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Samarium diiodide mediated 6-*exo* cyclisations of methylenecyclopropyl ketones

Jonathan J. Underwood,[a] Gregory J. Hollingworth,[b] Peter N. Horton,[a] Michael B. Hursthouse[a] and Jeremy D. Kilburn[a,*]

[a]*School of Chemistry, University of Southampton, Southampton SO17 1BJ, UK*
[b]*Merck Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Harlow, Essex CM20 2QR, UK*

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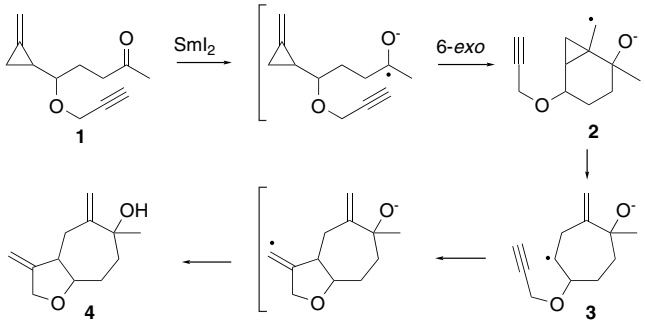
Abstract—6-*exo* Cyclisations of methylenecyclopropyl ketones, mediated by samarium diiodide, have been investigated with a series of substrates. The efficiency of the cyclisations are highly dependent on the stereochemistry of the cyclisation precursor.

SmI_2 mediated 5-*exo* cyclisations of methylenecyclopropyl ketones provide an efficient route to methylenecyclohexyl radicals, and have been used in several radical cascade sequences for the synthesis of polycyclic systems,[1,2] including a synthesis of paeonilactone B.[3] The corresponding 6-*exo* cyclisation (e.g., of **1**) is a more demanding reaction since the desired cyclisation (leading to **2**) is likely to have to compete with 7-*endo* cyclisation and direct reduction,[4] but should provide a route to methylenecycloheptanyl radicals (such as **3**), which again could be used in cascade sequences (Scheme 1). In particular we hoped to access the bicyclic 7,5 ring system **4**, which is found in many natural products.

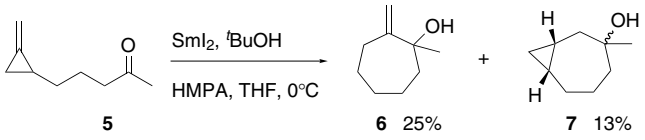


Scheme 1.

Herein we describe studies on such cyclisations, the efficiencies of which are highly dependent on the stereochemistry (and thus preferred conformation) of the cyclisation precursor.

Cyclisation of simple methylenecyclopropyl ketone **5** was investigated under a range of conditions, but generally gave little or no cyclised product. The best result was obtained by addition of SmI_2 (2.2 equiv of a 0.1 M solution in THF) to a solution of the ketone in THF with ^{t}BuOH (2.2 equiv) and HMPA (8 equiv),[5,6] which did give alcohol **6**, derived from a 6-*exo* cyclisation, in 25% yield, and alcohol **7**, derived from a 7-*endo* cyclisation, in 13% yield (Scheme 2).[7]

Treatment of propargyl ether **8** under the same conditions also gave a mixture of products **9** and **10** (Scheme 3) from 7-*endo* and 6-*exo* cyclisations, respectively, but the major product was **11** resulting from 8-*endo* cyclisation onto the terminal alkyne.[8]



Scheme 2.

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* Corresponding author. Tel.: +44-23-8059-3596; fax: +44-23-8059-6805; e-mail: jdk1@soton.ac.uk

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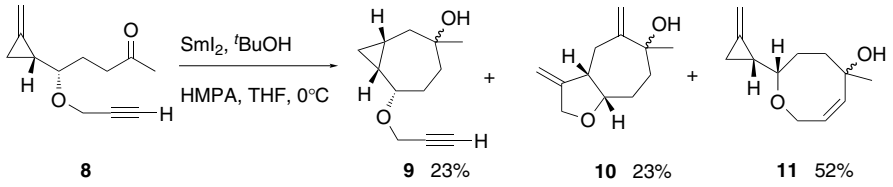


Scheme 3.

