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Stereoselective Dimerisation at the End of a Radical Cascade Sequence.

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Abstract

A novel cascade sequence, that begins with the samarium(II) iodide mediated formation of a ketyl radical, leads to a primary alkyl radical, which appears to be partially 'protected' from the anticipated further reduction to an organosamarium, and instead undergoes a highly stereoselective dimerisation.

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Samarium(II) iodide (SmI_2) has proved to be a very popular reagent in recent years as a selective one-electron reducing agent.[1] The versatility of SmI_2 is emphasised by the fact that it can be used to generate both carbon centred radicals and carbanions (by a further one-electron reduction of the radical species) and several cascade sequences utilising combinations of both of these aspects have been described.[2] Cascade processes, initiated by SmI_2, and using exclusively *radical* intermediates[3,4] are, however, complicated - and potentially limited - by the fact that each radical intermediate can undergo competitive reduction to the corresponding organosamarium species, which may then effectively terminate the intended cascade sequence.[2,3b] In this paper we wish to report a novel cascade sequence that begins with the SmI_2 mediated formation of a ketyl radical, and leads to an alkyl radical which appears to be partially 'protected' from further reduction to the organosamarium by ligation to the ketyl oxygen-bound samarium(III). The radical instead undergoes a highly stereoselective dimerisation.

We recently described[4] SmI_2-mediated cascade radical cyclisations of methylenecyclopropane derivatives **1** and **2**, which proceeded with high diastereoselectivity, in the presence of HMPA as an additive, to give predominantly bicyclic ethers **3** or **4** respectively (Scheme 1). Bicyclic ether **3** was then converted through to the monoterpene paeonilactone B **5**.

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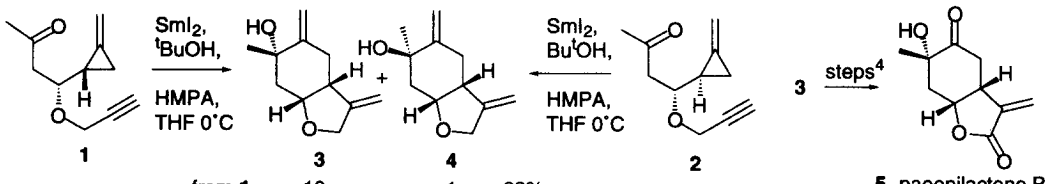
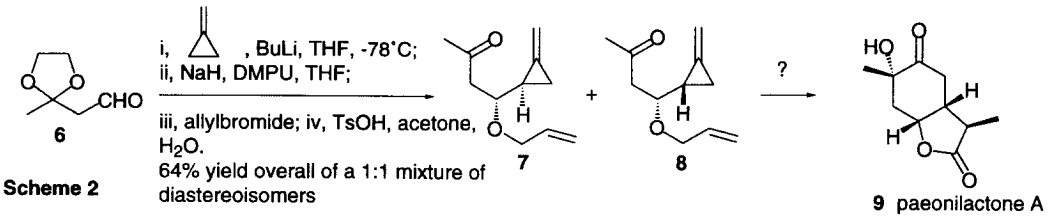


Scheme 1

from **1**	10	:	1	63%
from **2**	1	<	30	79%

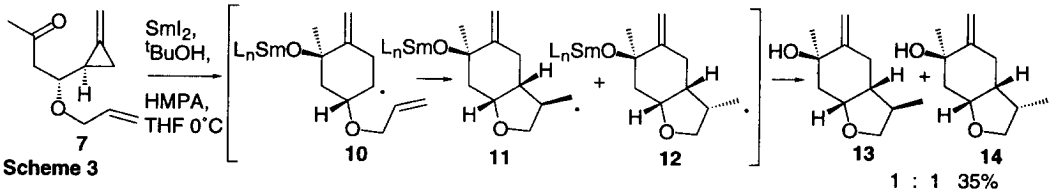
As an extension of this methodology we decided to investigate the cyclisation of the corresponding allyl ether **8**, which could provide a direct route to paeonilactone A (**9**), if the final cyclisation in the sequence produced the appropriate stereochemistry at the fourth chiral centre.[5]



Scheme 2

The diastereomeric allyl ethers **7** and **8** were prepared in analogous fashion to the corresponding propargyl ethers,[4] by addition of lithiated methylenecyclopropane to aldehyde **6** to produce a mixture of diastereomeric alcohols, followed by alkylation of the separated alcohols with allyl bromide, and subsequent ketal deprotection (Scheme 2).

