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Carbanion cyclisation of esters. Part 2:† Enantiospecific construction of the tricyclic framework of the marine sesquiterpenes, spirodysins ☆

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Abstract—Enantiospecific construction of the bicyclo[4.3.0]nonan-8-one **17** employing a lithium and liquid ammonia mediated carbanion cyclisation of the δ-methyl-δ,ε-unsaturated ester **13**, and its elaboration to the tricyclic framework of the marine sesquiterpenes spirodysins are described.

The marine sponge *Dysidea herbacia* is a prolific producer of structurally diverse secondary metabolites including sesquiterpene spirolactol/lactones, tricyclic furans (some based on the furodysin and furodysinin skeletons and their oxidised derivatives), modified steroids, polychlorinated alkaloids, brominated diphenyl ethers and other metabolites.[2] The spirodysins are a small group of sesquiterpenes isolated from *D. herbacia*, contain a furan spirofused to a bicyclo[4.3.0]nonane, and are probably the biogenetic precursors of furodysins and furodysinins. The isolation of the first members of this group spirodysin **1** and herbadysidolide **2** was reported by the research groups of Wells[3a] and Charles.[3b] A few other derivatives of spirodysins were isolated later from sponges collected at different geographical regions. Structures of various spirodysins isolated so far are depicted in Chart 1. The tricyclic framework in spirodysins made them interesting synthetic targets.[4] We have developed a methodology for the enantiospecific construction of the tricyclic framework present in spirodysins based on a carbanion cyclisation of esters, which is the subject of this communication.

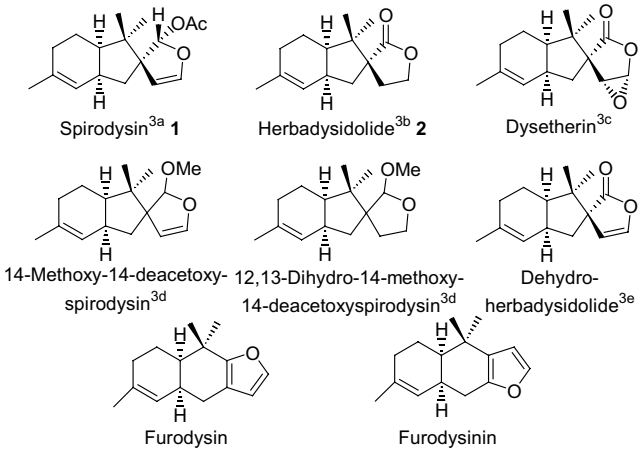
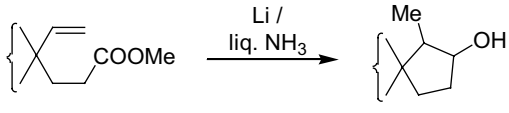


Chart 1.



(1)

In the preceding communication[1] we have reported a facile lithium in liquid ammonia mediated 5-*exo*-*trig* reductive cyclisation of δ,ε-unsaturated esters (Eq. 1) and demonstrated its utility in the annulation of a variety of fused, spiro and bridged cyclopentanes. In order to evaluate its efficacy for the construction of a quaternary carbon atom, we investigated the reaction with δ,ε-unsaturated esters containing a substituent at

