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Bicyclo[10.2.1]pentadecenone Derivatives By Free Radical Macrocyclisation

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Abstract: The synthesis of intermediates for the preparation of stereoisomeric bicyclo[10.2.1]pentadec-13-en-3-ones is described. The preparation and the addition of 6-functionalised hexylcuprate reagents to bicyclic lactone **5** is discussed and a method described for the epimerisation of the so-formed *trans*-disubstituted cyclopentene derivatives. The *cis*- and *trans*- 1,4-disubstituted cyclopentenes are both shown to undergo 13-*endo*-trig cyclisation affording the title bicyclic compounds in moderate yield.
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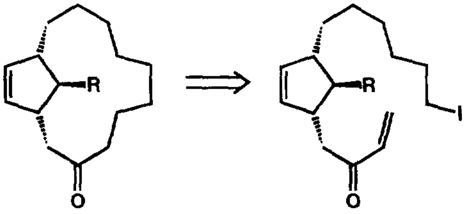
In connection with an ongoing total synthesis we required the preparation of bicyclic compound **1** and, having discarded an earlier Diels-Alder–fragmentation strategy,[1] chose to investigate a free-radical macrocyclisation approach on the basis of earlier work by Porter[2] and others.[3] This, in turn, necessitated the stereoselective preparation of iodoenone **3** but, in the early stages of this work, synthetic efforts were confined to the more easily synthesised nor-isopropyl analogue **4**. This account summarises the chemistry involved in connection with the preparation of enone **4**, its behaviour under conditions designed to promote free-radical macrocyclisation, and points to limitations in applying the methodology to the preparation of iodoenone **3**.



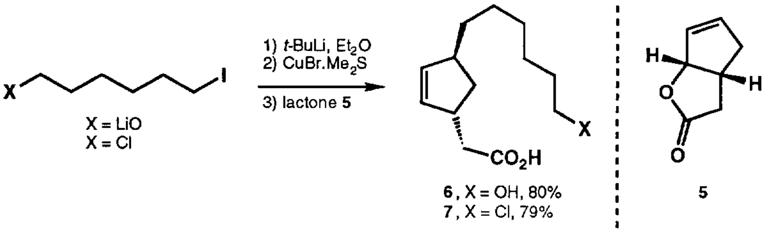
1, R = 2-propyl
2, R = H

3, R = 2-propyl
4, R = H

At the outset we were aware of the chemistry of Curran[4] and others[5] who had found that certain organocuprate reagents add in an S_N2' manner to the *exo*- face of bicyclic lactone **5**.[6] As a result of the *anti*-stereoselectivity of this process[7] conversion of the so-formed *trans*- disubstituted cyclopentene to the *cis*-isomer would be required at some point in the synthesis of enone **4**, a transformation not directly precedented to our knowledge.

The first step of the synthesis required the addition to lactone **5** of a 6-functionalised hexyl cuprate in order that the iodine atom could be introduced after formation of the enone from the carboxylic acid. In separate work we had discovered that ω-iodoalkanols could be deprotonated and lithiated directly[8] thus obviating the need for hydroxyl protection. Thus a solution of 6-iodohexanol[9] in ether was treated sequentially with *n*-BuLi (1.0 equiv., −78°C, 15 min), *t*-BuLi (2.10 equiv., −78°C, 15 min) and $CuBr.Me_2S$ (1.0 equiv., −78°C → −20°C, 20 min) to give "$LiO(CH_2)_6Cu$" via the previously unreported organolithium $LiO(CH_2)_6Li$. Lactone **5** was added and the reaction mixture allowed to warm up to room temperature. In this way the *trans*-disubstituted cyclopentene **6** was obtained in 80% isolated yield with no other regio- or stereoisomers being observed.

Later problems with cleanly converting the carboxylic acid function to the enone in the presence of the hydroxyl group led us to consider an alternative 6-substituent. 6-Chlorohexylcuprate has been prepared by treating 1-chloro-6-iodohexane with activated copper[10] but we opted instead to attempt a direct lithium-halogen exchange with *t*-BuLi as before. Thus, a solution of 1-chloro-6-iodohexane[11] in ether was treated sequentially with *t*-BuLi (2.10 equiv., −78°C, 15 min) and $CuBr.Me_2S$ (1.3 equiv., −78°C → −20°C, 20 min), giving "$Cl(CH_2)_6Cu$" via $Cl(CH_2)_6Li$, then lactone **5** was added. After warming to room temperature cyclopentene derivative **7** was isolated in 79% yield, again with no identifiable by-products (Scheme 1).



