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Total synthesis of panicein A_2

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Full Research Paper

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Abstract

The first total synthesis of the unusual aromatic sesquiterpene panicein A_2 is reported and the structure of the natural product has been confirmed. When tested by the NCI against a range of human cancer cell lines, it was found that panicein A_2 exhibits very little antiproliferative activity at 10 μM – an observation that is at odds with the earlier report that stated panicein A_2 exhibits in vitro cytotoxicity against a number of tumour cell lines.

Introduction

The panicein family is an unusual family of natural products, which generally consist of an aromatic sesquiterpene group linked to a quinone (as seen in panicein A (**1**), Figure 1), hydroquinone moiety (as seen in paniceins D (**2**), F (**3**) and F_1 (**4**)) or chromenol as seen in panicein A_2 (**5**).

The first members of the panicein family were isolated by Cimino et al. in 1973 from the marine sponge *Halichondria panacea* [1]; members of this family have since been isolated from *Reniera fulva* and *R. mucosa* [2,3]. It has been postulated that the biosynthesis of paniceins centres around the cyclisation of a farnesyl precursor **6** [4] to an abscisane derivative **7** followed by a 1,2-methyl migration and subsequent oxidation to give panicein A (**1**) [1,3]. Subsequent electrocyclisation [5,6] would afford panicein A_2 (**5**) (Figure 2). This hypothesis has been supported by the isolation of species believed to be intermediates along this proposed reaction pathway [3].

Panicein A_2 (**5**), an example of a cyclised variant of the panicein structure, is a racemic compound that was first isolated in 1994 from *Reniera mucosa* alongside its non-cyclised isomer **1**, and ten other members of the panicein family [3]. Panicein A_2 (**5**) and D (**2**) were reported to exhibit in vitro cytotoxicity against four cancer cell lines (P388 mice lymphoma, A549 human lung carcinoma, HT29 human colon carcinoma and MEL28 human melanoma) with an ED_{50} of 5 μg/mL [3]. Panicein F_1 (**4**) was active against P388, A549 and MEL20 cell lines (ED_{50} = 2.5 μg/mL). The diversity of antiproliferative activities shown by these compounds, and particularly panicein A_2 (**5**), presents them to be attractive synthetic targets.

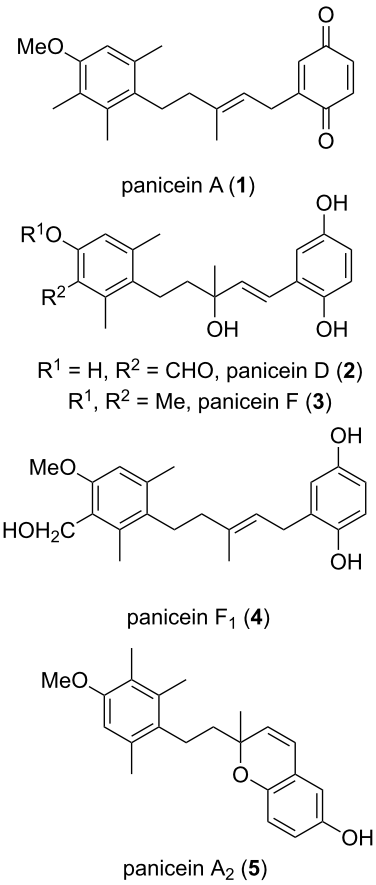


Figure 1: Members of the panicein family of aromatic sesquiterpenoids.

