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Samarium diiodide-mediated intramolecular cyclodimerisation of bis-α,β-unsaturated carbonyl compounds

Jonathan R. Powell, Sally Dixon, Mark E. Light, Jeremy D. Kilburn *

School of Chemistry, University of Southampton, Southampton SO17 1BJ, UK

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ABSTRACT

Samarium(II) diiodide-mediated intramolecular cyclodimerisation of simple bis-enones and -enoates in THF/MeOH has been investigated. Spirocyclic and elaborated polycyclic products, including stereodefined *cis*-bicyclo[3.3.0]octane and *trans*-bicyclo[4.3.0]nonanes, are obtained in synthetically useful yield.

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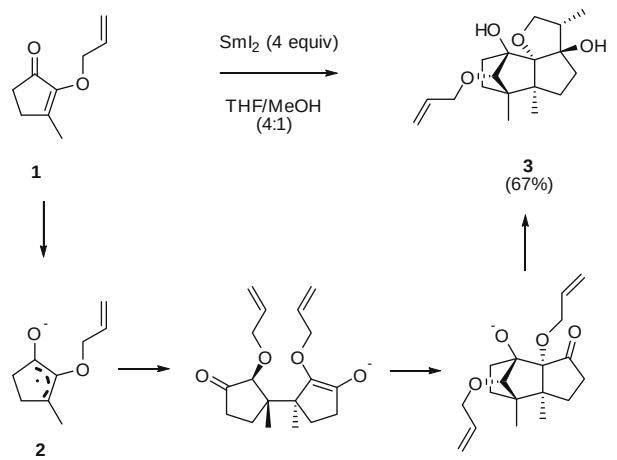
Samarium(II) diiodide-mediated homodimerisation of α,β-unsaturated carbonyl compounds[1] involves initial formation of a delocalised ketyl radical, for example, **2**, arising from single electron transfer to the enone, which may either couple with an identical radical, or undergo conjugate addition to another enone molecule, directly or following further reduction to the corresponding delocalised organosamarium anion. Cabrera[1b,c] and others[1e] have reported that acyclic enones, upon treatment with SmI_2 in the presence of HMPA, undergo homodimerisation followed by intramolecular aldol condensation to give β-hydroxyketone products, whilst cyclic enones only participate in the first homodimerisation step, without subsequent aldol reaction, yielding simple 1,6-dicarbonyl products.

Treatment of enones with SmI_2 in the presence of added HMPA and a proton source (stoichiometric ^{t}BuOH or MeOH) results in 1,4-reduction of the enone.[2] However, the complexity of the role of additives in Sm(II)-mediated reactions is well known[3,4] and a striking example is our report of SmI_2-mediated reduction of an α-allyloxy-substituted cyclopentenone, **1** (Scheme 1). Homodimerisation was shown to be an efficient process in a mixed THF/MeOH solvent system and subsequent intramolecular aldol condensation took place. Stereodefined tetracycle **3** was obtained without 1,4-reduction of the enone.[5]

To explore this reaction further, we have now examined the intramolecular cyclodimerisation of various bis-enones and -enoates,[6] of general structure **4**, in THF/MeOH solvent mixture. Trapping of the first formed radical, **5**, with a tethered enone or enoate as Michael acceptor, could be followed by intramolecular aldol or Dieckmann condensation, providing a novel cyclisation pathway for one-pot access to [3.3.0]bicyclooctane skeletons **6** and **7**, respectively (Scheme 2).

Cyclisation substrates, diketone **8a**,[6a] diester **8b**[7] and keto-ester **8c**[8] were each prepared from glutaraldehyde (Fig. 1). The results of cyclisation of **8a–c** upon treatment with SmI_2 in THF/MeOH are presented in Table 1.

