

Diastereoselective SmI₂-mediated cascade radical cyclisations of methylenecyclopropane derivatives—a synthesis of paeonilactone B

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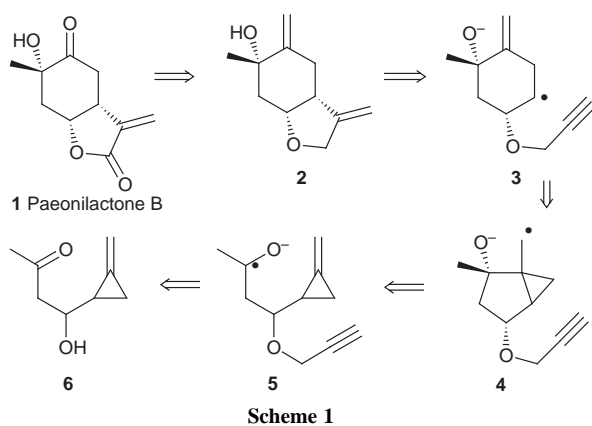
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The SmI₂-mediated cascade reaction of methylenecyclopropyl ketone **9** proceeds with high diastereoselectivity, which is critically dependent on the presence of HMPA, and provides a short route to paeonilactone B.

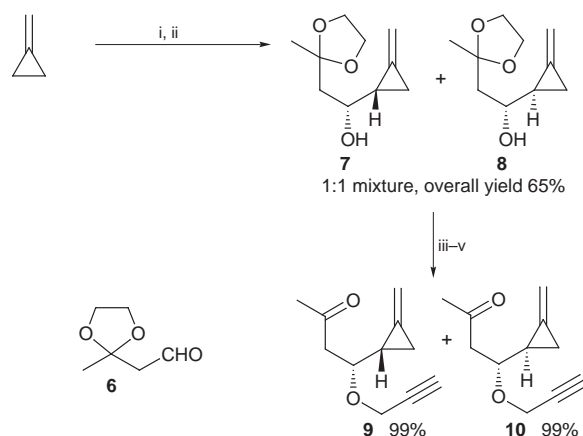
Cascade radical cyclisation reactions have proved to be very popular as a synthetic strategy as they allow the construction of several C–C bonds in one step and can provide elegant synthetic routes to complex polycyclic compounds and natural products.¹ Tandem reactions, initiated in particular by the versatile lanthanide reagent SmI₂, have also been a focus of recent attention.² We now report that SmI₂-promoted cascade cyclisations of methylenecyclopropyl ketone derivatives lead to bicyclic products in good yield and with excellent diastereoselectivity. This approach provides a short synthetic route to (±)-paeonilactone B **1**, one of several structurally related monoterpenes isolated from paeony roots,³ all of which feature a highly oxygenated cyclohexane nucleus.⁴

A retrosynthetic analysis of paeonilactone B (Scheme 1) suggested that the *cis*-fused bicyclic methylenecyclohexane **2** could be prepared by a 5-*exo* cyclisation of methylenecyclohexyl radical **3** onto a pendant alkyne, and **3** could, in turn, arise from cyclisation of ketyl radical **5** onto a methylenecyclopropane unit with subsequent 'endo' ring opening of **4**.⁵ Whether such a sequence would prove to be diastereoselective and provide the correct relative stereochemistry of the tertiary alcohol required for the natural product remained to be tested by experiment.

Addition of lithiated methylenecyclopropane to aldehyde **6**,⁶ produced the desired alcohols as a readily separable mixture of diastereoisomers **7** and **8** (Scheme 2).⁷ The relative stereochemistry for the two diastereoisomers was established by X-ray crystallographic structure analysis of the *p*-nitrobenzoate ester derived from alcohol **8**.⁸ Alkylation of the alcohols gave the corresponding prop-2-ynyl ethers, and subsequent ketal deprotection provided the two diastereomeric cyclisation precursors, **9** and **10** respectively, in essentially quantitative yield.



Scheme 1



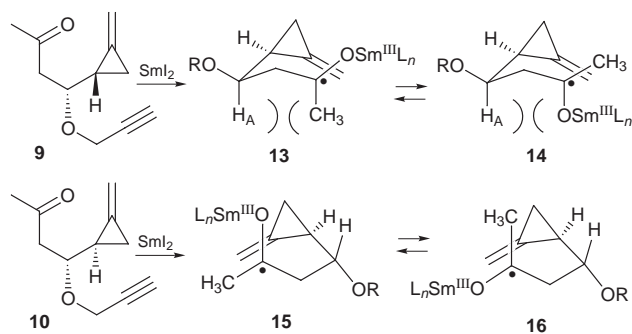
Scheme 2 Reagents and conditions: i, BuLi, THF, –78 °C; ii, compound **6**; iii, NaH, DMPU, THF; iv, HC≡CCH₂Br; v, TsOH, acetone, H₂O

Treatment of ketone **9** with SmI₂, under standard conditions⁹ (slow addition of **9** to 2.2 equiv. SmI₂, BuOH, HMPA, THF, 0 °C) gave the desired bicyclic products as a readily separable mixture of diastereoisomers, **11** and **12**, in 57 and 6% isolated yields respectively (ratio **11**:**12** = 10:1 by analysis of the ¹H NMR spectrum of the crude reaction mixture) (Table 1). In contrast, treatment of diastereomeric ketone **10** with SmI₂, under identical conditions, gave the bicyclic product **12** in 73% isolated yield, and only a trace of the diastereoisomer **11** (ratio **12**:**11** > 30:1).