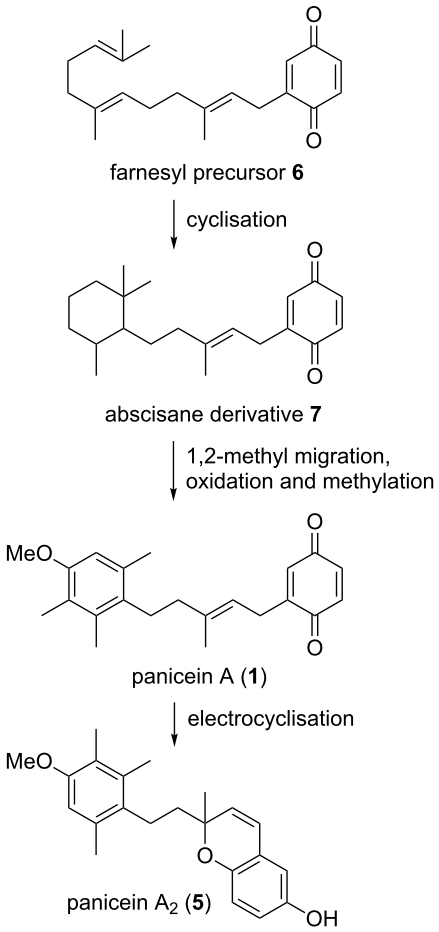


Figure 2: Proposed biogenesis of panicein A_2 (**5**).

We proposed that panicein A_2 (**5**) could be synthesised from the cyclisation and subsequent deprotection of propargyl ether **8**. Ether **8** could be formed through the addition of the appropriate phenol to acetylenic alcohol **9**, which itself can be derived from aldehyde **10** (Figure 3).

Results and Discussion

Synthesis of panicein A_2

Firstly, aldehyde **10** was required; it was prepared through methylation followed by Vilsmeier–Haack reaction of 2,3,5-trimethylphenol (**11**), giving **10** in 51% yield over two steps (Scheme 1) [7]. Aldehyde **10** then underwent an aldol reaction according to the procedures of Samokhvalov et al. to provide ketone **12** in 66% yield [8]. The selective reduction of the olefin in α,β-unsaturated ketone **12** was then attempted using the Raney nickel catalyst under hydrogen as previously reported [8]; unfortunately no product **13** was formed. Following this, a range of conditions were employed to reduce the double bond in the presence of the α,β-unsaturated ketone, including Pd/C and H_2, $NaBH_4$ and Pd/C in the presence of acetic acid [9], and