Scheme 1

To effect epimerisation of the *trans*- disubstituted cyclopentene to the *cis*- isomer required activation of the allylic position δ- to the carboxyl function. This was achieved by iodolactonisation followed by treatment with DBU to furnish the new bicyclic lactone **8** (Scheme 2) which was hydroborated regio- and stereoselectively on the less hindered *exo*- face to yield a borane of presumed general structure **9**. Although successful on a small scale (0.08 mmol), on a larger scale (up to 2.5 mmol), the hydroboration was best run with only 0.5 equivalents of borane to prevent competitive lactone reduction. Although this had the effect of leaving the reaction incomplete, the starting material was easily recovered and recycled.

The intention at this stage was to induce fragmentation of the borane **9**, via a boron ate complex,[12] with ejection of carboxylate. We expected this to be a relatively facile process as an almost antiperiplanar arrangement of C–B and C–O bonds appeared to be within the accessible conformational space of the molecule. Treatment of this intermediate with alkali led to competitive hydrolysis of the lactone giving, after acidification to protonate the organoborane and to effect relactonisation, significant quantities (*ca.* 60%) of the overall reduction product (Figure 1). Fortunately, switching to a more discriminating nucleophile, fluoride ion in the form of tetra-*n*-butylammonium fluoride, led to highly selective attack at the boron atom and a high isolated yield of desired *cis*- compound **10**.

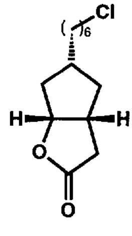
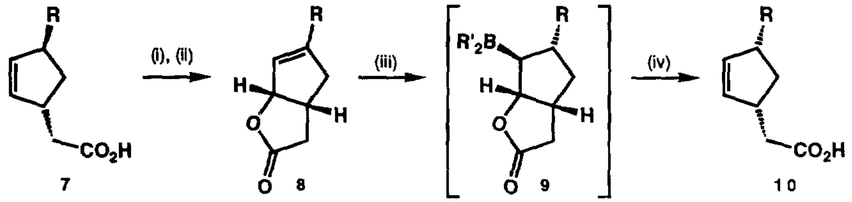


Figure 1

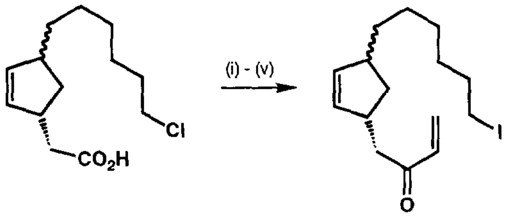


R = $-(CH_2)_6Cl$

(i) I_2, KI, $KHCO_3$, H_2O, Et_2O, 89%; (ii) DBU, PhH, 96%; (iii) BH_3.THF, THF; (iv) TBAF, THF; 92%

Scheme 2

Both isomers, **10** and **7**, were then converted to the radical precursors by standard methods. The most effective procedure was found to be a reduction–oxidation sequence, giving respectively aldehydes **15** and **16** (depicted in Scheme 4), followed in each case by vinyl magnesium bromide addition, oxidation of the allylic alcohol, and Finkelstein displacement of the chloride to give iodoenones **4** and **11** (Scheme 3).