† See Reference 1.
☆ Chiral synthons from carvone, Part 61. For Parts 59 and 60, see: Ref. 10.
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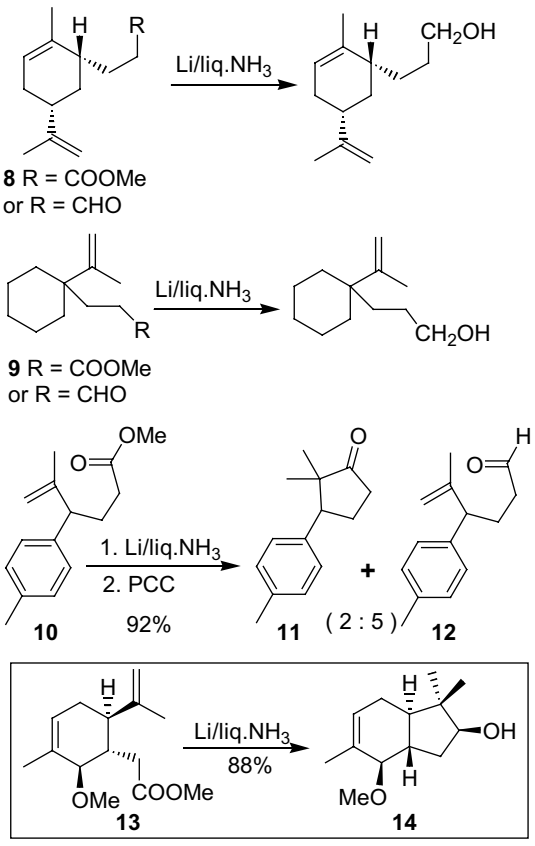
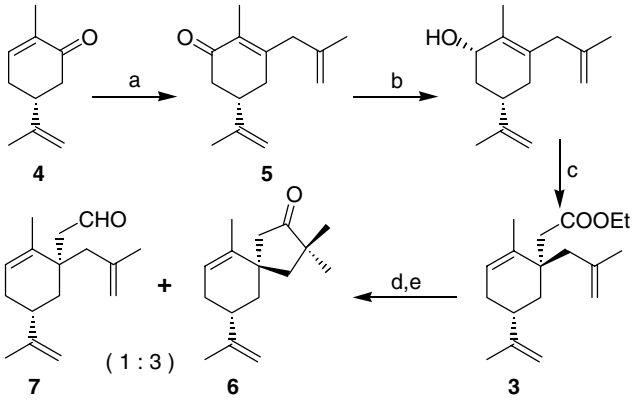
the δ-position to generate α,α-disubstituted cyclopentanones. To begin with, the ester **3**, which was prepared from (*R*)-carvone **4**, was chosen for investigating the cyclisation reaction (Scheme 1). Thus, (*R*)-carvone **4** was converted into 3-methallylcarveol **5** employing an alkylative 1,3-enone transposition followed by regioselective reduction. Johnson's ortho ester Claisen rearrangement[5] of the allyl alcohol **5** with triethyl orthoacetate and propionic acid transformed the allyl alcohol **5** into the ester **3**. Treatment of a solution of the ester **3** in liquid ammonia and THF with lithium at −33 °C furnished a mixture of primary and secondary alcohols, which on pyridinium chlorochromate (PCC) oxidation furnished an easily separable 3:1 mixture of the spiro ketone[††] **6** and the aldehyde **7** in 88% yield. Similarly, reaction of the aldehyde **7** with lithium in liquid ammonia followed by oxidation furnished a 5:2 mixture of the spiroketone **6** and the aldehyde **7** in 68% yield. It is worth noting that neither the ester **3** nor the aldehyde **7** produced any 6-*endo trig* cyclised product (a spiro[5.5]undecane) ruling out the possibility of a radical pathway in the present cyclisation (a commonly encountered reaction with 5-alkyl-5-hexenyl radicals).[6]

Reactions of a few other δ-substituted-δ, ε-unsaturated esters in liquid ammonia with lithium were also investigated, but the cyclisation was found to be substrate dependent. For example, the esters **8** and **9** and the corresponding aldehydes failed to produce any cyclisation products and resulted in only the primary alcohols, whereas reaction of the aryl system **10** in liquid ammonia–THF followed by PCC oxidation of the resultant mixture of alcohols generated an easily separable 2:5 mixture of the cyclised ketone **11** and the aldehyde **12** in 92% yield.[7] On the other hand, reaction of the ester **13** in liquid ammonia–THF with lithium resulted in the



