Cyclopentaannulation of Allyl Alcohols *via* a Radical Cyclisation Reaction. Total Synthesis of 4-Epibakkenolide-A

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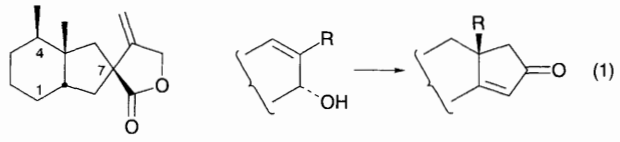
A four step cyclopentaannulation methodology starting from allyl alcohols using 5-*exo*-trig radical cyclisation as the key reaction, and its application to the total synthesis of 4-epibakkenolide is described.

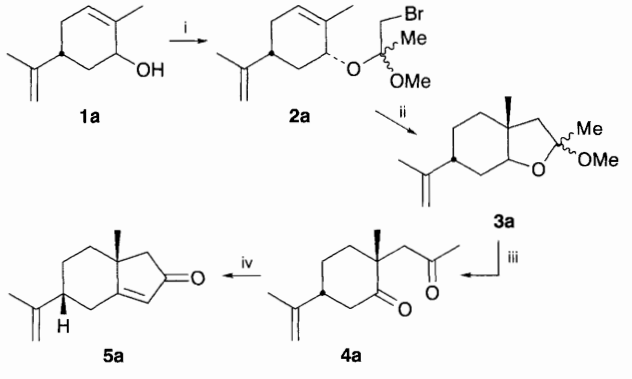
Methods for the annulation of five membered rings onto a pre-existing ring, with regio- and stereo-chemical control, are valuable in the synthesis of natural products as well as exotic organic compounds like spheroidal polyquinanes.[1] Application of the radical mediated cyclisations for the regio- and stereo-selective construction of carbon–carbon bonds continues to be of topical interest in contemporary organic synthesis.[2] Based on the bromoacetal radical cyclisation for the construction of butyrolactone moiety, originally developed by Stork and coworkers,[3] herein we report a four step, efficient and general methodology for the annulation of cyclopentenones starting from allyl alcohols [eqn. (1)], employing a highly regio- and



Bakkenolide-A **6** (1)

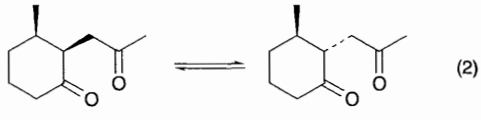
stereo-selective 5-*exo*-trig radical cyclisation as the key reaction, along with its extension to the total synthesis of epimers of the tricyclic sesquiterpene, bakkenolide-A.

The methodology starting from the allyl alcohol, carveol **1a**,[4] is depicted in the Scheme 1. Reaction of 2-methoxypropene with *N*-bromosuccinimide (NBS) at low temperature in the presence of carveol **1a** furnished the epimeric mixture of the radical precursor, bromoketal **2a**. The key 5-*exo*-trig radical cyclisation reaction was carried out by refluxing a 0.02 mol dm^{-3} benzene solution of the bromoketal **2a** with 1.1 equiv. of tri-*n*-butyltin hydride in the presence of a catalytic amount of azoisobutyronitrile (AIBN) to furnish the cyclised ketal **3a**, a 1 : 1 epimeric mixture at ketal carbon, in a stereo- and regio-specific manner. The sonochemically accelerated reaction of the ketal **3a** with Jones reagent furnished the 1,4-diketone **4a** *via* one pot hydrolysis followed by oxidation of the resultant ketol. Finally, intramolecular aldol condensation reaction of the diketone **4a** with methanolic KOH furnished the annulated product **5a**. In an analogous manner cyclopentaannulation of the allyl alcohols **1b–h**, obtained by the reduction of the corresponding enones with $LiAlH_4$ at low temperature, furnished the cyclopentenones **5b–h**,[5] establishing the generality of the



Scheme 1 *Reagents and conditions*: i, CH_2=C(OMe)Me, NBS, CH_2Cl_2, −50 °C; ii, Bu^n_3SnH, benzene, reflux, AIBN (catalytic); iii, Jones reagent, acetone, sonicate, 5 min.; iv, 10% aq. KOH, MeOH, 110 °C

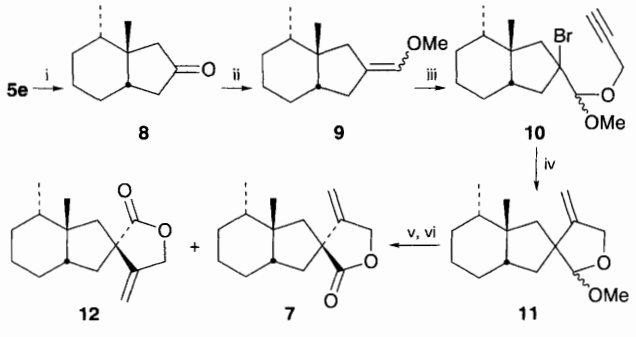
methodology. The results are summarised in the Table 1. The stereochemistry of the newly created *sec*-methyl group during radical cyclisation reaction (entries 4–8) was assigned based on the earlier reports[3] of similar reactions, which was further established by the conversion of the enone **5e** into the hydrindanone[7] **8**. Interestingly, in the case of enones **5f–h** (entries 6–8), even though the radical cyclisation reaction proceeded in a highly stereoselective manner, epimeric mixtures of the final annulated products were obtained, due to the base catalysed epimerisation of the diones **4f–h** [eqn. (2)] prior