Pleasingly, intramolecular cyclisation of diketone **8a** took place in good overall yield (Table 1, entry 1). *trans*-Bicyclo[4.3.0]nonane **9** was isolated as the major product, and its stereochemistry was confirmed by X-ray analysis, alongside two minor, diastereomeric *cis*-bicyclo[3.3.0]octanes, **10** and **11**, the stereochemistry of each of which was also confirmed by X-ray analysis.[11] Substrate **8b** gave rise to a ~1:1 separable mixture of products, **12** and **13**, again in a good combined yield (Table 1, entry 2). Cyclodecane **12** arises from tandem inter- then intramolecular enoate homodimerisation, and **13** arises from intramolecular conjugate addition followed by Dieckmann condensation. In the case of mixed keto-ester substrate **8c**, intermolecular enone homodimerisation predominates, followed by intramolecular aldol reaction and 1,4-reduction of the enoate moieties, giving diastereomeric cyclopentanes **14** (Table 1, entry 3).



Scheme 1.

* Corresponding author. Tel.: +44 23 80 593 596; fax: +44 23 80 596 805.
E-mail address: jdk1@soton.ac.uk (J.D. Kilburn).

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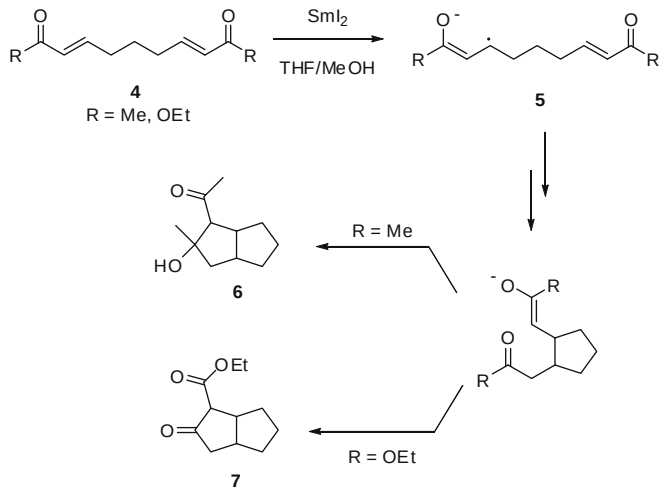
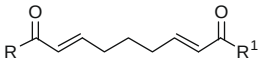


Scheme 2.



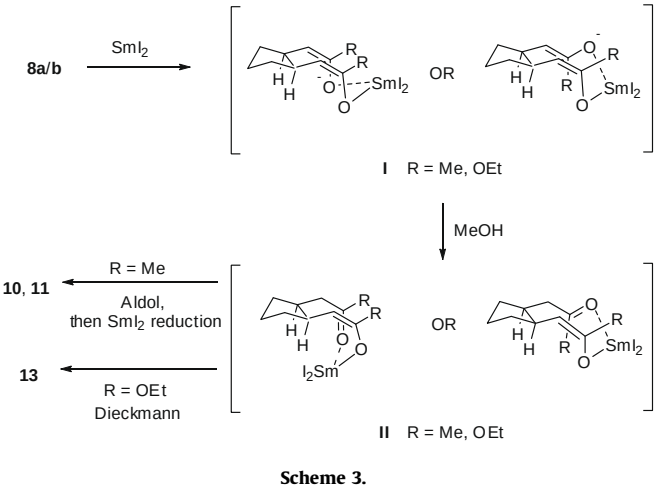
8a R = R^1 = Me
8b R = R^1 = OEt
8c R = Me, R^1 = OEt

Figure 1.

Table 1
SmI_2-mediated cyclisation of enone–enoate, bis-enone and bis-enoate substrates[a]

Entry	Substrate	Product(s) [yield%][b]
1	**8a**	**9** [53][c]; **10** [12][c]; **11** [6][c]
2	**8b**	**12** [38][d]; **13** [35]
3	**8c**	**14a** [23],[e] **14b** [33][e]

[a] Reactions were conducted on 1.60–1.94 mmol scale, in 4:1 THF/MeOH at −78 °C.[9]
[b] Isolated yield.
[c] The relative stereochemistry of each of the products **9**, **10** and **11** was determined by X-ray analysis.
[d] Isolated as a 4:1 inseparable mixture of diastereomers with an unidentified side product.
[e] C7 epimers **14a**/**b** were isolated, of which one (**14a**) was inseparable from a further minor diastereomer (**14a** dr = 3.5:1).[10] Stereochemical assignments are based upon the known SmI_2-mediated coupling of α,β-unsaturated ketones.[5]



Scheme 3.