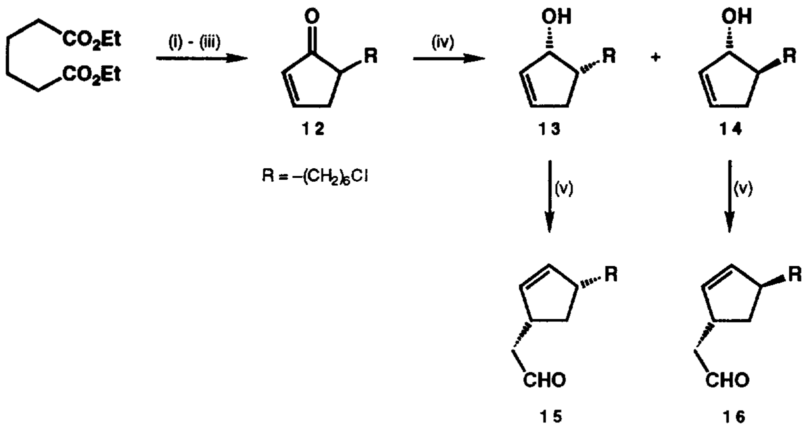
1 0, *cis-*
7 , *trans-*

4, *cis-*
1 1, *trans-*

(i) $LiAlH_4$, THF; (ii) PDC, MS4Å, CH_2Cl_2; (iii) vinyl-MgBr, THF; (iv) Jones' oxidation; (v) NaI, 2-butanone; 48% (**4**), 47% (**11**) over five steps.

Scheme 3

In an alternative synthesis of these iodoenones we made use of the Claisen rearrangement to transfer the relative 1,2-stereochemistry in cyclopentenyl alcohols **13** and **14** (Scheme 4) to a defined 1,3-relationship in aldehydes **15** and **16** respectively. Thus enone **12** was prepared by standard methods and the stereoselectivity of its reduction investigated. In the event, most reductions were insufficiently clean, giving products of competing 1,4-reduction in addition to the two diastereomers obtained by non-selective 1,2-reduction. This problem was particularly significant in reductions with lithium aluminium hydride (unless used in large excess in diethyl ether) or sodium borohydride/cerium trichloride[13] at −15°C. Use of the latter reagent at room temperature or a slight excess of di-isobutylaluminium hydride at −78°C resulted in clean 1,2-reduction however in no case could the stereoselectivity be usefully controlled. Ultimately the conditions shown in Scheme 4 were used as the isolated yields were routinely excellent even though a 1:1 ratio of the diastereomers was produced. Fortunately the diastereomeric allylic alcohols were separable and could be independently submitted to sigmatropic rearrangement providing aldehydes **15** and **16** in good yield. These aldehydes were found to be identical in all respects to those obtained after step (ii) in Scheme 3 thus confirming our stereochemical assignments within both series.

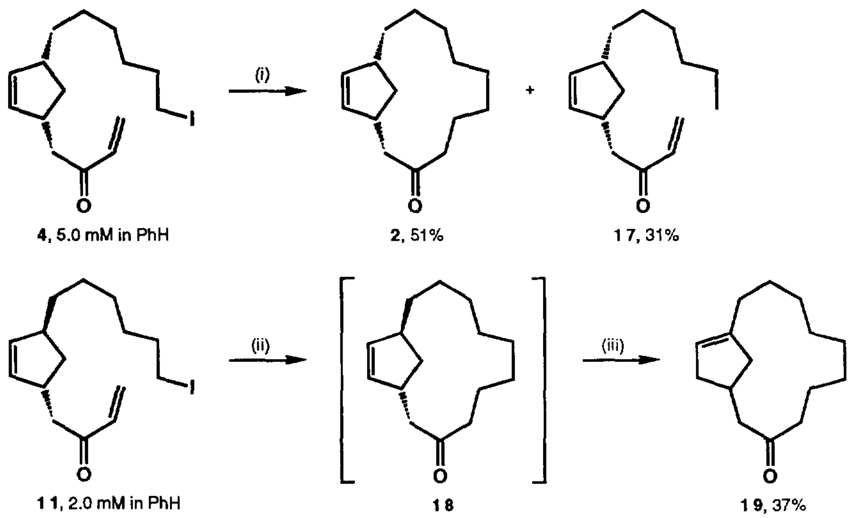


(i) NaH, xylene, 140°C; then 1-chloro-6-iodohexane, THF, 71%; (ii) AcOH, HCl (aq.), 80%; (iii) LDA; PhSeBr, THF; then H_2O_2, pyridine, H_2O, 60%; (iv) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 93% (combined yield); (v) *n*-butylvinyl ether, $Hg(OAc)_2$ (cat.), heat (see experimental), 63% (**15**), 69% (**16**).