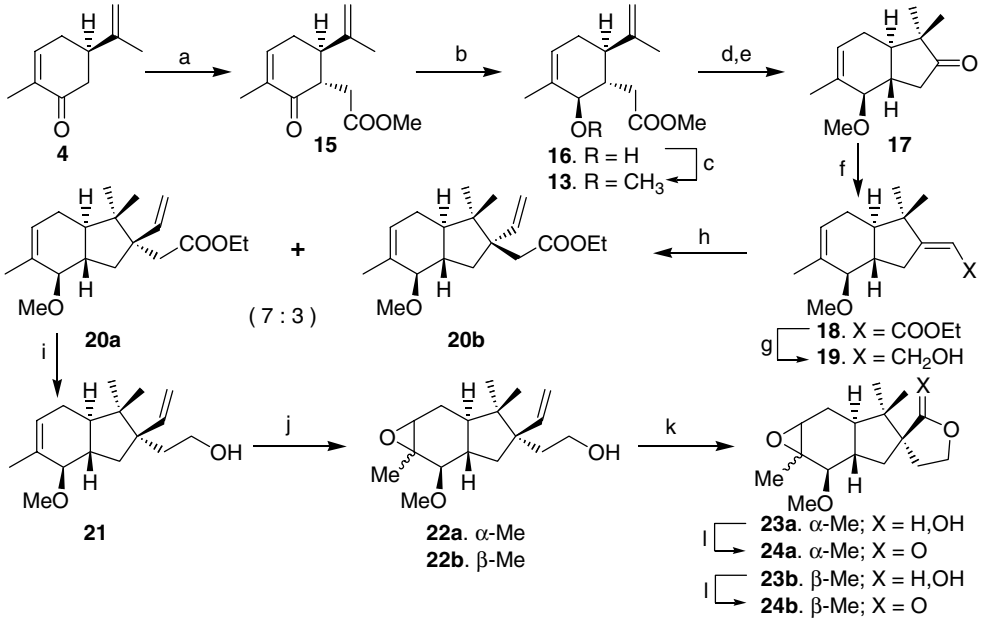
[††] All the compounds exhibited spectral data consistent with their structures. Yields (unoptimised) refer to isolated and chromatographically pure compounds. Selected spectral data for the spiroketone **6**: $[\alpha]_D^{22}$ +50.0 (*c* 0.84, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1740, 888. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.43 (1H, br s, C=C*H*), 4.68 (2H, s, C=CH_2), 2.76 and 1.99 (2H, 2×d, *J* 17.0 Hz), 2.35–2.15 (1H, m), 2.15–1.80 (5H, m), 1.72 (3H, s) and 1.67 (3H, s) (2×olefinic CH_3), 1.45–1.20 (1H, m), 1.16 (3H, s) and 1.10 (3H, s) (2×*tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 220.7 (C), 148.6 (C), 137.0 (C), 124.3 (CH), 109.5 (CH_2), 48.5 (CH_2), 47.8 (CH_2), 44.1 (C), 42.4 (CH_2), 40.8 (C), 37.7 (CH), 31.1 (CH_2), 28.2 (CH_3), 27.7 (CH_3), 21.0 (CH_3), 18.9 (CH_3). HRMS: *m*/*z* calcd for $C_{16}H_{24}ONa$ (M+Na): 255.1725; found: 255.1725. For the hydrindanone **17**: $[\alpha]_D^{22}$ +79.2 (*c* 3.6, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1740. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.56 (1H, s, H-4), 3.63 (1H, d, *J* 6.9 Hz), 3.35 (3H, s, OCH_3), 2.72 (1H, dd, *J* 16.8 and 6.0 Hz), 2.20–1.90 (4H, m), 1.75–1.60 (1H, m), 1.71 (3H, s, olefinic CH_3), 1.03 (3H, s) and 0.87 (3H, s) (2×*tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 220.2 (C, C=O), 136.3 (C, C-3), 124.6 (CH, C-4), 85.6 (CH, C-2), 56.7 (CH_3, OCH_3), 48.8 (CH, C-6), 47.3 (C, C-7), 42.7 (CH_2), 39.5 (CH, C-1), 25.2 (CH_2), 22.8 (CH_3), 19.5 (CH_3), 18.6 (CH_3). HRMS: *m*/*z* calcd for $C_{13}H_{20}O_2Na$ (M+Na): 231.1361; found: 231.1360. For the ester **20a**: $[\alpha]_D^{20}$ −37.5 (*c* 1.6, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1736, 910. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.79 (1H, dd, *J* 17.5 and 11.0 Hz, C*H*=CH_2), 5.50 (1H, br s, H-4′), 5.05 (1H, d, *J* 11.0 Hz) and 4.98 (1H, d, *J* 17.5 Hz) (C*H*=CH_2), 4.04 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.66 (1H, br d, *J* 9.6 Hz, H-2′), 3.39 (3H, s, OCH_3), 2.40 (1H, d, *J* 13.5 Hz), 2.28 (1H, d, *J* 13.5 Hz), 2.30–1.55 (6H, m), 1.69 (3H, s, olefinic CH_3), 1.22 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 0.87 (3H, s) and 0.68 (3H, s) (2×*tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 