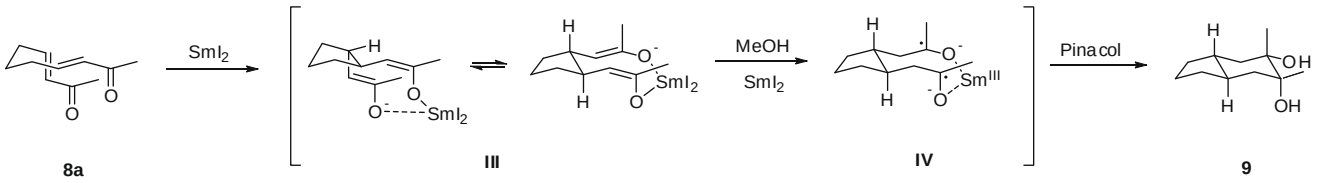
The formation of **10**, **11** and **13** is readily rationalised. SmI_2-mediated reduction of **8a** or **8b** and 5-*exo*-*trig* cyclisation lead to Sm(III)-chelated[12] *cis*-intermediate **I** and partial protonation then gives an enolate intermediate, **II**. Aldol condensation (R = Me) leads to diastereomeric β-hydroxy ketones, further SmI_2-mediated reduction of which accounts for the observed diol products **10** and **11**. Similarly, Dieckmann condensation of **II** (R = OEt) gives rise to **13** (Scheme 3).

Diastereoselective formation of **9** as the major product from diketone **8a** can be explained by assuming that initial cyclisation of **8a** proceeds via a conformation in which one enone group occupies a pseudo axial position. Reduction and conjugate addition lead to a *trans*-intermediate **III**. Following protonation, aldol condensation does not occur since a highly strained *trans*-bicyclo[3.3.0]octane would result; instead a second protonation, reduction of the resulting bis-ketone to a (bis)-ketyl radical **IV** and pinacol coupling, then leads to *cis*-diol **9** (Scheme 4).

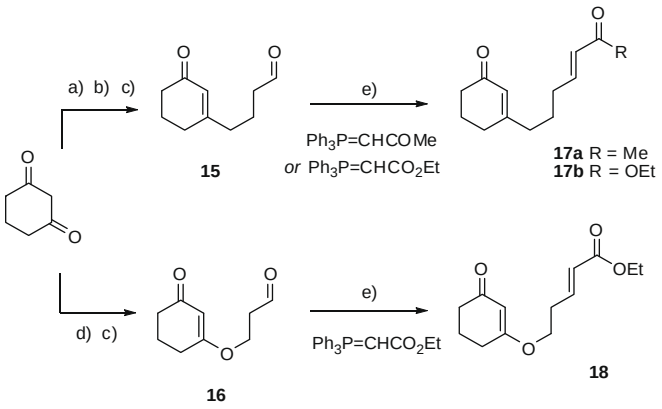
We now sought to extend this method to the preparation of polycyclic systems. β-Substituted cyclic enones **17a** and **17b**,[13] respectively, functionalised with remote enone or enoate functionality, were readily prepared from 1,3-cyclohexandione via conversion to aldehyde **15**[14–16] and Wittig olefination. Similarly a mixed enone–enoate **18**, tethered via an ether linkage, was also prepared[13] (Scheme 5). The results of cyclisation of **17a**/**b** and **18**, upon treatment with SmI_2 in THF/MeOH, are presented in Table 2.

