A Short Synthesis of Karahana Ether by a Radical Cyclisation Path

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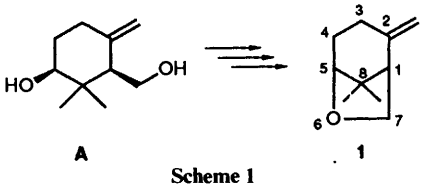
A novel synthesis of karahana ether has been developed by employing a radical-mediated 6-*exo*-*dig* intramolecular cyclisation as a key step.

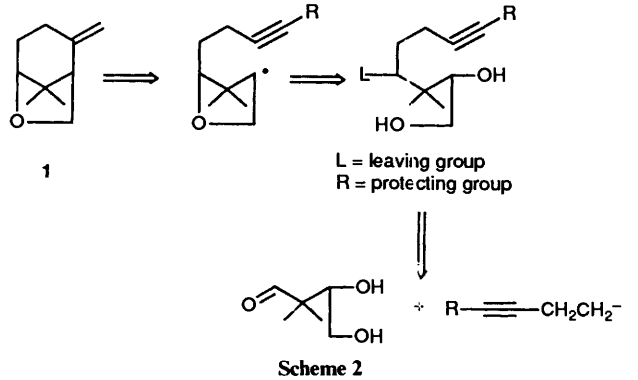
Karahana ether **1** has been isolated from Japanese hop, 'Shinshu-wase', *Humulus lupulus* L., as a volatile monoterpene.[1,2] Although several synthetic routes to karahana ether have been reported to date,[3–7] formation of the ether bond from the *cis*-diol **A** serves as the final step in many of these syntheses (see Scheme 1).



A **1**

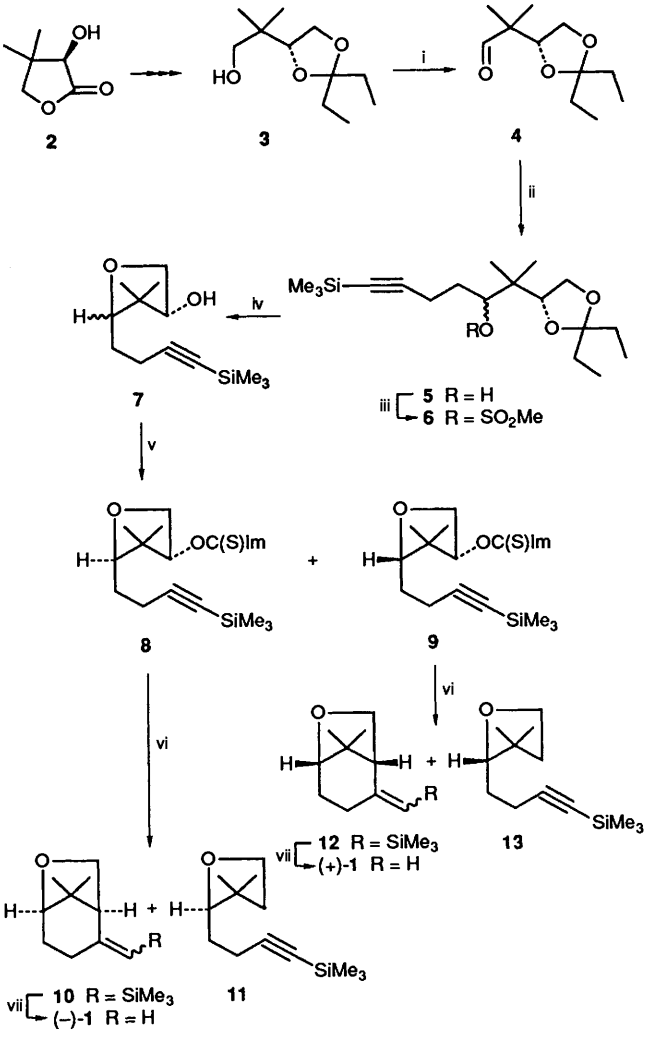
Scheme 1

Our own interest in the synthesis of **1** grew out of a desire to find a new route for the total synthesis of karahana ether and its congeners. In searching the structure of **1** for retrosynthetic disconnections, we focused our attention on the formation of the *exo*-methylene function by a radical-mediated 6-*exo*-*dig* intramolecular cyclisation[8] (see Scheme 2).



