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Concise Synthesis of 1,4a-Bifunctionalised Decalin Building Blocks by C-H Activation of Decalin

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Abstract: Friedel–Crafts acylation of decalin introduces functionality at C1 and C4a, which may be elaborated to novel building blocks possessing a methyl ketone, methyl carbinol or vinyl group at the ring junction.

**Key words:** hydrocarbons, acylation, bicyclic compounds, alkenes, Wittig reaction.

Functionalised decalins occur widely in steroid[1] and terpenoid[2] natural products. As such, great efforts have been expended on developing synthetic routes to both *cis*-[3] and *trans*-decalins.[4] There has been particular interest in decalins bearing functionality both at C1 and at C4a, as these have found diverse applications in the pharmaceutical and fragrance industries.[5] In the course of ongoing studies in total synthesis, we required access to alcohol **1**, a 4a-vinyl-*trans*-decalin bearing an axially disposed substituent at C1. Access to this vinyl alcohol **1** may be envisaged by means of a one-carbon homologation of 4a-vinyl-*trans*-1-decalone **2** (Scheme 1). Vinyl alcohol **1** has not been reported to date; surprisingly, nor has vinyl ketone **2**. We therefore sought a concise, scalable route to these potentially useful building blocks from inexpensive starting materials.
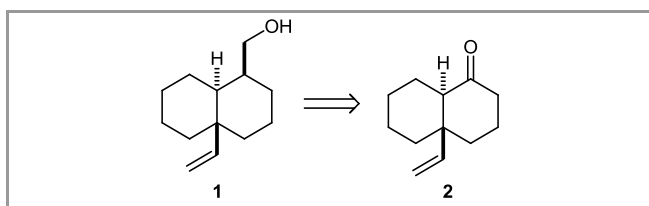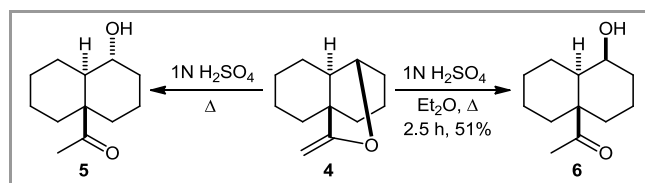

Scheme 1

Baddeley and co-workers have reported an unusual Friedel–Crafts acylation of decalin **3** with aluminium trichloride and acetyl chloride.[6] The reaction is believed to proceed by acylium ion-mediated hydride abstraction.[7] Although such acylations have been reported for a variety of saturated hydrocarbon substrates,[8] the decalin case is of particular synthetic utility, since careful control of the reaction conditions allows for formation of tricyclic enol ether **4** as the major product (Scheme 2). Furthermore, the boiling point of **4** is distinct from that of the starting material (which accounts for most of the mass balance) or byproducts, allowing for large scale non-chromatographic purification by distillation. It has been shown[8j,k,9] that *cis*-decalin is much more reactive

than *trans*-decalin under these reaction conditions; if a commercial mixture of *cis*- and *trans*-decalin is used, unreacted starting material is recovered that is enriched in the *trans* isomer. We have repeated this reaction on a large scale and disclose NMR data for **4** for the first time. Despite the apparent synthetic utility of this access to a selectively functionalised decalin, **4** has been exploited in synthesis only infrequently thus far.[10]
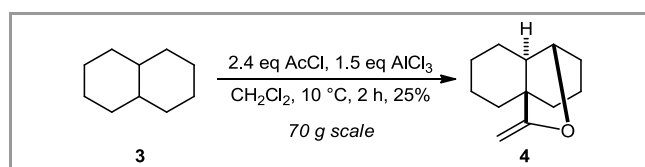
Scheme 2