Intramolecular coupling to the pendant enone was observed for **17a**, followed by tandem pinacol coupling or aldol condensation, to give tricyclic products **19** and **20a**/**b,** respectively (Table 2, entry 1), and we rationalise the formation of each according to the analogous acyclic system **8a**. Thus, reduction of one enone moiety and intramolecular coupling to the other enone lead to diastereomeric, spirocyclic intermediates **V** and **VI**. This is followed either by intramolecular aldol condensation to give **20a** and **20b** with an embedded *cis*-fused bicyclo[3.3.0]octane, or by a pinacol coupling to give **19**. As with the acyclic system, the aldol reaction appears to be favoured over pinacol when it is not precluded by ring strain (Scheme 6).

Diols **21a**/**b**, obtained from mixed enone/enoate **17b**, demonstrate that intramolecular coupling with a pendant enoate appears to proceed more slowly than with an enone since intermolecular homodimerisation of the enone predominates (Table 2, entry 2). Once again, intramolecular aldol condensation follows the dimerisation and further reduction then occurs to give the product diols. The result is consistent with that observed in the acyclic series (Table 1, entry 3). Interestingly, intramolecular conjugate addition of β-alkoxy tethered analogue, **18**, does take place in high yield. Sub-



Scheme 4.



Scheme 5. Reagents and conditions: (a) Catalytic *p*-TsOH, $HC(OMe)_3$, MeOH, rt, 48 h (58%); (b) 5-bromo-1-pentene, Mg, Et_2O, rt, then Δ, 2 h (46%); (c) $RuCl_3$, $NaIO_4$, CH_3CN:H_2O (6:1), rt, 4 h (**15**, 54%), (**16**, 21%); (d) 3-buten-1-ol, catalytic *p*-TsOH, toluene, Δ, 5 h, Dean–Stark conditions (79%); (e) $Ph_3P{=}CHCOMe$ or $Ph_3P{=}CHCO_2Et$, toluene, Δ, 3–16 h (**17a**, 61%), (**17b**, 71%), (**18**, 50%).

sequent protonation and further SmI_2-mediated reduction lead to spirocycles **22a**/**b** (Table 2, entry 3).

Finally, we also investigated the intramolecular (9-*endo*-*trig*) cyclisation of dione **23**.[18] However, treatment of **23** under the same reducing conditions resulted in a mixture of diastereomeric products, **24a** and **24b**, in modest yield, from which we were able to separate one diastereomer (**24a**) and identify its structure by X-ray analysis.[11] Tricyclic tetraols **24** arise from a remarkable cascade sequence involving reduction of **23** followed by intermolecular homodimerisation to give a samarium bis-enolate, double intramolecular aldol condensation, further reduction of the resultant ketone functionality and pinacol coupling (Scheme 7).

In conclusion, we have investigated the SmI_2-mediated, intramolecular cyclodimerisation of several (bis)-α,β-unsaturated carbonyl compounds, which provide a rapid entry to *cis*-bicyclo[3.3.0]octane and *trans*-bicyclo[4.3.0]nonane products from simple acyclic starting materials. Similarly, tricyclic products can be obtained from cyclohexanone-containing precursors. In addition, ready access to other elaborate polycyclic and spirocyclic products can be achieved, from simple starting materials and via cascade sequences involving the iterative formation of multiple carbon–carbon bonds and stereogenic centres.

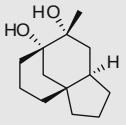
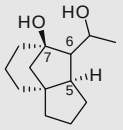
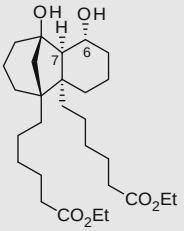
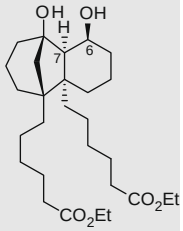
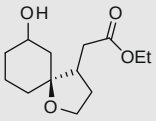
Acknowledgement

We thank the EPSRC for a studentship (J.R.P.).