171.9 (C, OC=O), 141.8 (CH, HC=CH_2), 137.0 (C, C-3′), 125.2 (CH, C-4′), 112.9 (CH_2, CH=CH_2), 86.5 (CH, C-2′), 59.7 (CH_2, OCH_2CH_3), 56.8 (CH_3, O–CH_3), 52.7 (C, C-8′), 49.1 (CH), 45.2 (C, C-7′), 43.1 (CH), 41.7 (CH_2), 34.8 (CH_2), 26.2 (CH_2), 21.6 (CH_3), 20.2 (CH_3), 19.4 (CH_3), 14.4 (CH_3, OCH_2CH_3). HRMS: *m*/*z* calcd for $C_{19}H_{30}O_3Na$ (M+Na): 329.2093; found: 329.2081. For the lactone **24a**: mp 126–127 °C. $[\alpha]_D^{22}$ −47.8 (*c* 0.9, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1751. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.19 (1H, d of t, *J* 5.4 and 1.5 Hz) and 4.06 (1H, d of t, *J* 5.7 and 4.2 Hz) (H-5′), 3.37 (3H, s, OCH_3), 3.33 (1H, d, *J* 6.0 Hz, H-5), 3.02 (1H, d, *J* 3.0 Hz, H-2), 2.57 (1H, dd, *J* 8.4 and 6.0 Hz, H-7), 2.48 (1H, ddd, *J* 8.1, 4.2 and 1.5 Hz, H_a-4′), 2.26 (1H, m, H_a-6), 2.04 (1H, t of d, *J* 13.2 and 9.3 Hz, H_b-4′), 1.85–1.70 (1H, m, H-1), 1.65 (1H, dd, *J* 14.1, 12.3 Hz, H_a-10), 1.48 (1H, dd, *J* 14.1 and 7.5 Hz, H_b-6), 1.40–1.20 (1H, m, H_b-10), 1.38 (3H, s, C_3–CH_3), 1.01 (3H, s) and 0.92 (3H, s) (CH_3–C–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 178.6 (C, OC=O), 84.6 (CH, C-2), 77.0 (C, C-3), 64.7 (CH_2, C-5′), 60.7 (C, C-9), 59.3 (CH, C-5), 54.5 (CH), 51.0 (CH_3, O–CH_3), 46.0 (C,C-8), 39.3 (CH_2, C-4′), 36.0 (CH_2), 35.8 (CH), 24.1 (CH_2), 23.1 (CH_3), 19.9 (CH_3), 19.6 (CH_3). HRMS: *m*/*z* calcd for $C_{16}H_{24}O_4Na$ (M+Na): 303.1572; found: 303.1572. Crystal data for **24a**: X-ray data were collected at 293 K on a Smart CCD–Bruker diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.7107 Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. $C_{16}H_{24}O_4$, MW = 280.167, colourless crystal, crystal system: monoclinic, space group: *P*2(1); cell parameters: *a* = 8.278(2) Å, *b* = 6.706(2) Å, *c* = 13.449(4) Å, β = 90.116(5), *V* = 746.69 Å^3; *Z* = 2; D_c = 1.247 g cm^{-3}; *F*(0 0 0) = 304.0, μ = 0.09 mm^{-1}. Total number of l.s. parameters = 277; R_1 = 0.043 for 2245 $F_0 > 4\sigma(F_0)$ and 0.0623 for all 2919 data. wR_2 = 0.0941; GOF = 1.107; Restrained GOF = 1.106 for all data. Crystallographic data (without structure factor) have been deposited with the Cambridge Crystallographic Data Centre and the depository number is CCDC 205781.



