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Enantioselective total synthesis of (−)-neovibsanin G and (−)-14-*epi*-neovibsanin G†

Jeffrey Y. W. Mak and Craig M. Williams*

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The first total synthesis of vibsane-type diterpenoids neovibsanin G and 14-*epi*-neovibsanin G has been achieved. Key to this endeavour was a late stage $EtAlCl_2$ mediated skeletal rich cascade leading to the bicyclo[3.3.1]nonane core in one step.

Vibsanins are rare diterpenes that exist exclusively in a selection of the Viburnum species such as *V. awabuki*, *V. odoratissimum* and *V. suspensum*.[1] These natural products can be divided into three subtypes based on their carbon skeleton; eleven membered ring compounds, seven-membered ring compounds, and the rearranged type, also known as the neovibsanins.

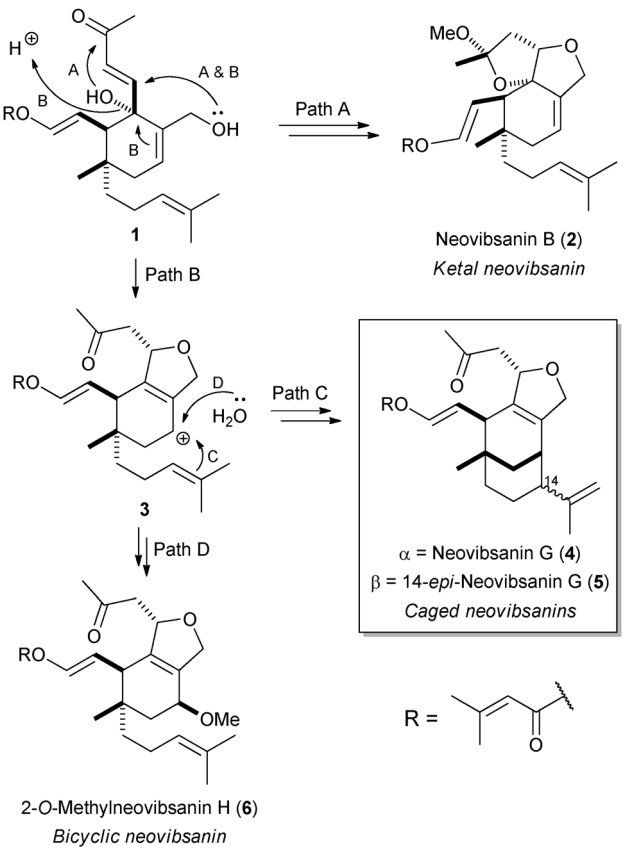
The neovibsanins, certain members of which display potent neurotrophic activity,[2–7] can be further divided into three subclasses; the (1) bicyclic, (2) ketal, and (3) caged neovibsanins. According to Fukuyama's elegantly proposed biosynthesis,[3,8] the chemical fate of intermediate **1** dictates the formation of each neovibsanin subtype. If **1** undergoes dihydrofuran cyclisation followed by hemiketalisation (Path A, Scheme 1), this leads to the formation of the ketal neovibsanins (*e.g.* **2**). If **1** undergoes elimination instead (Path B), allylic cation **3** is formed. Subsequent capture of this cation by water (Path D) gives rise to the bicyclic neovibsanins (*e.g.* **6**), while an intramolecular capture of the cation by the endogenous olefin (Path C) leads to the construction of the bicyclo[3.3.1]nonane ring system of the caged neovibsanins (*e.g.* **4** and **5**).

The natural products (±)-2-*O*-methylneovibsanin H[9] (**6**) and (±)-neovibsanin B (**2**)[5–7,10,11] represent respective targets from the bicyclic and ketal subclasses that have succumbed to total synthesis following a biomimetic route. As the synthesis of the caged neovibsanins had not previously been explored, the synthesis of this subclass was needed in order to substantiate the proposed biosynthetic pathway beyond doubt (Scheme 1). It is in this light that the total synthesis of two targets belonging to the caged subclass, (−)-neovibsanin G (**4**) and (−)-14-*epi*-neovibsanin G (**5**), was undertaken, the results of which are herein reported.