Supplementary data

X-ray crystallographic data for compounds **9**, **10** and **11** and **24a** are provided in cif. format. Spectroscopic characterisation of compounds **9**–**11**, **13**, **14b**, **17a**/**b**, **18**, **19**, **20a**/**b** and **21a**/**b**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.031.

Table 2
SmI_2-mediated cyclisation of cyclic enone–enoate, bis-enone and bis-enoate substrates[a]

Entry	Substrate	Product(s) [yield%][b]	
1	**17a**	 **19** [18]	 **20a** [16],[c] **20b** [9][c]
2[d]	**17b**	 **21a** [14][e]	 **21b** [25][f]
3	**18**	 **22a** [23],[g] **22b** [48][g]	

[a] Reactions were conducted on 1.18–1.29 mmol scale, in 4:1 THF/MeOH at −78 °C.[9]

[b] Isolated yield.

[c] Single diastereoisomers **20a** and **20b** were separated by column chromatography. Relative stereochemistry at C5 and C7 is rationalised according to the formation of **11**.

[d] A third product of unidentified structure was isolated in 10% yield.

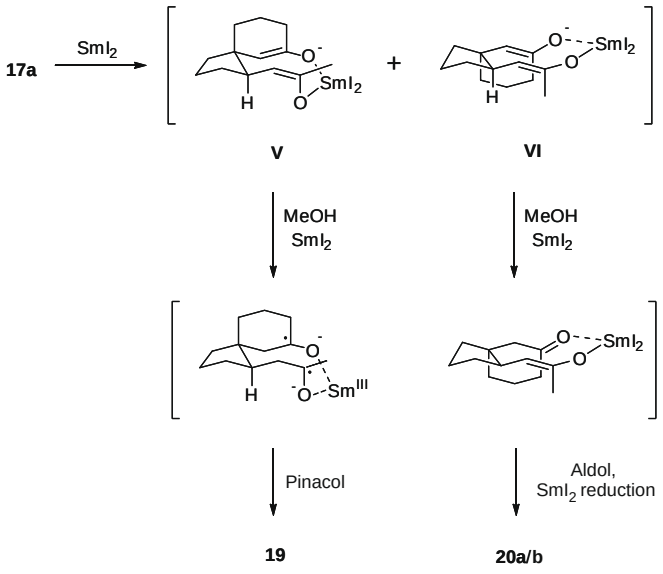
[e] A $^3J_{H6-H7}$ = 10.0 Hz axial–axial coupling (^{1}H NMR, 400 MHz, $CDCl_3$) is diagnostic of the *exo*-*cis* equatorial diastereomer.

[f] We were unable to confirm the stereochemistry of this expected[5] *exo*-*cis* axial diastereomer due to overlap of the H6 resonance in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$).

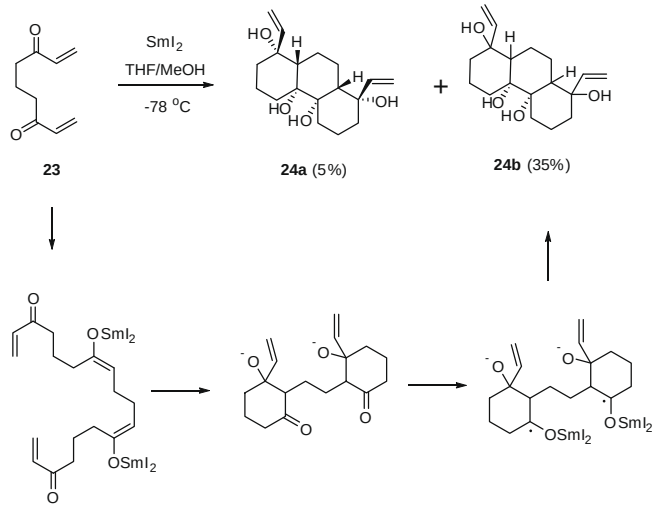
[g] Two diastereomeric mixtures **22a** and **22b** were isolated by column chromatography (**22a** dr = ~2.5:1, **22b** dr = ~2:1).[10,17]