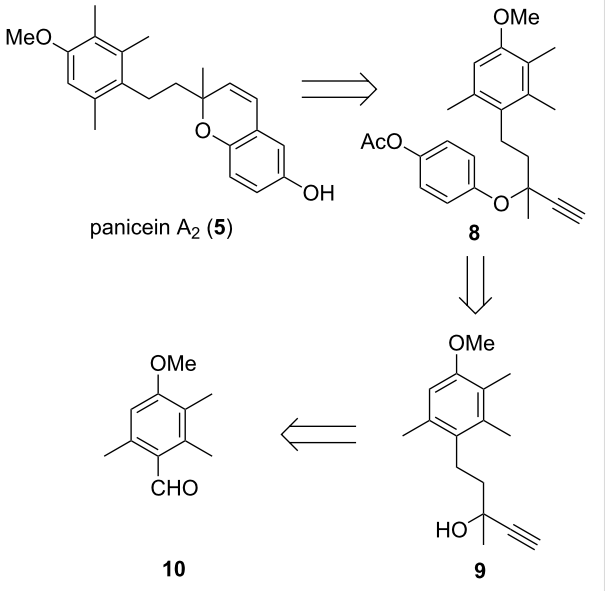
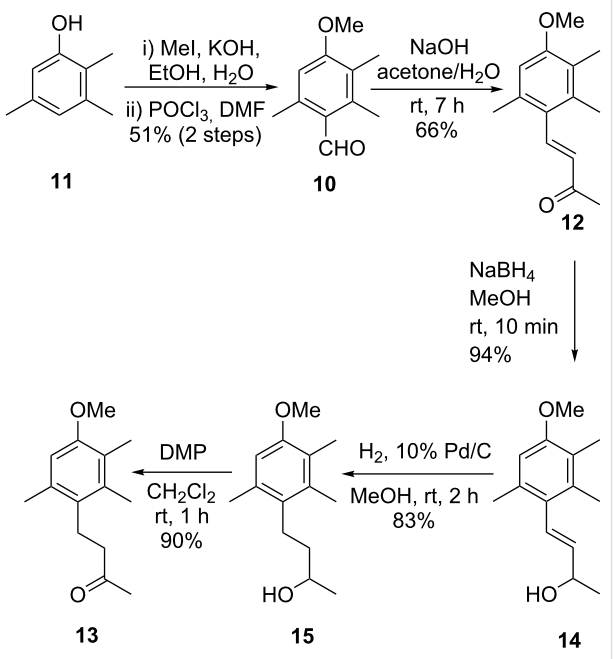
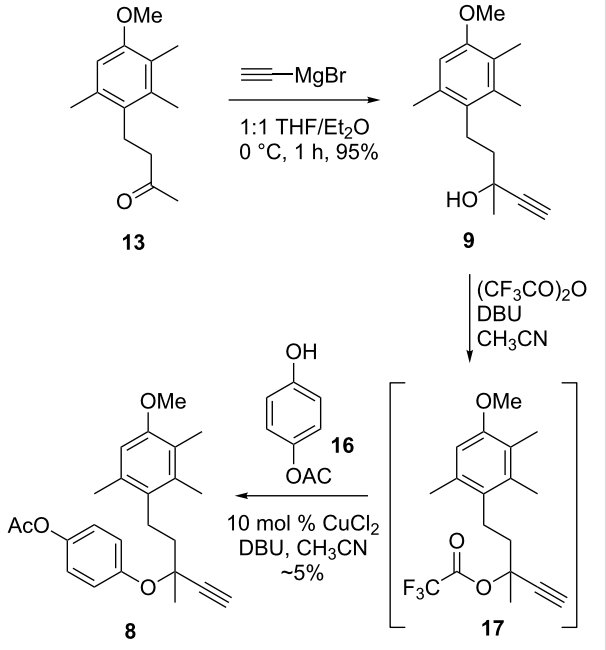


Figure 3: Retrosynthetic analysis of panicein A_2 (**5**).



Scheme 1: Synthesis of ketone **13**.



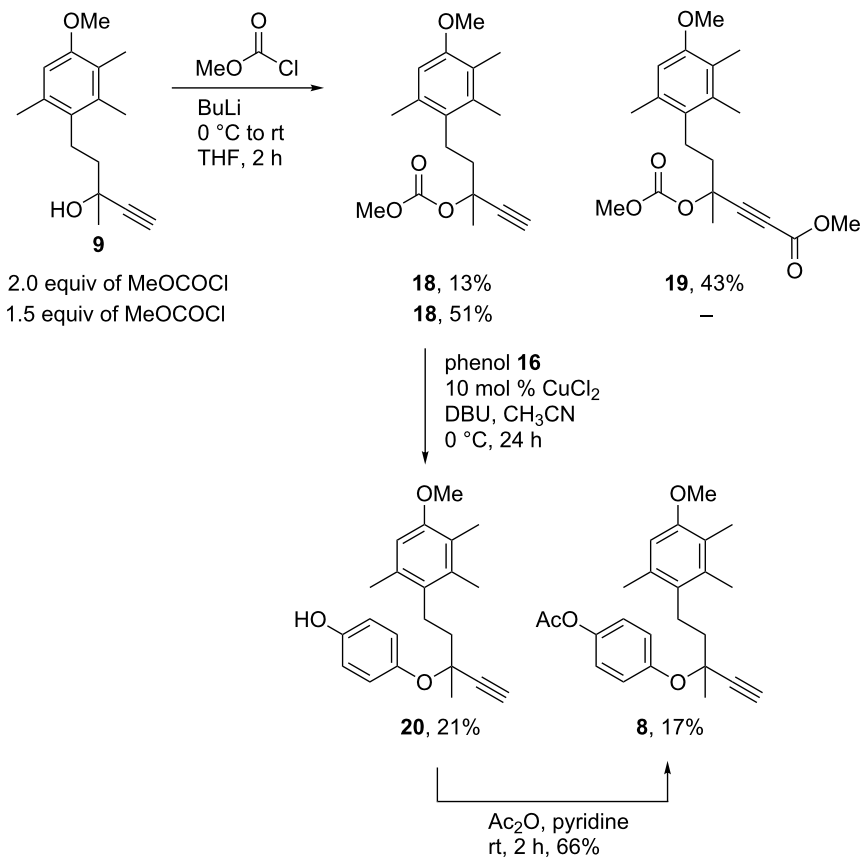
Scheme 2: Synthesis of propargyl ether **8** through formation of trifluoroacetate intermediate **17**.