A central aim for the translation of this proposed biosynthesis to a total synthesis would involve access to a synthetic equivalent of biosynthetic intermediate **1**. This was a role that **11** (Scheme 2), an intermediate in the synthesis of racemic 2-*O*-methylneovibsanin H[9] (**6**), could well satisfy, if it could be accessed in an enantioenriched form.

Towards the synthesis of key intermediate **11**, ketone **10** was formed *via* an asymmetric Cu catalysed 1,4-addition of Grignard reagent **8** to cyclohexenone **7** (70%), using the chiral NHC ligand **9**[12–14] (Scheme 2) [synthesised[15] from commercially available (*S*)-*tert*-leucinol] forming the all-carbon quaternary centre in 91% *ee*. This reaction could be performed on a 12 g scale without any reduction in yield or selectivity.

Having obtained **10** for the first time in an enantioenriched form, key intermediate **11** was synthesised following the procedures prescribed in the racemic series,[9] setting the stage for



Scheme 1 Proposed biosynthesis of the three neovibsanin subclasses.

School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, 4072, Australia. E-mail: c.williams3@uq.edu.au
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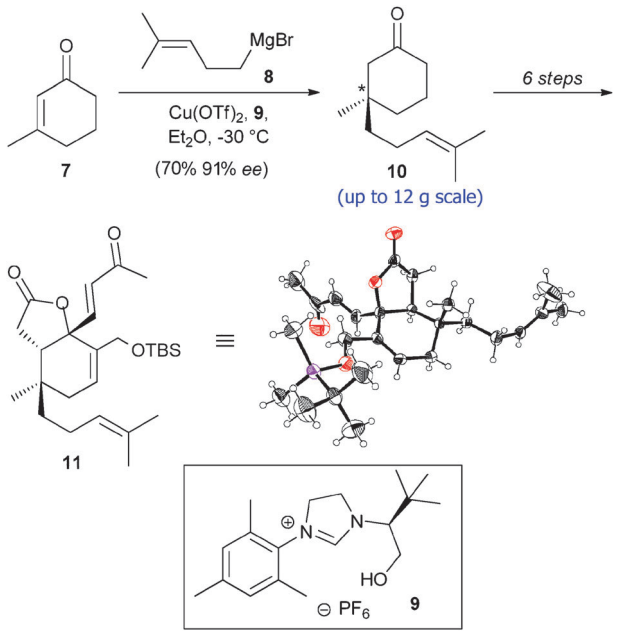


Scheme 2 Enantioselective synthesis of key intermediate **11** *via* chiral NHC-chelated copper catalysed 1,4-addition to **7**. (Inset: ORTEP diagram of **11**; ellipsoids are shown at 30% probability.)

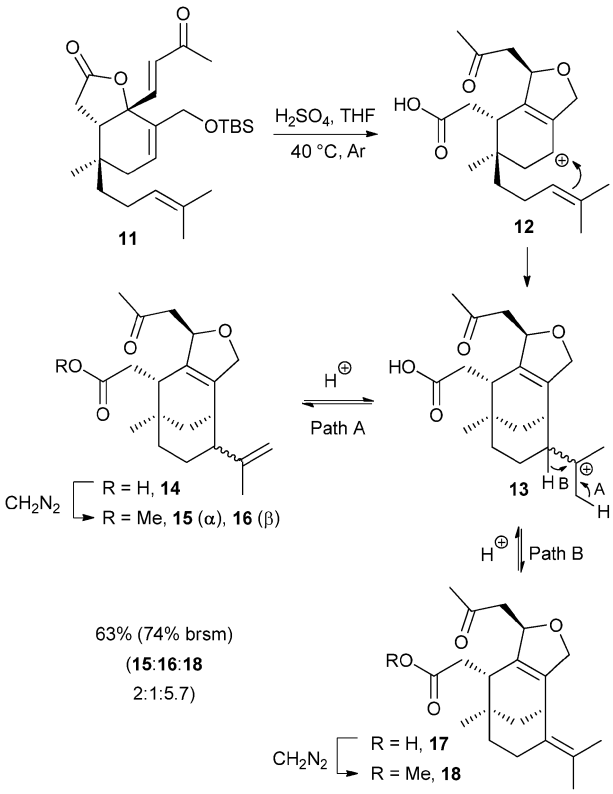
the crucial bicyclo[3.3.1]nonane cyclisation. The absolute configuration of **11** was established as 11*R* through X-ray crystallography (Scheme 2, inset).