References and notes

1. (a) Cabrera, A.; Alper, H. *Tetrahedron Lett.* **1992**, *33*, 5007–5008; (b) Cabrera, A.; Le Lagadec, R.; Sharma, P.; Arias, J. L.; Toscano, R. A.; Velasco, L.; Gavino, R.; Alvarez, C.; Salmon, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3609–3617; (c) Cabrera, A.; Rosas, N.; Sharma, P.; Le Lagadec, R.; Velasco, L.; Salmon, M. *Synth. Commun.* **1998**, *28*, 1103–1108; (d) Inanaga, J.; Handa, Y.; Tabuchi, T.; Otsubo, K.; Yamaguchi, M.; Hanamoto, T. *Tetrahedron Lett.* **1991**, *32*, 6557–6558; (e) Zhou, L. H.; Zhang, Y. M. *Synth. Commun.* **2000**, *30*, 597–607.
2. Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2121–2124.
3. For detailed mechanistic studies of the role of additives, see: (a) Flowers, R. A. *Synlett* **2008**, 1427–1439; (b) Sadasivam, D. V.; Antharjanam, P. K. S.; Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2008**, *130*, 7228–7229.
4. For an elegant example of the use of alcohol proton donors in directing the reaction pathway, see: Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811–4814.
5. Howells, D. M.; Barker, S. M.; Watson, F. C.; Light, M. E.; Hursthouse, M. B.; Kilburn, J. D. *Org. Lett.* **2004**, *6*, 1943–1945.



Scheme 6.



Scheme 7.

