Radical Reactions in Synthesis: Intramolecular S_H2' Macrocyclisations

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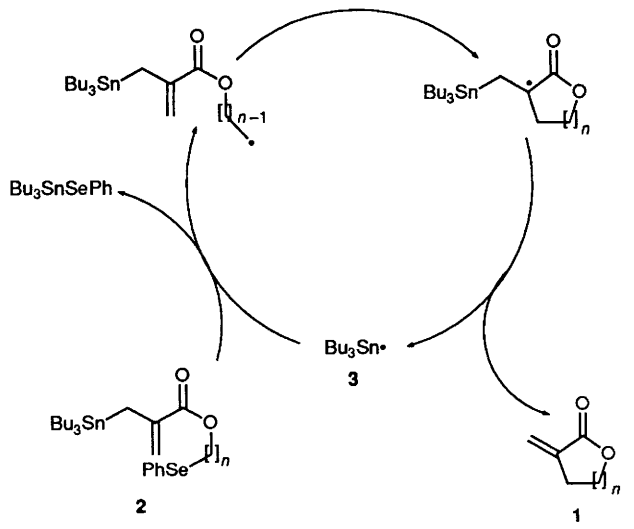
The synthesis of 10–15 membered α-methylene lactones **1** from the functionalised allyl stannanes **2** occurs cleanly in moderate to high yield under free radical conditions *via* an intramolecular S_H2' reaction.

The identification by Porter and co-workers of the structural requirements for successful alkyl radical macrocyclisation reactions[1] has led to the recent interest in these procedures.[2] We now report the synthesis of large ring α-methylene lactones **1** from the functionalised allyl stannanes **2** by means of an intramolecular S_H2' reaction (Scheme 1).

Thus, the esters **2**, prepared from **4** and **9** (Scheme 2), cleanly afforded 10–15 membered α-methylene lactones **1** in moderate to high yield (Table 1) under high dilution (5 mM) free radical conditions [cat. azoisobutyronitrile (AIBN), cat. Bu_3SnH, benzene, reflux, 48 h].† Since the chain transfer agent **3** is produced by virtue of a fragmentation reaction, only a catalytic quantity of tributyltin hydride is required to effect initiation of the process; direct reduction of the radical centre is not observed. The use of selenides as the radical precursor was preferable to either iodides or bromides since this avoided the need for a work-up procedure to remove tributyltin halides, which hydrolyse on silica. Reaction mixtures were simply concentrated and directly chromatographed.

Table 1 Yields of macrocycles **1** from **2**

n	Ring size	Yield (%)
6	10	54
7	11	46
8	12	61
9	13	50
10	14	80
11	15	72



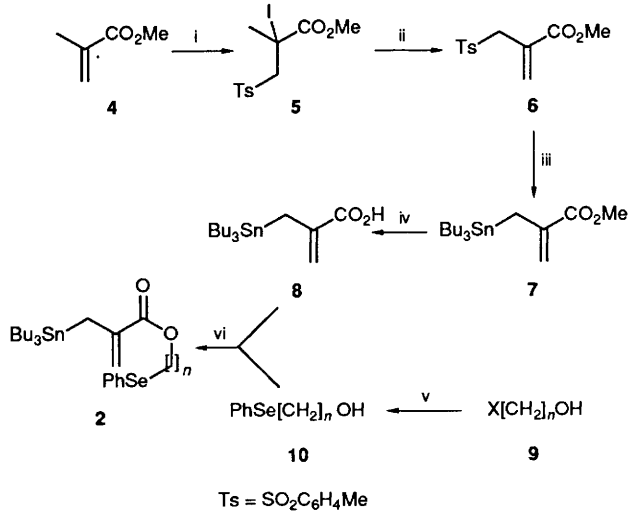
Scheme 1

† *Typical procedure for macrocyclisation*: To a degassed solution of the ω-phenylselenoalkyl 2-(tri-n-butylstannylmethyl)propenoate ester **2** in benzene (5 mM solution) was added tri-n-butyltin hydride (0.1 equiv.) and AIBN (0.05–0.1 equiv.). The mixture was heated at reflux under argon for 48 h, recharging the system with further AIBN (0.05 equiv.) every 12 h. Upon complete consumption of **2** (TLC), the solvent was removed *in vacuo*, and the macrocycle **1** isolated by standard flash chromatography on silica gel.

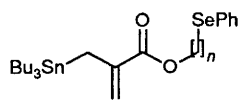
Attempts to synthesise analogous 6–9 membered lactones were unsuccessful; substrates **11–13** affording the dilactones **15–17** in low yield and in addition a variety of minor AIBN derived adducts, while the only isolable product from **14** was the AIBN adduct **18** (Table 2).