In finding suitable conditions for the bicyclo[3.3.1]nonane cyclisation, the use of H_2SO_4 was a logical starting point, as it was known from the synthesis[9] of 2-*O*-methylneovibsanin H (**6**) that treatment of **11** with H_2SO_4 in MeOH at room temperature gave the bicyclic core of **6** *via* cation **12**. Although the polarity of methanol was presumed to be important in promoting the formation of cation **12**, in accordance with classical carbocation theory, in this case **12** must be generated in the absence of a nucleophile in order to encourage intramolecular cation capture. Thus, a polar non-nucleophilic solvent was required.

The solvent tetrahydrofuran appeared to be the best candidate, and in this vein, **11** was treated with H_2SO_4 in THF at 40 °C, followed by methylation with diazomethane (Scheme 3). Although the cyclisation was successful, the selectivity was poor (**15** : **16** : **18** 2 : 1 : 5.7), presumably due to the Brønsted acid catalysed isomerisation of the desired terminal alkenes to the thermodynamically more stable tetrasubstituted isomer.

All attempts to improve the selectivity of the Brønsted acid cyclisation proved to be futile. Thus, the employment of a Lewis acid to kinetically control the regiochemical outcome of the final elimination step was a logical choice. To this end, **11** was TBS deprotected with catalytic HCl, which also triggered an intramolecular 1,4-addition to form the dihydrofuran ring of **19**, providing a substrate that allowed the critical cyclisation to be probed using Lewis acids.

The Lewis acid TMSOTf[12] and the Meerwein salts[13] appeared to be the ideal reagents for the desired transformation, but each failed to induce the bicyclo[3.3.1]nonane cyclisation when tested in a range of solvents. Treatment of **19** with $BF_3{\cdot}Et_2O$ in THF returned starting material, while treatment with Et_2AlCl in the same solvent resulted in gradual substrate decomposition.