Enol ether **4** serves as a useful entry to **2**, as it possesses functionality in the desired positions, including the quaternary centre. Conditions have been established for the acidic hydrolysis of **4** and it is reported[6c,d] that both epimeric alcohols **5** and **6** may be accessed depending on the reaction conditions. We undertook hydrolysis of **4** under mild reaction conditions, obtaining **6** in 51% yield (Scheme 3). Unreacted **4** persisted regardless of reaction times, suggesting the ready reversibility of the ring opening; when **6** was resubjected to reaction conditions, **4** was observed to form. Hydroxyketone **6** may be isolated in pure form by crystallisation from the reaction mixture, as **4** is liquid at room temperature. The structures of **5** and **6** had been assigned initially by chemical correlation and on the basis of their IR spectra.[6c,d] Crystalline **6** was subjected to x-ray crystallographic analysis (Figure 1), confirming the original structural assignment.[11]
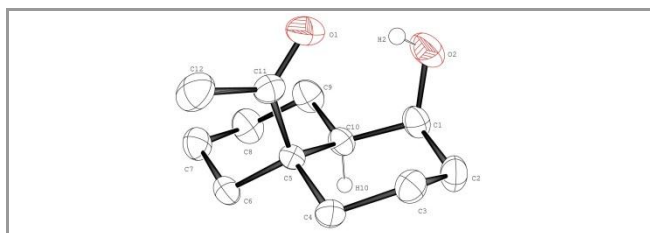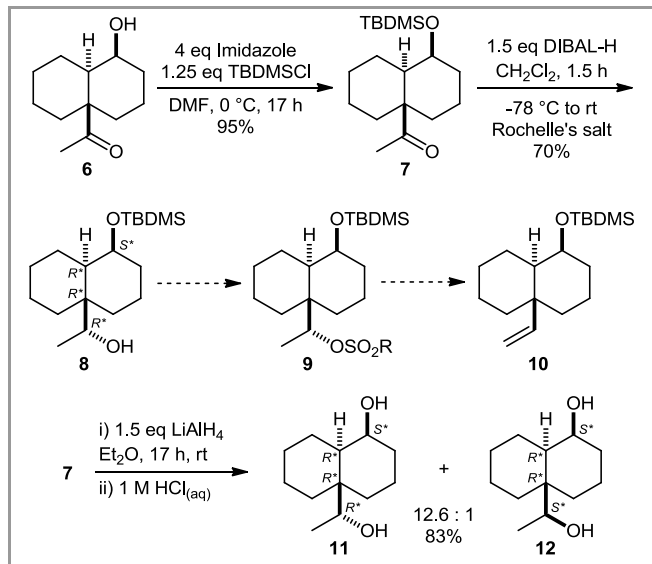

Scheme 3

Figure 1 ORTEP diagram of **6,** ellipsoids at 50% probability. Selected H atoms are shown as spheres of arbitrary radius.

Conversion of the methyl ketone functionality in **6** to a vinyl group is formally a reductive transformation. Accordingly, the alcohol in **6** was protected as a silyl ether, followed by reduction with DIBAL-H to furnish **8** as a single diastereomer. In order to assign the relative configuration of the newly-installed stereocentre in **8**, precursor **7** was also reduced with LiAlH$_4$, which was not entirely diastereoselective. An acidic workup of this latter reaction served to remove the protecting group *in situ*, furnishing diastereoisomeric diols **11** and **12** (Scheme 4). The major epimer was diol **11**, identical to material formed by desilylation of **8**. The relative configuration of **11** was confirmed by x-ray crystallography (Figure 2).[11] Attempts at sulfonylation of **8** in order to effect elimination to the desired vinyldecalin **10** were unsuccessful, which we ascribe to steric hindrance of the neopentylic hydroxyl group.
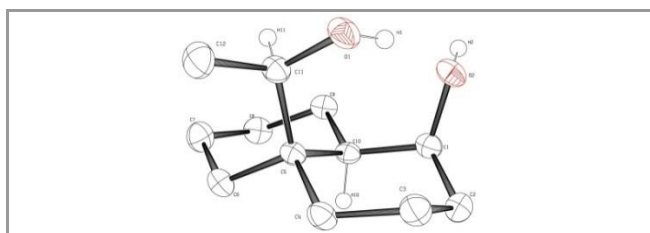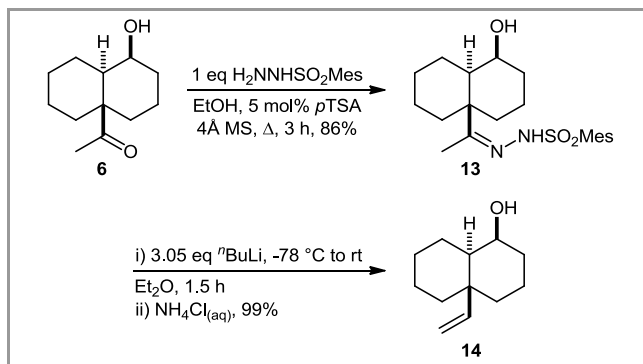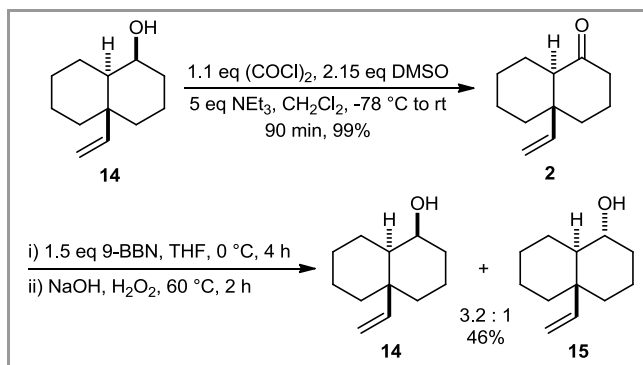