The failure to effect these ring closures can be accounted for in terms of the slow rate of cyclisation to the 6–9 membered lactones since the substrates **11–14** must adopt the unfavourable s-*E* conformation to accommodate the required radical transition-state geometry. Only for the longer alkyl chains, presumably $n > 5$, can the desired disposition of reactive centres be adopted while the preferred s-*Z* conformation[6] is maintained (Fig. 1). Consequently intermolecular processes compete effectively for the 6–9 ring closures, even under the high dilution conditions employed, to afford the observed dilactones and AIBN adducts.

Two recent radical cyclisation procedures report the formation of similar intermolecular addition adducts when attempt-

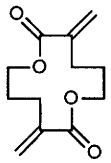
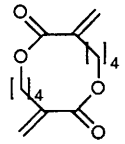
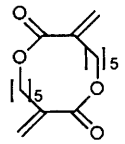
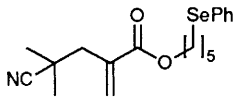


Scheme 2 *Reagents and conditions*: i, I_2 (1 equiv.), $NaTs{\cdot}H_2O$ (2 equiv.), MeOH, stir 2.5 h (ref. 3); ii, NEt_3, CH_2Cl_2, reflux, 8 h (ref. 4); iii, Bu_3SnH (1.5 equiv.), AIBN (cat.), toluene, reflux, 1 h (*cf.* ref. 5); iv, $LiOH{\cdot}H_2O$ (2 equiv.), tetrahydrofuran (THF)–H_2O (8 : 1), reflux, 36 h; v, $NaBH_4$ (1.1 equiv.), Ph_2Se_2 (0.55 equiv.), EtOH (X = Br or Cl); vi, dicyclohexylcarbodiimide (1.1 equiv.), dimethylaminopyridine (0.1 equiv.), **10** (1.1 equiv.), **8** (1 equiv.), THF



11 *n* = 2
12 *n* = 3
13 *n* = 4
14 *n* = 5

Table 2 Products from attempted cyclisation of substrates **11–14**

Substrate	Product	
11	 **15**	34%
12	 **16**	~15%
13	 **17**	~20%
14	 **18**	~20%

ing intramolecular closures.[7] O-Yang *et al.* obtained varying yields of mono-, di-, and tri-lactones when a range of 5 and 6-*endo*-trig cyclisations were attempted, while Boger *et al.* failed to effect a 10-*endo*-trig ring closure; only a dilactone derived species was isolated in low yield.

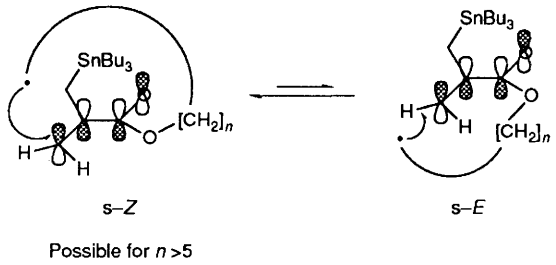


Fig. 1

In summary we have synthesised 10 membered or larger α-methylene lactones under free radical conditions, generating the chain carrying tri-n-butyl stannyl radical by means of an intramolecular S_H2' fragmentation reaction.

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References

1 N. A. Porter and V. H. T. Chang, *J. Am. Chem. Soc.*, 1987, **109**, 4976; N. A. Porter, V. H. T. Chang, D. R. Magnin and B. T. Wright, *J. Am. Chem. Soc.*, 1988, **110**, 3554.
2 See for example: S. A. Hitchcock and G. Pattenden, *Tetrahedron Lett.*, 1990, **31**, 3641; N. J. Cox, S. D. Mills and G. Pattenden, *Tetrahedron Lett.*, 1989, **30**, 621.
3 C. M. M. da Silva Corrêa and W. A. Waters, *J. Chem. Soc.* (*C*), 1968, 1874.
4 I. W. Harvey, E. D. Phillips and G. H. Whitham, *J. Chem. Soc., Chem. Commun.*, 1990, 481.
5 Y. Ueno, M. Ohta and M. Okawara, *J. Organomet. Chem.*, 1980, **197**, C1.
6 M. Oki and H. Nakanishi, *Bull. Chem. Soc. Japan*, 1970, **43**, 2558.
7 F. Barth and C. O-Yang, *Tetrahedron Lett.*, 1990, **31**, 1121; D. L. Boger and R. J. Mathvink, *J. Am. Chem. Soc.*, 1990, **112**, 4008.