$NaBH_4$ with $CoCl_2$ [10]; all of these reductive conditions gave complex, inseparable mixtures of overreduction products of the ketone functionality. We therefore decided to selectively reduce the ketone to an alcohol – this would allow for the uncomplicated hydrogenolysis of the olefin. Following this, subsequent oxidation of the alcohol would give the desired ketone **13**. The reduction of ketone **12** to alcohol **14** with $NaBH_4$ was complete after a reaction time of 10 minutes, giving **14** in an excellent 94% yield. Hydrogenolysis of the alkene in **14** using Pd/C in MeOH proceeded in 2 hours, providing alcohol **15** which was then oxidised to the desired ketone **13** with Dess–Martin periodinane in 75% yield over two steps. Although this approach was ultimately two steps longer than initially planned, ketone **13** was provided in three short steps from **12**, all of which were high yielding, even when conducted on a multigram scale.

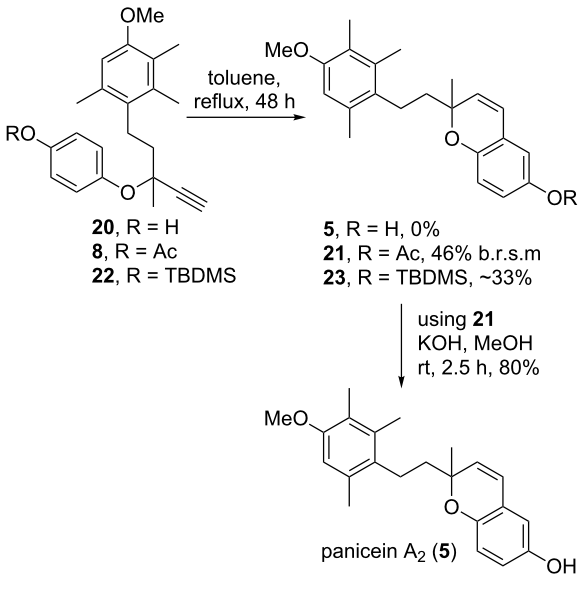
The addition of ethynylmagnesium bromide to ketone **13** was initially attempted using THF as the solvent, only providing alcohol **9** in 47% yield (Scheme 2). Altering the solvent system to a 1:1 mixture of THF and diethyl ether, which also improved the solubility of the Grignard reagent, increased the yield of **9** to 95%. With alcohol **9** in hand, the next step was the key coupling of alcohol **9** and phenol **16** [11] to form the required propargyl ether **8**. Godfrey et al. demonstrated an efficient, one-step method to synthesise propargyl ethers bearing electron withdrawing groups under mild conditions, achieved through the in situ formation of a trifluoroacetate intermediate and subsequent addition of a phenol [12], a method that has since been utilised in a number of syntheses [13-17]. The conversion of alcohol **9** to trifluoroacetate **17** by the addition of trifluoroacetic anhydride and DBU was monitored by TLC and observed to be complete after 1 hour. The phenoxide of phenol **16**, prepared by the deprotonation of **16** by DBU, was then added to intermediate **17**. Unfortunately, the desired product **8** was only obtained in trace amounts.