Scheme 4

Figure 2 ORTEP diagram of **11**, ellipsoids at 50% probability. Selected H atoms are shown as spheres of arbitrary radius.

As an alternative approach to **1** and **2**, we opted to elaborate **6** by means of a Shapiro reaction. Treatment with 2-mesitylenesulfonohydrazide gave hydrazone **13**, which could also be accessed directly from enol ether **4** (in a yield of 66%). When **13** was exposed to 3 equivalents of butyllithium (required due to the presence of the free hydroxyl group) followed by protic quench, vinyl alcohol **14** was accessed in good yield (Scheme 5).
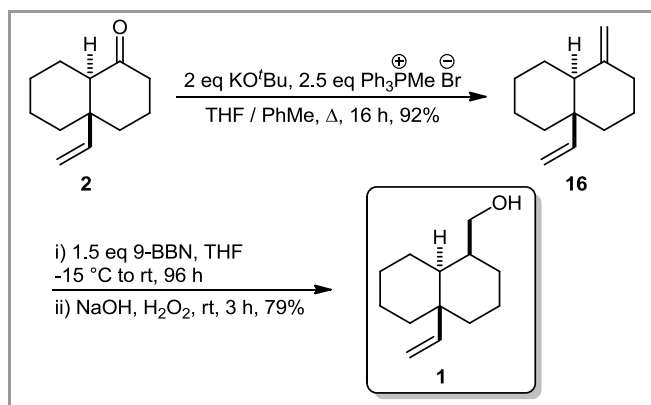

Scheme 5

From vinyl alcohol **14**, vinyl ketone **2** was accessed by Swern oxidation. A subsequent serendipitous observation was that the vinyl group in **2** is inert to hydroboration with 9-BBN, this reagent instead effecting unexpected ketone reduction back to **14** and its epimer **15**; no other products were recovered (Scheme 6).

Scheme 6

The inertness of the vinyl group in fact permits access to the desired target **1** in a simple two-step sequence. Wittig methylenation of the ketone in **2** (best achieved with KO^{t}Bu as base) provides bis(alkene) **16** without epimerisation at the ring junction. In a remarkable transformation, hydroboration of **16** with 9-BBN displays total regio- and diastereoselectivity; treatment of the hydroboration product with basic peroxide furnishes **1** as the sole isomer and in good yield (Scheme 7).

Scheme 7

The relative configuration of **1** was established by Swern oxidation to the corresponding aldehyde **17**. In the NOESY spectrum of **17**, correlation was observed between the aldehyde proton and the vinyl group methine (Scheme 8).
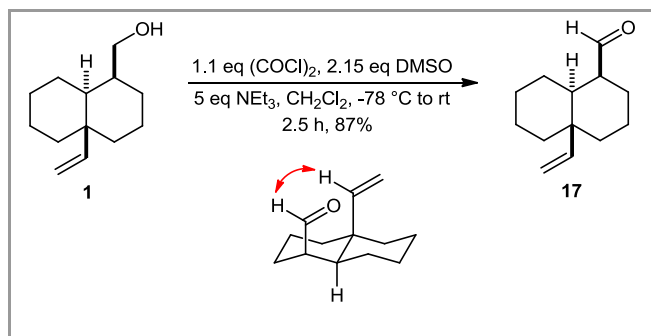
Scheme 8 NOESY correlation shown in red.

In summary, we have demonstrated concise access to a range of 1,4a-bifunctionalised decalin derivatives which are likely to find diverse applications in synthesis. Our studies in total synthesis employing these building blocks are ongoing and results will be reported in due course.

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

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(11)   **6**: CCDC #824429. **11**: CCDC #824430.

1,4a-Bifunctionalised Decalins

R^1, R^2 = H, OH, OTBDMS,
=O, =CH$_2$, CH$_2$OH, CHO
R^3 = COCH$_3$, CH(OH)CH$_3$,
CH=CH$_2$