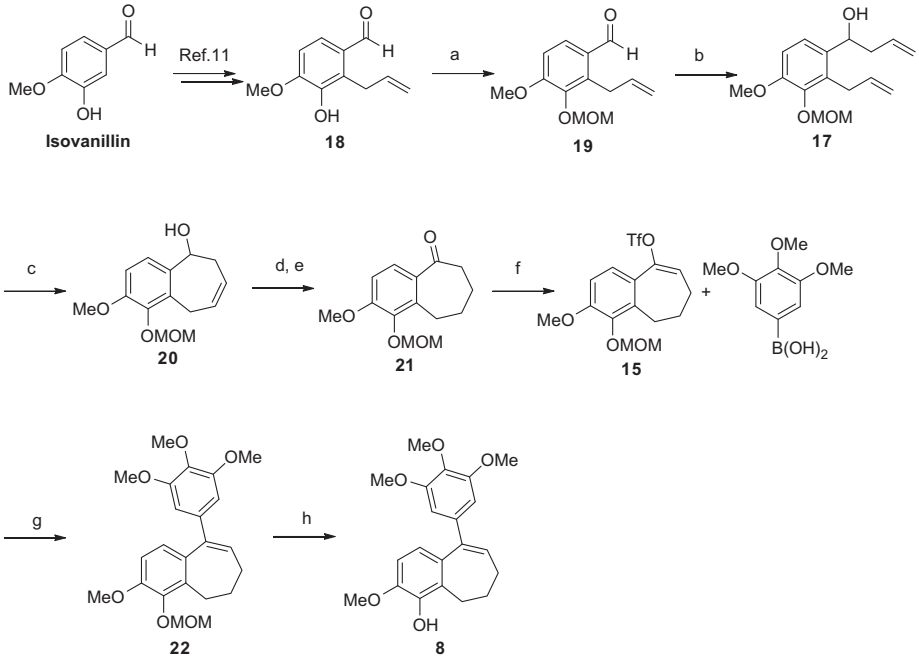


Scheme 1. Pinney's synthesis of benzosuberene (**8**).[7]



Scheme 2. Retrosynthetic analysis of benzosuberene (**8**).



Scheme 3. New synthesis of benzosuberene **8**. Reagents and conditions: (a) MOM–Br, iPr$_2$NEt, CH_2Cl_2, rt (78%); (b) allylMgBr, THF, −78 °C (85%); (c) Grubb's 2nd catalyst (3 mol %), CH_2Cl_2, 40 °C, 1 h (90%); (d) TsNH–NH_2, NaOAc, DME, 80 °C; (e) Dess–Martin periodinane, CH_2Cl_2, rt (58% for two steps); (f) $PhNTf_2$, KHDMS, THF, −78 °C; (g) $Pd(PPh_3)_4$ (3 mol %), $Ba(OH)_2$, DME, H_2O, 70 °C (62% for two steps); (h) HCl, MeOH, 60 °C (85%).

Recently, Pinney and co-workers discovered the benzosuberene analog **8** (Fig. 1) as a potent tubulin polymerization inhibitor at concentrations comparable to that of combretastatin A4 (CA4).[7] Furthermore, this compound demonstrated remarkable cytotoxicity against a variety of cancer cell lines in the low nanomolar range. As shown Scheme 1, this 10-step synthesis included five low yielding steps and provided the target compound **8** in 0.01% overall yield from tetraline **9**.[7]

In considering an alternative strategy to the synthesis of benzosuberene **8**, a higher yielding C–C bond forming reaction to install the trimethoxyphenyl group is highly desirable. Additionally, a better synthesis should be able to access diverse structural analogs to facilitate the SAR study for lead optimization. As such we envisioned utilizing a Claisen rearrangement/ring closing metathesis (RCM) sequence to construct the benzocycloheptene ring system and a late stage Suzuki coupling to install the trimethoxyphenyl ring as the key steps.

Scheme 2 shows the retrosynthetic analysis of our designed route for **8**. We envisioned preparing **8** through a late stage Suzuki coupling of trimethoxy phenylboronic acid with enol triflate **15**.

The benzosuberone **16** could be obtained from diene **17** via a RCM reaction.[10,11] Diene **17** could be elaborated from isovanillin by adopting an O-allylation/Claisen rearrangement sequence via the known compound **18**.[12]

Our synthesis commenced with the O-allylation of the phenol group in isovanillin followed by Claisen rearrangement under thermal conditions to provide **18** in high yield (Scheme 3).[11,12] Protection of the phenol group in **18** as its MOM ether through reaction with methoxymethyl bromide gave **19**, which was reacted with allylmagnesium bromide to produce the corresponding secondary alcohol **17**. The subsequent RCM reaction of **17** was performed in dichloromethane using Grubb's 2nd generation catalyst[13] (3 mol % loading) to give the bicyclic compound **20** in 90% isolated yield. It was found that Grubb's 1st generation catalyst also can be employed for this RCM reaction, but the catalyst loading needs to be higher (from 3 mol % to 6 mol %), and the reaction time needs to be longer (from 1 h to 6 h) for completion. Diimide reduction of the double bond in **20** and oxidation of the benzylic hydroxyl group by Dess–Martin periodinane gave the MOM-protected benzosuberone **21** in moderate yield over two steps. Reaction of **21** with potassium hexamethydisilazane and *N*-phenyl triflimide resulted in the corresponding enol triflate **15**, which was directly used for the succeeding Suzuki coupling[14] with 3,4,5-trimethoxyphenyl boronic acid to provide the MOM protected benzosuberene precursor **22** in 62% yield over two steps. Finally, deprotection using methanolic hydrogen chloride provided the target benzosuberene 3-methoxy-9-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[7]-annulen-4-ol (**8**) in 85% isolated yield.[15] Overall, the target compound **8** was synthesized in eight steps and 18% yield starting from the literature known compound **18**.

In summary, we have developed a novel and efficient synthesis for the benzosuberene analog 3-methoxy-9-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[7]-annulen-4-ol (**8**), a powerful antineoplastic agent that binds to the colchicine binding domain of tubulin. Efforts on the application to the synthesis of other benzosuberene analogs with the structural modifications in the B-ring for further biological studies are undergoing in our laboratory, and the results will be reported in due course.

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15. *Compound* ***8***: White solid, mp 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (q, J = 7.0 Hz, 2H), 2.15 (quin, J = 6.9 Hz, 2H), 2.77 (t, J = 6.9 Hz, 2H), 3.81 (s, 6H), 3.87 (s, 3H), 3.92 (s, 3H), 5.75 (s, 1H), 6.34 (t, J = 7.0 Hz, 1H), 6.51 (s, 2H), 6.58 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 25.4, 33.3, 55.6, 55.8 (2C), 60.6, 104.9 (2C), 107.3, 120.5, 126.9, 127.4, 133.9, 136.9, 138.2, 141.9, 142.4, 144.7, 152.5 (2C); MS (ESI) m/z 357 (M+H); HRMS calcd for $C_{21}H_{24}O_5$ (M+H) 357.1696, obsd 357.1699.