Carbonate intermediates have been shown to be an effective alternative to trifluoroacetate intermediates [18], and have the added advantage to being stable to an aqueous work-up and thus can be isolated. With that knowledge, it was decided to synthesise carbonate **18** through the addition of methyl chloroformate to alcohol **9** following treatment of **9** with *n*-BuLi. Unfortunately, when the reaction was first attempted using 2 equivalents of methyl chloroformate, only 13% of the desired carbonate was formed, with the major product (43%) being the double-addition species **19** (Scheme 3). Lowering the amount of methyl chloroformate to 1.5 equivalents provided the desired product **18** in 51% yield. Phenol **16** was successfully added to carbonate **18** using the conditions previously attempted, giving a mixture of propargyl ether **8** and its deacetylation product **20**.

The direct conversion of deacetylated product **20** to panicein A_2 (**5**) through a modified Claisen rearrangement [19,20] was then attempted. Unfortunately, after heating **20** in toluene for



Scheme 3: Synthesis of propargyl ether **8** through carbonate **18**.



Scheme 4: Synthesis of panicein A_2 (**5**).

48 hours, no desired product **5** was obtained, with a complex mixture of compounds produced (Scheme 4). The reaction was then attempted with the acetyl-protected propargyl ether **8**. Gratifyingly, cyclised product **21** was obtained in a 46% yield, based on returned starting material. To investigate the effect of an alternative protecting group on the cyclisation reaction, TBDMS ether **22** was synthesised from alcohol **20**. Cyclisation of **22** did proceed to give the desired product **23**, however in a yield of about 33%, further complicated by being inseparable from the starting material **22** (Scheme 4). Due to the poor yields of this reaction, we decided to proceed with the acetate-protected species, and thus alcohol **20** was converted to acetate **8** in 66% yield with acetic anhydride in pyridine (Scheme 3). Finally, acetate **21** was deprotected to give the natural product panicein A_2 (**5**) in 80% yield. The NMR data for synthetic panicein A_2 (**5**) matched literature values (see Supporting Information File 1 for data comparison tables).

Biological testing

When isolated, natural panicein A_2 (**5**) exhibited activity against four cancer cell lines with ED_{50} = 5 μg/mL ≈ 15 μM. To further

expand upon these promising results, synthetic panicein A_2 (**5**) was tested by the NCI against 57 human cancer cell lines, through their developmental therapeutics program. Interestingly, at the tested concentration of 10 μM, panicein A_2 (**5**) showed very little activity against most cell lines. The best performance of panicein A_2 (**5**) was against T-47D, a breast cancer cell line, in which it showed a 43% reduction of growth when compared to a control. Two of the cell lines tested by the NCI were the same as those tested against in the original isolation study (A549 and HT29). Our results show that panicein A_2 (**5**) only reduces growth of A549 human lung carcinoma by 14% and had no effect on the HT29 human colon cancer cell line compared to control. These results indicated panicein A_2 (**5**) to have poor antiproliferative activity and the possibility that the originally tested natural material was contaminated with trace amounts of an even more active compound.

Conclusion

In conclusion, the first total synthesis of aromatic sesquiterpine panicein A_2 (**5**) has been achieved. This synthesis hinges on key steps involving the addition of phenol **16** to carbonate **18** to provide propargyl ether **8** which was then cyclised through a modified Claisen rearrangement to ultimately give the desired cyclic structure of **5**. The correlation of literature values for the isolated natural product and synthetic panicein A_2 (**5**) confirm the structure of the natural product. Of particular note, when synthetic **5** was tested against a broad range of human cancer cell lines, it was found to exhibit very little activity at 10 μM – this observation is at odds with the earlier report that stated **5** exhibits in vitro cytotoxicity against a number of cell lines (ED_{50} = 5 μg/mL).

Supporting Information

Supporting Information File 1

Experimental procedures, characterisation data of new compounds, NMR comparison tables of natural and synthetic **5** and NCI testing results sheet.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-215-S1.pdf]

Supporting Information File 2

$^1H/^{13}C$ NMR spectra of synthesised compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-215-S2.pdf]

Acknowledgements

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