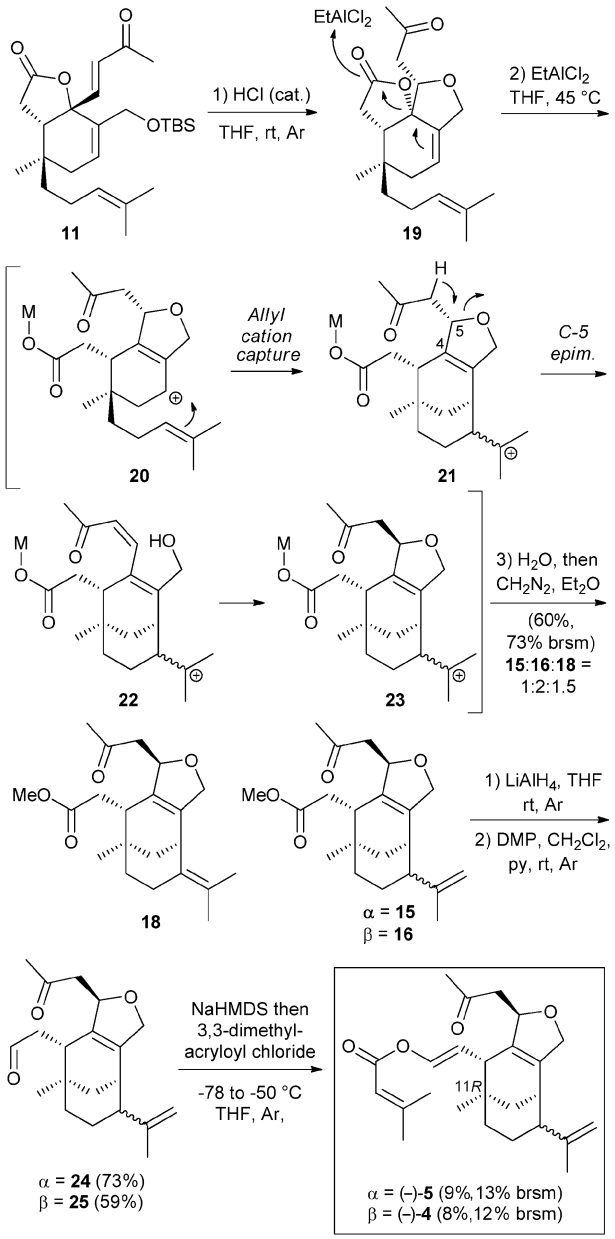


Scheme 3 Bicyclo[3.3.1]nonane cyclisation with H_2SO_4 and the Brønsted acid promoted equilibrium between **13**, **14** and **17**.

After extensive investigations, the only acid/solvent combination that could coerce the highly oxygenated substrate to undergo the desired cyclisation was $EtAlCl_2$ in THF (Scheme 4). Gratifyingly, the regioselective outcome (**15** : **16** : **18** 1 : 2 : 1.5) was drastically improved over the reaction with H_2SO_4. Only trace amounts of the products were observed when Et_2O was used as the solvent, while performing the reaction in 1,2-dichloroethane resulted in the formation of an unidentifiable mixture. Notably, when $EtAlCl_2$ was employed, the ratio of **16** : **15** increased relative to the H_2SO_4 reaction. While **16** was presumably the kinetically favoured product, thermodynamically it was less stable than **15** due to the proximity of its C-14 pendant group to the dihydrofuran ring. Thus, when the cyclisation was carried out using a Brønsted acid, the ratio of **16** : **15** was decreased due to the preferential isomerisation of the former isomer to the tetrasubstituted olefin **18**.

In this intriguing cascade, initial treatment of **19** with $EtAlCl_2$ induced elimination of the carboxylate to form allylic carbocation **20**, which in the absence of a nucleophile, was captured by the endogenous olefin to give **21**. The change in hybridisation at C-4 forced **21** to undergo C-5 epimerisation to **23**, *via* **22**, to alleviate the steric strain between the two carbonyl functionalities. Finally, aqueous work up followed by methylation with CH_2N_2 gave **15**, **16** and **18** in a combined yield of 60% (73% brsm). Separation of the three isomers was achieved with careful silver nitrate chromatography.[14]

Individual conversion of **15** and **16** to their respective aldehydes (**24** and **25**) was achieved through successive treatment with $LiAlH_4$ and DMP (Scheme 4). Trapping the sodium enolates of **24** and **25** with 3,3-dimethylacryloyl chloride[5]



Scheme 4 $EtAlCl_2$ mediated bicyclo[3.3.1]nonane cyclisation and the completion of the total synthesis.

completed the synthesis of (−)-**5** and (−)-**4** respectively. The moderate yields obtained for the installation of the side-chain was typical using this approach. Although we have developed methodology[15] to access this functional group in one step and in higher yields, it was not applicable in this case.

In conclusion, six years after their isolation,[3] the first total synthesis of (−)-neovibsanin G [(−)-**4**] and (−)-14-*epi*-neovibsanin G [(−)-**5**] was achieved in an enantioselective manner. This established the absolute configuration of neovibsanin G and 14-*epi*-neovibsanin G as 11*S*, which is amongst the strongest evidence for Fukuyama's proposal that the biosynthetic progenitor of the neovibsanins is vibsanin B[3] (which was also shown to possess the 11*S* configuration[16]). The success of this biogenetically inspired synthesis lends overwhelming support for Fukuyama's postulated biosynthesis[3] of the neovibsanins.

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