6. For intramolecular cyclodimerisation of tethered bis-enone and enone/enoate systems under Bu_3 SnH/AIBN/Δ conditions, see: (a) Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850–4855; For α-tethered bis-cyclohexenones, see: (b) Handy, S. T.; Omune, D. *Tetrahedron* **2007**, *63*, 1366–1371; For an α-tethered mixed enone/enoate under strongly reducing conditions (Li/NH_3) see: (c) Wasnaire, P.; Wiaux, R. T.; Markó, I. E. *Tetrahedron Lett.* **2006**, *47*, 985–989.
7. Davies, S. G.; Diez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284–1301.
8. Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 8777–8787.
9. *Typical procedure*: MeOH (19 mL) was added to a stirring solution of SmI_2 in dry THF (0.1 M, 78 mL) and the resultant purple mixture was cooled to −78 °C. A solution of diketone **8a** (350 mg, 1.94 mmol) in dry THF (5 mL) was then added dropwise over a period of 10 min, and the mixture was stirred at −78 °C for a further 2 h. Brine (40 mL), followed by citric acid (489 mg, 2.33 mmol) was then added before stirring for 20 min. EtOAc (80 mL) was added to the stirring solution and, after 10 min, the organic phase was separated. This process was then repeated (5 × 80 mL EtOAc in total). The aqueous phase was further extracted with EtOAc (80 mL), before the combined organic extracts were washed with brine (2 × 50 mL) and dried over $MgSO_4$ before concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with 10%→20% EtOAc in petrol) gave **9** (190 mg, 1.03 mmol, 53%) as a white crystalline solid, R_f = 0.36 (40% EtOAc in petrol), **10** (43 mg, 0.23 mmol, 12%) as a pale yellow solid, R_f = 0.22 (40% EtOAc in petrol) and **11** (21 mg, 0.11 mmol, 6%) as a yellow solid, R_f = 0.17 (40% EtOAc in petrol). Spectroscopic characterisation of compounds **9**–**11**, **13**, **14b**, **19**, **20a**/**b** and **21a**/**b** is provided as Supplementary data.
10. Diastereomeric product mixtures **14a**, **22a** and **22b** were satisfactorily characterised by ^{1}H and ^{13}C NMR spectroscopy, IR and high resolution mass spectrometry.
11. Crystallographic data (excluding structure factors) for structures **9**, **10** and **11** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 715426, 715427 and 715428. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Data were collected on a Bruker Nonius KappaCCD with a Mo rotating anode generator; standard procedures were followed. All hydrogen atoms were identified from the difference map and then positioned geometrically and refined using a riding model. *Crystal data for* **9**: $C_{11}H_{20}O_2$, Mr = 184.27, T = 120(2) K, triclinic, space group P-1, a = 9.8736(4), b = 10.5209(3), c = 11.2839(7) Å, α = 89.986(2), β = 72.579(1), γ = 74.358(2)°, V = 1072.84(7) Å^3, ρ_{calc} = 1.141 g cm^{-3}, μ = 0.076 mm^{-1}, Z = 4, reflections collected: 15537, independent reflections: 4887 (R_{int} = 0.0560), final R indices [$I > 2\sigma I$]: R_1 = 0.0567, wR_2 = 0.1439, R indices (all data): R_1 = 0.0924, wR_2 = 0.1642. *Crystal data for* **10**: $C_{11}H_{20}O_2$, Mr = 184.27, T = 120(2) K, monoclinic, space group $P2_1/c$, a = 14.5734(19), b = 5.6030(7), c = 14.6007(17) Å, β = 117.153(6)°, V = 1060.8(2) Å^3, ρ_{calc} = 1.154 g cm^{-3}, μ = 0.077 mm^{-1}, Z = 4, reflections collected: 9485, independent reflections: 2418 (R_{int} = 0.1289), final R indices [$I > 2\sigma I$]: R_1 = 0.0913, wR_2 = 0.1550, R indices (all data): R_1 = 0.1951, wR_2 = 0.1877. *Crystal data for* **11**: $C_{11}H_{20}O_2$, Mr = 184.27, T = 120(2) K, monoclinic, space group $P2_1/c$, a = 9.5216(2), b = 7.0923(1), c = 15.8780(3) Å, β = 107.270(1)°, V = 1023.90(3) Å^3, ρ_{calc} = 1.195 g cm^{-3}, μ = 0.080 mm^{-1}, Z = 4, reflections collected: 14420, independent reflections: 2355 (R_{int} = 0.0518), final R indices [$I > 2\sigma I$]: R_1 = 0.0484, wR_2 = 0.1269, R indices (all data): R_1 = 0.0805, wR_2 = 0.1508. *Crystal data for* **24a**: $C_{18}H_{28}O_4$, Mr = 308.4, T = 120(2) K, orthorhombic, space group $Pca2_1$, a = 18.0495(8), b = 20.9129(7), c = 35.4953(16) Å, V = 13398.3(10) Å^3, ρ_{calc} = 1.070 g cm^{-3}, μ = 0.074 mm^{-1}, Z = 28. These data are from an isotropic refinement of sub-publication quality. The coordinates are available in CIF format as Supplementary data.
12. An oligomeric samarium species is probable, and expected from a radical-radical 5-*exo*-*trig* homodimerisation. Only for the purpose of clarity, monomeric samarium(III) chelation control is shown: Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172–2173.
13. Spectroscopic characterization of compounds **17a**/**b** and **18** is provided as Supplementary data.
14. Mattay, J.; Banning, A.; Bischof, E. W.; Heidbreder, A.; Runsink, J. *Chem. Ber.* **1992**, *125*, 2119–2127.
15. Takahashi, K.; Tanaka, T.; Suzuki, T.; Hirama, M. *Tetrahedron* **1994**, *50*, 1327–1340.
16. Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814–4818.
17. Approximate diastereomeric ratios are reported based upon measurement of the peak height and integral of resonances of paired diastereomeric carbons in the ^{13}C NMR spectrum (400 MHz, $CDCl_3$).
18. Christoffers, J.; Oertling, H.; Onal, N. *J. Prakt. Chem.* **2000**, *342*, 546–553.