Scheme 4

With both *cis-* and *trans-* macrocyclisation precursors in hand the cyclisations could be tested. Predictably, moderate dilution (5 mM) and slow addition (6 h) of the tributyltin hydride were required in order to realise acceptable yields of the bicyclic ketone **2** from *cis-* precursor **4** (Scheme 5). At this dilution yields were generally *ca.* 50% with the bulk of the residual material arising from reduction of the iodide without cyclisation (a proportion of compound **17** may arise from 1,n-hydrogen atom abstraction[14]).

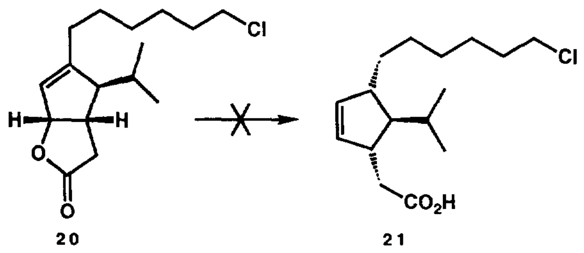
Subjecting the *trans-* substrate **11** to the earlier conditions (5 mM, 6h) resulted in only traces of the macrocycle **18** however a substrate concentration of 2 mM and a stannane addition time of 10 h did produce cyclised material as observed in the crude ^{1}H n.m.r. spectrum which also showed that essentially no direct reduction product had formed. Interestingly the product, isolated in 37% yield after repeated chromatography on silica gel, was found to be different to that present in the crude reaction mixture; in the ^{1}H n.m.r. spectrum of that mixture the only resonances in the olefinic region were two broad singlets at 5.64 and 5.69 p.p.m. whereas in the isolated material a single one-proton resonance was present at 5.19 p.p.m. Additionally, the t.l.c. behaviour changed during purification – a pair of weakly staining spots corresponding to cyclisation products converged to a single spot at R_f 0.50 (1:1 petrol:ether). Both of these features indicated that isomerisation of a relatively unstable intermediate had occurred to give bicyclic ketone **19** (shown by rigorous spectroscopic analysis); it is assumed that the intermediate is the unusual *in-out* isomer **18** (Scheme 5).



(i) Bu_3SnH (added over 6 h), AIBN, PhH; (ii) Bu_3SnH (added over 10 h), AIBN, PhH; (iii) SiO_2 (chromatography).

Scheme 5

Although we have been able to demonstrate that free-radical macrocyclisation is a viable route to bicyclo[10.2.1]pentadecenones these routes do not easily allow the necessary 2-propyl substituent to be incorporated; in particular we have been unable to effect the conversion of lactone **20** (the preparation of this compound will be reported separately) into the trisubstituted cyclopentene **21** since, under all conditions studied for the hydroboration reaction, the lactone was reduced first as a result of the increased steric encumbrance of the olefin. For this reason we are currently modifying our second precursor synthesis to generate a single enantiomer of iodoenone **3** and will report upon this chemistry in due course.



EXPERIMENTAL

Infra-red spectra are quoted in cm^{-1}; coupling constants in ^1H n.m.r. spectra are quoted to the nearest 0.5 Hz and, although not included here, assignments were made on the basis of chemical shift, coupling constant information, COSY and n.O.e. experiments as appropriate; assignments for ^{13}C n.m.r. spectra were made with the aid of DEPT and ^1H–^{13}C correlation experiments; mass spectra were recorded using either chemical ionisation (C.I., NH_3), or atmospheric pressure chemical ionisation (A.P.C.I.) using a mixed solvent system ($MeOH$:$MeCN$:H_2O, 40:40:20). All solvents were purified and dried using standard procedures; copper (I) bromide - dimethyl sulfide complex,[15] phenylselenyl bromide,[16] Jones' reagent,[17] 6-iodohexanol,[9] 1-chloro-6-iodohexane[11] and lactone 5[6] were prepared by literature methods. 'Petrol' refers to the fraction of light petroleum ether boiling within the range 30–40°C.