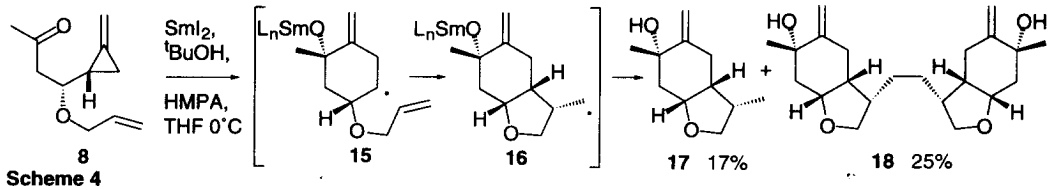
Treatment of allyl ether **7** with SmI_2 under standard conditions[6] (slow addition of **7** to 2.2 equivs SmI_2, ^{t}BuOH, HMPA, THF, 0°C) gave a 1:1 mixture of diastereoisomeric bicycles, **13** and **14**, in 35% isolated yield (Scheme 3).[7] A slightly improved yield (40%) of the same 1:1 mixture was obtained by carrying out the reaction at –78°C. No other bicyclic products could be isolated from these reactions (nor could they be detected in the ^{1}H or ^{13}C NMR spectra of the crude reaction mixture).



Scheme 3

The stereochemical outcome of this cyclisation is readily rationalised in terms of the model presented previously[4] for the cyclisation of the analogous propargyl ether **2**. Thus the cyclisation of the initially formed ketyl radical may proceed *via* a boat-like transition state to give methylenecyclohexyl radical **10**, as essentially a single diastereoisomer, which then cyclises to give a 1:1 mixture of alkyl radicals **11** and **12**, which in turn are reduced to the organosamarium and quenched by ^{t}BuOH. Replacement of HMPA with DMPU in the reaction (0°C) led to a lower yield (20%) of bicyclic products, but with no change to the diastereoselectivity, again mirroring the results observed with the corresponding propargyl ether **2**.[4]

Cyclisation of **8** (slow addition of **8** to 2.2 equivs SmI_2, ^tBuOH, HMPA, THF, 0°C), on the other hand, gave a single diastereomeric bicycle **17** in just 17% isolated yield,[7] but accompanied by a 25% yield of a dimeric product **18**, as a single diastereoisomer,[7] with the same relative stereochemistry for the bicyclic portion as for **17** (Scheme 4).



Scheme 4

Again, no other bicyclic or dimeric products could be isolated from the reaction (nor could they be detected in the ^1H or ^{13}C NMR spectra of the crude reaction mixture) and again the stereochemical outcome of this cyclisation is readily rationalised in terms of the model presented previously for the cyclisation of the analogous propargyl ether **1**.[4] Thus the cyclisation of the initially formed ketyl radical may proceed *via* a chair-like transition state to give methylenecyclohexyl radical **15**, as essentially a single diastereoisomer. Intermediate radical **15** then cyclises to give exclusively alkyl radical **16** which is either reduced to the organosamarium and quenched to give **17**, or dimerises to give **18**. The sequence therefore appears to be highly stereoselective, although it does not give the desired stereochemistry for the natural product paeonilactone A. As before with the analogous propargyl ether **1**,[4] replacement of HMPA with DMPU in the cyclisation led to a loss of stereoselectivity in the first steps of the cascade, and thus to the formation of both methylenecyclohexyl radicals **10** and **15**, which in turn gave a mixture of all three bicyclic products **13**, **14** and **17**, but no dimeric products were detected, indicating that the presence of HMPA is essential for the formation of **18**.