Scheme 1. Reagents, conditions and yields: (a) i. CH_2=C(Me)-CH_2MgCl, THF, 0 °C → rt, 1 h; ii. PCC, silica gel, CH_2Cl_2, rt, 2 h; 86%; (b) LAH, Et_2O, −70 °C, 1 h, 92%; (c) $MeC(OEt)_3$, EtCOOH, sealed tube, 180 °C, 60 h, 63%; (d) Li, liquid NH_3, THF, −33 °C, 1 h; (e) PCC, silica gel, CH_2Cl_2, rt, 1 h; 88% (from ester **3**).

cyclisation to produce **exclusively** the *trans*-bicyclo[4.3.0]nonanol **14**, in 88% yield in a highly stereoselective manner.[8,9] The factors, which are responsible for cyclisation of the δ-substituted-δ,ε-unsaturated esters are not clear at the moment and are currently being investigated. Ready access to the bicyclo[4.3.0]nonanol **14** prompted us to apply the methodology for the enantiospecific construction of the tricyclic framework of spirodysins.

It was contemplated that spiroannulation of a furan to the hydrindanol **14** would lead to spirodysins. The ester **13** was prepared from the readily and abundantly available monoterpene (*R*)-carvone **4**. The synthetic sequence is depicted in Scheme 2. Thus, generation of the kinetic enolate of carvone with lithium diisopropylamide (LDA) followed by alkylation with methyl bromoacetate generated the ketoester **15**, in 76% yield, in a highly stereoselective manner. Regiospecific reduction of the ketone in **15** with sodium borohydride in methanol furnished the hydroxy ester **16**, in 81% yield, in a highly stereoselective manner, which on Williamson etherification furnished the methoxy ester **13**, in 70% yield. Reaction of the ester **13** in liquid ammonia–THF with lithium followed by oxidation of the resultant alcohol **14** with PCC and sodium acetate furnished exclusively the hydrindanone **17**.[††] A Claisen rearrangement based spiroannulation of a furan was contemplated for the conversion of the ketone **17** in to spirodysins. Thus, Horner–Wadsworth–Emmons reaction of the ketone **17** with triethyl phosphonoacetate and sodium hydride at 120 °C in a sealed tube furnished the conjugated ester **18** in a highly stereoselective manner, which on regioselective reduction with lithium aluminium hydride (LAH) in ether at low temperature furnished the allyl alcohol **19**. Johnson's orthoester Claisen rearrangement[5] of the allyl alcohol **19** with triethyl orthoacetate and propionic acid in a sealed tube at 180 °C furnished a 7:3 mixture of the γ,δ-unsaturated esters[††] **20a** and **20b**, in 71% yield, which were separated by column chromatography on silica gel. Reduction of the ester in the major isomer **20a** with LAH in ether furnished the primary alcohol **21**. An ozonolytic cleavage was contemplated for the degradation of the extra carbon atom present, and to prevent the regiochemical problems the trisubstituted olefin in **21** was blocked. Regioselective epoxidation of the ring olefin in **21** in methylene chloride with *m*-chloroperbenzoic acid (*m*-CPBA) furnished, as expected, a 1:1



Scheme 2. Reagents, conditions and yields: (a) LDA, THF, −70 °C; $BrCH_2COOMe$, 70 °C → rt, 6 h; 76%; (b) $NaBH_4$, MeOH, −30 °C, 81%; (c) NaH, THF, Bu_4NI, MeI, reflux, 8 h, 70%; (d) Li, liquid NH_3, THF, −33 °C, 1 h, 88%; (e) PCC, NaOAc, CH_2Cl_2, rt, 2 h, 88%; (f) NaH, $(EtO)_2P(O)CH_2COOEt$, sealed tube, 120 °C, 85%; (g) LAH, Et_2O, −40 °C, 86%; (h) $MeC(OEt)_3$, EtCOOH, sealed tube, 180 °C, 72 h; (i) LAH, Et_2O, 0 °C, 1 h, 90%; (j) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 81% (**22a**:**22b** 1:1); (k) O_3/O_2, CH_2Cl_2/MeOH (5:1), −70 °C; Me_2S, rt, 8 h, 90–93%; (l) PCC, NaOAc, CH_2Cl_2, rt, 1 h, 82–84%.