(2)

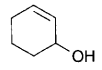
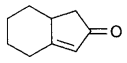
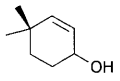
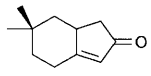
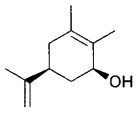
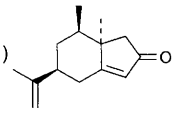
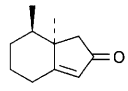
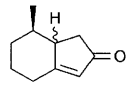
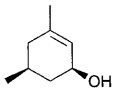
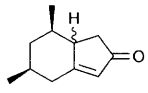
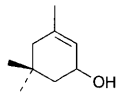
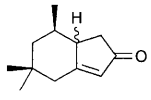
to the aldol cyclisation as reported[5] earlier. Presence of a substituent at the C-2 position of the starting allyl alcohol, prevented the epimerisation of the diketones **4** resulting in the final annulated products (entries 1, 4, 5) in a highly stereo-selective manner. This clearly established the suitability of the present methodology for the highly regio- and stereo-selective cyclopentaannulation of 2-substituted cyclic allyl alcohols. As an application of this methodology, the annulated product **5e** obtained from 2,3-dimethylcyclohexenone was transformed into 4-epibakkenolide-A.

Bakkenolide-A **6**, first isolated[6] from the bud of *Petasites japonicus* subsp. *giganteus Kitam*, is the simplest member of the bakkane class of tricyclic sesquiterpenes containing a novel α-spiro-β-methylene-γ-butyrolactone fused to a hydrindane framework and has been shown to possess cytotoxic and antifeedant properties. The total synthesis of 4-epibakkenolide-A **7** along with its spiroepimer, starting from the annulated product **5e** is depicted in the Scheme 2. Catalytic hydrogenation of the enone **5e** over 10% Pd/C quantitatively furnished the hydrindanone **8**.[7] A radical cyclisation based methodology[8] was adopted for the spirannulation of the hydrindanone **8**. Thus, Wittig reaction of the ketone **8** with methoxymethyl-enetriphenylphosphorane furnished the enol ether **9**, which on treatment with NBS and an excess of prop-2-ynyl alcohol in dichloromethane generated the radical precursor, acetylenic

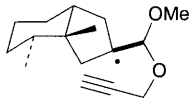


Scheme 2 *Reagents and conditions*: i, H_2–10% Pd/C, MeOH, 1 atmosphere, 5 h, 100%; ii, Ph_3P^+–CH_2OMe^-Cl, $EtC(Me_2)OK$, THF, room temp., 6 h, 62%; iii, NBS, CH_2Cl_2, HC≡C–CH_2OH, −40 °C, 0.5 h, 75%; iv, Bu^n_3SnCl (0.15 equiv.), $NaCNBH_3$ (2 equiv.), AIBN (catalytic), Bu^tOH, reflux, 1.5 h, 83%; v, 2 mol dm^{-3} HCl, THF, sonic irradiation, 4 h, 76%; vi, PCC, CH_2Cl_2, 2 h, 95%

Table 1 Cyclopentaannulation of allyl alcohols[a]

Entry	Allyl alcohol	Bromo ketal yield (%)	Cyclised ketal yield (%)	Diketone yield (%)	Enone yield (%)
1	**1a**	**2a**(66)	**3a**(73)	**4a**(70)	**5a**(79)
2	 **1b**	**2b**(79)	**3b**(72)	**4b**(89)	**5b**(68) 
3	 **1c**	**2c**(83)	**3c**(75)	**4c**(73)	**5c**(92) 
4	 **1d**	**2d**(67)	**3d**(74)	**4d**(64)	**5d**(81) 
5	 **1e**	**2e**(59)	**3e**(74)	**4e**(72)	**5e**(92) 
6	 **1f**	**2f**(67)	**3f**(68)	**4f**(76)	**5f**(99)[b] 
7	 **1g**	**2g**(89)	**3g**(62)	**4g**(99)	**5g**(91)[b] 
8	 **1h**	**2h**(83)	**3h**(73)	**4h**(84)	**5h**(85)[b] 

[a] Yields refer to isolated (unoptimised) and chromatographically pure products. [b] *ca.* 1 : 1 mixture of epimers.



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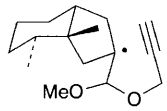

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bromoacetal **10**. The 5-*exo*-dig radical cyclisation reaction of the bromoacetal **10** using an *in situ* generated catalytic tri-*n*-butyltin hydride ($Bu^n_3SnCl/NaCNBH_3$)[9] in refluxing *tert*-butanol in the presence of a catalytic amount of AIBN furnished the hemiacetal **11**. Finally, hydrolysis of the hemiacetal **11** followed by oxidation of the resultant lactol with pyridinium chlorochromate (PCC) furnished a *ca.* 1 : 1 mixture of 4-epi-bakkenolide-A **7** and its spiroepimer **12**. The formation of the two epimers at the spirocentre was a consequence of the cyclisation of the intermediate *endo* and *exo* radicals **13** and **14**. Even though, normally the *endo* radical **13** will be energetically preferred,[8] the 1,3-interaction of the side chain with the equatorial methyl group at the 3-position, perhaps, made both the radicals **13** and **14** comparable in energy.

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