In order to rationalise the observed diastereoselectivity we repeated the cyclisations under identical conditions, but replacing HMPA with the less effective chelator DMPU.¹⁰ These cyclisation reactions gave the bicyclic products with reduced overall yields and required a larger excess of SmI₂ (~6 equiv.) for consumption of starting material.^{2b} Notably, for the cyclisation of **9**, the diastereoselectivity was reduced (ratio **11**:**12** = 1.5:1), whereas for the cyclisation of **10** the

Table 1 Reaction of **9** or **10** with different additives

Starting material	Additive	Yield (%)	11 : 12
9	HMPA	63	10:1
9	DMPU	40	1.5:1
9	—	~20	1:1.3
10	HMPA	79	< 1:30
10	DMPU	62	< 1:30
10	—	0	—



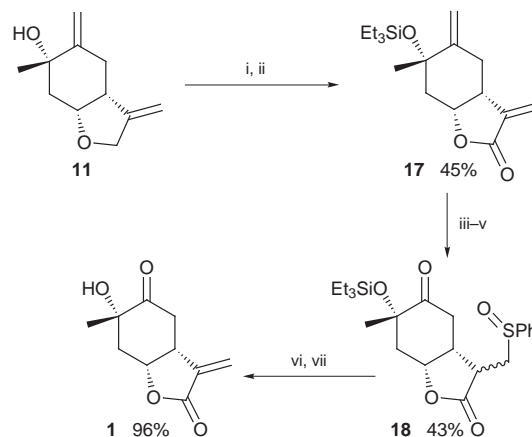
Scheme 3

diastereoselectivity was seemingly unaffected (ratio **12:11** > 30 : 1). In the absence of either DMPU or HMPA the cyclisation was, as expected, a poor reaction. Thus **9** gave an overall yield of ~20% of **11** and **12**, but with a reversal of stereoselectivity (ratio **11:12** = 1 : 1.3), while cyclisation of **10** yielded none of the desired bicyclic compounds.

The selectivity for the cyclisation of **9** in favour of **11**, in which the tertiary alcohol and ether oxygen are *cis* in the bicyclic product, might be the consequence of chelation control from the weakly basic prop-2-ynyl ether oxygen to the samarium(III) bound to the ketyl radical. However, the decrease in selectivity for the cyclisation of **9** as HMPA is replaced by the weaker chelator DMPU, and reversal of selectivity when neither is present, effectively rules out this possibility. It seems probable that the first step of the cyclisation of **9**, which effectively sets the relative stereochemistry of the product, proceeds through a chair-like transition state, allowing the prop-2-ynyl ether substituent to adopt a pseudo-equatorial position (Scheme 3). As a consequence of the bond angles of the methylenecyclopropyl group, the alkene appears to be essentially staggered between the ketyl radical oxygen and the ketyl methyl group. Thus the preference for conformer **13** over **14** may largely result from the preference for the bulky OSm^{III}(HMPA)_n moiety to also adopt a pseudo-equatorial position and avoid a 1,3-diaxial interaction with H_A. Replacement of HMPA with DMPU may effectively reduce the steric bulk of the OSm^{III}L_n moiety,¹⁰ leading to a lower selectivity for conformer **13**. In the absence of either HMPA or DMPU the ketyl methyl becomes sterically dominant, leading to a reversal in selectivity.

In contrast, the first step of the cyclisation of **10** may well proceed through a boat-like transition state, since a chair-like transition state would force the prop-2-ynyl ether substituent into a severely hindered axial orientation. In the boat-like transition state the alkene now appears to be largely eclipsed with either the ketyl methyl group (**15**) or the ketyl radical oxygen (**16**). Conformer **15** may now be preferred over **16** since it alleviates the electronic repulsion between the ketyl oxygen functionality and the alkene π-system,¹¹ and this preference is unaffected by replacing HMPA with DMPU.

Completion of the synthesis of paeonilactone **B** firstly required protection of the tertiary allylic alcohol as the triethylsilyl ether,¹² followed by oxidation of the allyl ether to the desired α-methylene lactone **17** using CrO₃ and pyridine (Scheme 4).¹³ The selective oxidation of the ostensibly more electrophilic cyclohexyl alkene of **17** proved to be impossible with both alkenes reacting rapidly with ozone at -110 °C in EtOH in almost quantitative yield. Even more frustratingly, treatment of **17** with OsO₄ led to dihydroxylation of just the α-methylene lactone, presumably due to steric congestion around the cyclohexyl alkene. Instead, base-mediated Michael addition of PhSH to **17** gave the thioether which was then successfully ozonolysed to give the desired ketone, with concomitant oxidation of the thioether to the corresponding sulfoxide **18**. Thermal elimination of phenylsulfenic acid¹⁴ then reinstalled the α-methylene lactone and deprotection of the silyl



Scheme 4 Reagents and conditions: i, Et₃SiOTf, Et₃N, CH₂Cl₂, 0 °C; ii, CrO₃, pyridine, CH₂Cl₂, room temp.; iii, PhSH, Et₃N, MeOH; iv, O₃, MeOH, -78 °C; v, Me₂S; vi, CCl₄, reflux; vii, HF-pyridine, THF

ether was successfully achieved using pyridine-HF,¹⁵ to give (±)-paeonilactone **B**, whose structure was confirmed by comparison of its NMR and IR spectroscopic data to those reported previously for the natural paeonilactone.³

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