Cyclisation of the diastereomeric propargyl ether **12** likewise gave a mixture of products **13–15** with 8-*endo* cyclisation onto the alkyne again leading to the major product. However, this latter mode of cyclisation can be suppressed by blocking the alkyne terminus with a trimethylsilyl (TMS) group, so, for example, cyclisation of **16** gave a good overall yield of cyclised products **17** and **18** (Scheme 4).[7]

Introduction of the propargyl ether clearly gives better yields of cyclised products overall (compared with **5**), possibly due to chelation of the ether and ketyl oxygens by the samarium metal, but 6-*exo* cyclisation is not the dominant reaction.

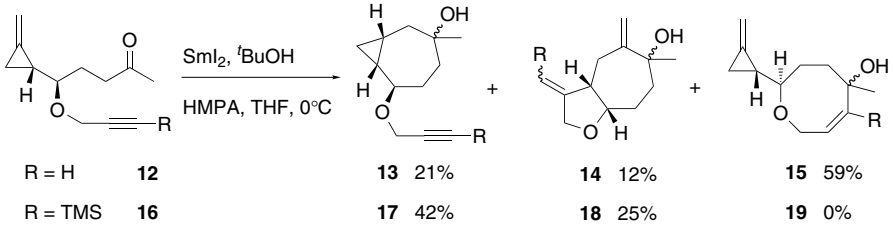
Cyclisation of ketones **20** and **23**, however, gave no 7-*endo* cyclisation products. Instead ketone **20** gave the *cis* fused bicyclic alcohol **21**, resulting from initial 6-*exo* cyclisation, in excellent yield (Scheme 5). The diastereomeric ketone **23**, on the other hand, also gave an excellent yield, but of a 1:1 mixture of alcohol diastereoisomers **24**.

The selective reactivity of the diastereomeric ketones, **20** and **23**, can be rationalised by considering the conformation of the methylenecyclopropyl ketyl radical necessary for cyclisation. For diastereoisomer **23**, 6-*exo* cyclisation would require eclipsing of the ketyl C–O bond with the alkene (conformation **25**) and the consequent electronic repulsion disfavours this arrangement.[9] The eclipsing is avoided on cyclisation of **20**, via conformation **22**.

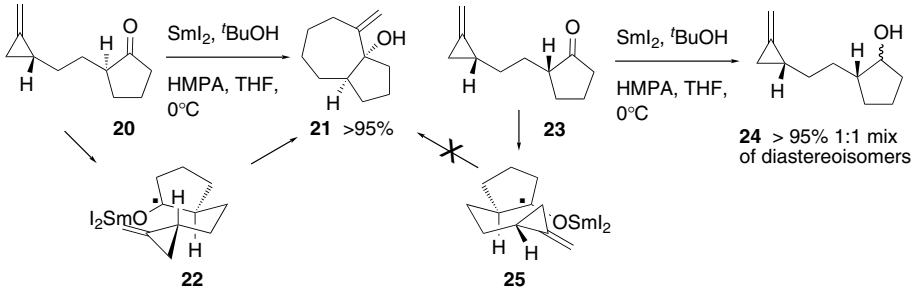
Incorporating the successful elements of the cyclisations described above, we prepared all four diastereoisomers of the silylated propargyl ethers **27**, by addition of lithiated methylenecyclopropane to aldehyde **26** and subsequent etherification (Scheme 6).

Attempted cyclisation of three of these isomers gave only complex mixtures of products. The fourth diastereoisomer **28**, however, cyclised very efficiently to give the tricyclic ether **29** in 76% yield and as a mixture of vinylsilane isomers (Fig. 1: X-ray crystal structure[10] of *Z*-vinylsilane **29**) (Scheme 7).