The formation of dimer **18** was quite unexpected since it is formed under conditions of relatively high SmI_2 concentration (0.16M) with slow, syringe pump addition of the precursor **8** over 30 minutes, where rapid reduction of the primary radical **16** and subsequent quenching would be expected, as observed for intermediates **10** and **11**. In a further experiment we treated a 1:1 mixture of starting allyl ethers **7** and **8** with SmI_2, under the same conditions as before, and obtained a mixture of all three bicyclic products **13**, **14** and **17** and the single dimeric product **18**. Thus, under conditions that generate all three primary radicals **10**, **11** and **16**, it is only **16** which dimerises. Even more remarkably, the dimerisation occurs only between opposite enantiomers of **16**, to give the dimer as a *meso* isomer, and none of the 'homo' coupling of identical enantiomers is observed![8] Clearly radical intermediate **16** is more stable than any of the other radical intermediates formed in the cyclisation sequence, and we believe this can be explained most readily by the fact that this intermediate has both the OSm(III) and the alkyl radical on the *endo* face of the bicyclic structure, allowing stabilisation of the radical by interaction with the samarium(III). This would effectively 'protect' the radical from further reduction by SmI_2, allowing build up of the radical species and eventual dimerisation. The exclusive formation of the *meso* dimer is harder to rationalise.[9] The dimerisation may involve formation of a diradical intermediate from two monomers **16** (eg bridging of two ketyl oxygens with two samariums) followed by radical coupling to give the dimeric product. For the formation of such an intermediate, approach of identical enantiomers to each other may be impeded relative to approach of opposite enantiomers. Alternatively, the structure of the *rac* diradical intermediate, if formed, may not readily allow coupling of the two alkyl radicals and may be slowly quenched to

give **17**, or it may equilibrate with a *meso* diradical intermediate whose structure does allow radical coupling. In any event, the formation of **18** is unusual and further studies on this reaction are continuing in our laboratory.

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Notes and References

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5. Rajanbabu and others have shown that cyclisation of 2-(1-but-3-enyl)cyclohexyl radicals invariably gives *cis*-fused bicyclic products, but control of the stereochemistry of the additional chiral centre is critically dependent on whether the butenyl chain is axial or equatorial on the cyclohexyl radical transition state: a) RajanBabu, T. V. *J. Am. Chem. Soc.*, **1987**, *109*, 609; b) RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc.*, **1989**, *111*, 296; c) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.*, **1989**, *111*, 1759.
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7. All compounds were characterised by ^{1}H and ^{13}C NMR and IR spectroscopy, and by HRMS or microanalysis. The stereochemistry of products **13**, **14** and **17** were established by nOe studies. In addition the ^{13}C NMR spectrum of **17** was essentially identical to that for the dimer **18** (excepting for the signals of the ethylene bridge between the two monomer units). The structure of **18** was determined unequivocally by X-ray crystallographic analysis. (We thank A. Genge, University of Southampton for carrying out the analysis. Details will be published elsewhere.)
8. Dimerisation (Wurz coupling) of organosamariums such as benzyl samarium diiodide are well known (see ref. 1a) and recently a non-stereoselective dimerisation of a samarium derived glucosyl radical has been described: Doisneau, G.; Beau, J. M. *Tetrahedron Lett.*, **1998**, *39*, 3477. However, the only example of dimerisation at the end of a radical cyclisation sequence, that we are aware of, was reported by Molander *et al* (ref. 6b) which led to a mixture of diastereomeric dimers when the cyclisation substrate was added rapidly to the SmI_2 solution, allowing a high local concentration of the cyclised radical intermediate. The dimerisation was not observed when the cyclisation substrate was added slowly to the 0.15M SmI_2 solution - as in our work described here.
9. Stereoselective pinacol couplings are, of course, well known: Robertson, G. M. in *Comprehensive Organic Synthesis (Vol 3)*, Trost, B. M.; Fleming, I., Eds.; Pergamon Press, **1991**, 563-611, and the stereoselective β-dimerisation of 3,5,5 trimethylcyclohexenone, using organomanganese reagents, has been described: Cahiez, G.; Alami, M. *Tetrahedron Lett.*, **1986**, *27*, 569.