Scheme 2

Thus, the alcohol **3**,[9] readily accessible from (−)-pantoyl lactone **2**, was oxidised with pyridinium chlorochromate (PCC) to give the aldehyde **4** in 75% yield. The Grignard reaction of **3** with 4-trimethylsilylbut-3-ynylmagnesium bromide in tetrahydrofuran (THF) afforded the alcohol **5** as an inseparable mixture of the diastereoisomers (1:1) in 85% yield, the expected chelation-controlled stereoselectivity giving (*S*)-OH being absent. Treatment of the mixture **5** with methanesulfonyl chloride, followed by deacetalisation of the methanesulfonate **6** with 10% hydrochloric acid induced ether formation and provided the tetrahydrofuran derivative **7** in 58% yield from **5**. In order to prepare the radical precursor, compound **7** was treated with 1,1-thiocarbonyldiimidazole in 1,2-dichloroethane in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) to give the corresponding thiocarbonylimidazolides **8** and **9**, in 40 and 41% yields, respectively.† The enantiomerically pure imidazolide **8** was subjected to a radical cyclisation using tributyltin hydride in refluxing benzene in the presence of a catalytic amount of azoisobutyronitrile (AIBN) to afford the bicyclo compound **10** in 75% yield as a mixture of the olefinic isomers (in a ratio of *ca.* 1:1), together with the deoxygenation product **11** in 22% yield. Desilylation of **10** with 50% aqueous hydrofluoric acid in acetonitrile furnished (−)-karahana ether (−)-**1** {$[\alpha]_D$ −47.5‡ (*c* 0.3, pentane) lit.,[6] $[\alpha]_D$ −70.0 (pentane)}, in 90% yield, whose spectroscopic data were identical with those reported.[6] Hence the absolute stereo-



Scheme 3 *Reagents and conditions:* i, PCC, AcONa, CH_2Cl_2, room temp.; ii, $Me_3SiC{\equiv}C(CH_2)_2MgBr$, Et_2O, 0 °C; iii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; iv, 10% HCl, THF, 50 °C; v, $Im_2C{=}S$, $ClCH_2CH_2Cl$, DMAP, reflux; vi, Bu_3SnH, AIBN, benzene, reflux; vii, 50% aq. HF, MeCN, room temp.

† The absolute stereochemistries of the two imidazolides could not be determined at this stage, although they were finally established by conversion into (+)- and (−)-karahana ethers, respectively.

‡ $[\alpha]_D$ Values are quoted in units of 10^{-1} deg cm^2 g^{-1}.

chemistry of the imidazolide **8** was unambiguously deduced (see Scheme 3). Similar radical cyclisation of the antipodal imidazolide **9** gave the bicyclo compound **12** as a mixture of olefinic isomers as above and the reduction product **13**, in 73 and 20% yields, respectively. The former compound **12** was also desilylated as above to provide (+)-karahana ether (+)-**1** {$[\alpha]_D$ +47.1 (*c* 0.2, pentane)} in 89% yield.

In conclusion, we have developed a novel synthesis of karahana ether by means of a radical cyclisation, a synthetic path applicable to other naturally occurring oxabicyclo compounds.

Experimental

Radical Cyclisation of Compounds **8** *and* **9**.—To a stirred solution of **8** (106 mg, 0.03 mmol) in refluxing benzene (10 cm^3) was slowly added a solution of tributyltin hydride (0.095 cm^3, 0.036 mmol) and a catalytic amount of AIBN (5 mg) in benzene (100 cm^3) over a 4 h period; the resulting mixture was further heated at reflux for 1.5 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (24:1, v/v) afforded the deoxygenation product **11** (15 mg, 22%); $\delta(CDCl_3)$ 0.14 (9 H, s, $SiMe_3$), 0.91 and 1.04 (each 3 H, each s, Me), 1.53–1.61 (2 H, m, CCH_2), 1.68–1.80 (2 H, m, CCH_2), 2.21–2.52 (2 H, m, CCH_2), 3.39 (1 H, dd, *J* 4.88 and 7.93, OC*H*H), 3.74–3.86 (2 H, m, OCH*H* and OCH). Further elution with the same solvent system provided the cyclisation product **10** (51 mg, 75%) as a mixture of olefinic isomers as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2890 and 1640; $\delta(CDCl_3)$ 0.08 and 0.10 (each 4.5 H, each s, $SiMe_3$), 0.93 and 0.97 (each 1.5 H, each s, Me), 1.06 and 1.09 (each 1.5 H, each s, Me), 1.61–1.81 (2 H, m, CCH_2), 2.03–2.60 (3 H, m, CCH_2 and CH), 3.75–3.84 (2 H, m, OCH_2), 3.99–4.06 (1 H, m, OCH), 5.04 and 5.18 (each 0.5 H, each s, olefinic proton). Radical cyclisation of the epimer **9** (106 mg, 0.03 mmol) under the same reaction condition as above gave the bicyclo compound **12** (49.5 mg, 73%) and reduction product **13** (13.4 mg, 20%), whose spectroscopic data were identical with those of **10** and **11** respectively.

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