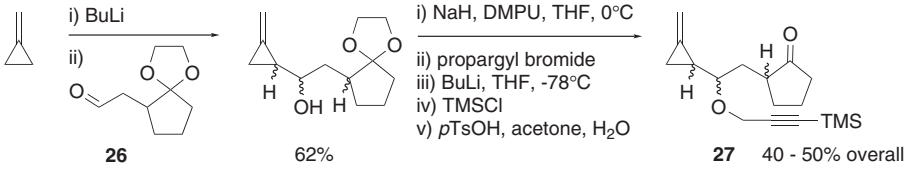
Thus, 6-*exo* cyclisation of methylenecyclopropyl ketones can be used for the efficient synthesis of cycloheptane derivatives provided the stereochemistry of the starting material favours suitable conformations for the cyclisation. Such cyclisations can be incorporated into cascade reaction sequences, providing routes to polycyclic products with natural product-like structures.



Scheme 4.



Scheme 5.



Scheme 6.

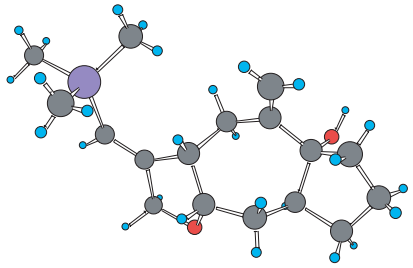
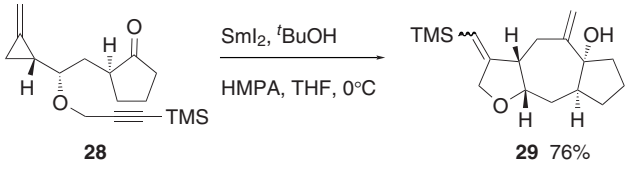


Figure 1. X-ray crystal structure of *Z*-vinylsilane **29**.



Scheme 7.

Acknowledgements

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References and notes

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4. For previous studies on 6-*exo*/7-*endo* malonyl radical cyclisations of methylenecyclopropane derivatives, see: Destabel, C.; Kilburn, J. D.; Knight, J. *Tetrahedron* **1994**, *50*, 11267–11288; Destabel, C.; Kilburn, J. D.; Knight, J. *Tetrahedron* **1994**, *50*, 11289–11302.
5. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872–878.
6. We have previously used MeOH as a co-solvent in place of ^{t}BuOH–HMPA in related 5-*exo* cyclisations, but use of THF–MeOH solvent systems was not successful for the 6-*exo* cyclisations described herein. See Ref. 1c and Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913–4916.
7. All products were characterised by ^{1}H and ^{13}C NMR, MS and IR. All of the cyclisation products **7**, **9**–**11**, **13**–**15** and **17** were obtained as single diastereoisomers, but the stereochemistry of the tertiary alcohol stereocentre was not determined. Compound **18** was obtained as a 3:2 mixture of *E* and *Z* vinyl silanes.
8. 8-*endo* Cyclisations of samarium diiodide derived ketyl radicals have been described: (a) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **1999**, *38*, 789–791; (b) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267–4277.
9. Similar effects have been observed in related samarium diiodide mediated 5-*exo* cyclisations of methylenecyclopropyl ketones: see Refs. 1c,d. Electronic repulsion between the ketyl oxygen functionality and the alkene π-system is generally accepted as being a major factor determining stereoselectivity in SmI_2 mediated cyclisations of unactivated olefinic ketones: see Ref. 5, and Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100.
10. Crystallographic data (excluding structure factors) for *Z*-vinylsilane **29** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC222319. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Crystal data: colourless blocks, $C_{17}H_{28}O_2Si$, $M_r = 292.48$, $T = 120(2)$ K, monoclinic, space group $P2_1$, $a = 6.8522(14)$ Å, $b = 17.611(4)$ Å, $c = 7.0718(14)$ Å, $\beta = 90$, $V = 853.4(3)$ Å^3, $\rho_{(calcd)} = 1.138$ Mg/m^3, $\mu = 0.138$ mm^{-1}, $Z = 2$, reflections collected: 8552, independent reflections: 3732 ($R_{int} = 0.1321$), final R indices [$I > 2\sigma I$)]: $R_1 = 0.0858$, $wR_2 = 0.1512$, R indices (all data): $R_1 = 0.1813$, $wR_2 = 0.1834$.