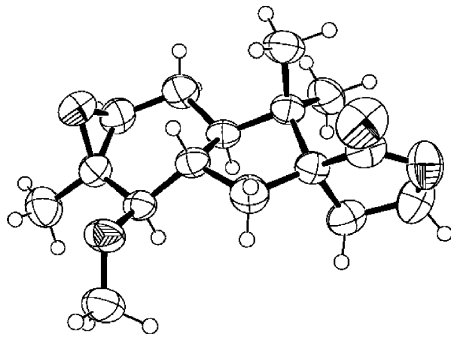


Figure 1. X-ray structure of the lactone **24a**.

mixture of the epoxides **22a** and **22b**, which were separated by column chromatography on silica gel. Ozonolysis of the vinyl group in **22a** followed by reductive work-up with dimethyl sulfide furnished the hemiacetal **23a**, which on oxidation with PCC and sodium acetate furnished the lactone[††] **24a** containing the complete tricyclic framework of spirodysins. In a similar manner ozonolysis and oxidation transformed the epoxide **22b** in to the lactone **24b**. The stereostructures of the lactones **24a**,**b** were established from their spectral data, and the stereochemistry at various centres was unambiguously established by a single crystal X-ray analysis[††] of the lactone **24a**, which is depicted in Figure 1.

In conclusion, we have discovered a convenient methodology for the enantiospecific construction of the *trans*-bicyclo[4.3.0]nonan-8-one **17** employing lithium in liquid ammonia mediated carbanion cyclisation of the ester **13**. The ketone **17** was further elaborated into the tricyclic framework of the sesquiterpenes spirodysins. Currently, we are investigating the extension of this methodology for the generation of the corresponding *cis* isomer and further elaboration to natural spirodysins.

Acknowledgements

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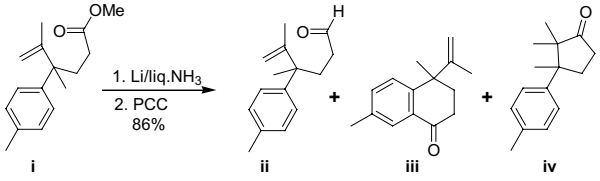
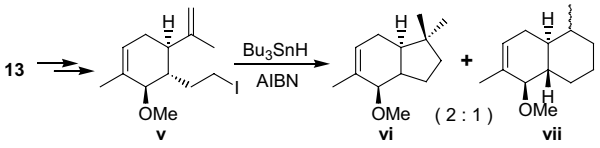
7. In contrast, reaction of the ester **i**, containing an extra methyl group at the benzylic position, in liquid ammonia with lithium followed by oxidation of the resulting mixture of alcohols furnished 1:3 mixture of the aldehyde **ii** and the tetralone **iii** containing a small amount of α-cuparenone **iv**, in 86% yield, perhaps due to the steric crowding of two vicinal quaternary carbon atoms in the cuparanes.



8. The structure of the alcohol **14** was established from its spectral data and was further confirmed by single crystal X-ray diffraction analysis of the corresponding 4-nitrobenzoate ester. The crystallographic data has been deposited with the Cambridge Crystallographic Data Center (CCDC 218889).
9. It is worth mentioning that the radical cyclisation of the iodide **v**, obtained from the ester **13** in two steps, produced a 2:1 (by NMR) mixture of the 5-*exo trig* and 6-*endo-trig* cyclisation products **vi** and **vii**.



10. Part 59: Srikrishna, A.; Kumar, P. P.; Reddy, T. J. *Arkivoc* **2003**, *iii*, 55–66; Part 60: Srikrishna, A.; Dethe, D. H. *Tetrahedron Lett.* **2003**, *44*, 7817–7820.