Preparation and cupration of O,6-Dilithiohexan-1-ol

To a cooled (–78°C) suspension of 6-iodohexan-1-ol (2.55 g, 11.8 mmol) in ether (30 ml) was added dropwise *n*-butyllithium (7.43 ml of a 1.6 M solution in hexanes, 11.9 mmol) and, after 15 min, *t*-butyllithium (14.7 ml of a 1.6 M solution in pentane, 24.8 mmol) was added. After a further 15 min a solution of $CuBr.SMe_2$ (2.44 g, 11.8 mmol) in Me_2S (15 ml) was added and the mixture warmed to –20°C with vigorous stirring. After 20 min the dark blue solution of the cuprate was cooled to –78°C ready for use in the reaction with lactone **5**.

Preparation and cupration of 6-Chloro-1-lithiohexane

To a cooled (–78°C) solution of 1-chloro-6-iodohexane (1.96 g, 7.94 mmol) in ether (30 ml) was added dropwise *t*-butyllithium (11.1 ml of a 1.5 M solution in pentane, 16.7 mmol) followed by, after a further 15 min, a solution of $CuBr.SMe_2$ (2.12 g, 10.3 mmol) in Me_2S (20 ml). The mixture was warmed to –20°C with vigorous stirring. After 20 min the solution of the cuprate was cooled to –78°C ready for use in the reaction with lactone **5**.

trans-*4-(6-Hydroxyhexyl)cyclopent-2-ene-1-acetic acid* (**6**)

A solution of lactone **5** (0.88 g, 7.1 mmol) in ether (3ml) was added dropwise to the solution of the cuprate prepared above from 6-iodohexan-1-ol. The mixture was allowed to reach ambient temperature over 14 h then diluted with ether (40 ml) and extracted with sat. aq. $NaHCO_3$ solution (3 x 30 ml). The combined aqueous portions were acidified by the dropwise addition of conc. hydrochloric acid until the pH fell below 7.0 then extracted with ether (4 x 20 ml). The combined organic portions were washed with brine (40 ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (1:1, EtOAc:petrol) to give the title compound **6** (1.2 g, 80%) as a white solid. m.p. (EtOAc/petrol) 27-30°C; R_f (EtOAc) 0.24; Found: C, 69.12; H, 10.16%. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%. $\nu_{max.}$ (KBr) 3406 (br), 2927 (s), 2856 (s), 1708 (s), 1407 (w), 1271 (w), 1168 (w), 1054 (w), 910 (s), 736 (s), 650 (w); δ_H (500 MHz, $CDCl_3$) 1.24-1.41 (8H, m), 1.54-1.60 (2H, m), 1.71-1.76 (2H, m), 2.35 (1H, dd, *J* 14.0, 7.0), 2.41 (1H, dd, *J* 14.0, 8.5), 2.68-2.73 (1H, m), 3.09-3.16 (1H, m), 3.65 (2H, t, *J* 6.5), 5.66-5.74 (2H, m); δ_C (125 MHz, $CDCl_3$) 25.7, 27.8, 29.5, 32.7, 35.7, 36.4, 41.2, 44.6, 44.6, 63.0, 132.8, 136.8, 178.7; *m/z* (C.I., NH_3) 244 (MNH_4^+, 100), 227 (MH^+, 15), 226 (MNH_4^+–H_2O, 5), 209 (MH^+–H_2O, 30%).

trans-*4-(6-Chlorohexyl)cyclopent-2-ene-1-acetic acid* (**7**)

A solution of the lactone **5** (0.4 g, 3.17 mmol) in ether (2 ml) was added dropwise to the solution of the cuprate prepared above from 1-chloro-6-iodohexane. The mixture was allowed to reach ambient temperature over 14 h then diluted with ether (40 ml) and extracted with sat. aq. $NaHCO_3$ solution (3 x 20 ml). The combined aqueous portions were acidified by the dropwise addition of conc. hydrochloric acid until the pH fell below 7.0 then extracted with ether (3 x 20 ml). The combined organic portions were washed with brine (30 ml), dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the title compound **7** (0.61 g, 79%) as an oil. R_f (1:1, petrol:ether) 0.28; Accurate Mass: Found: 262.1574, $C_{13}H_{25}ClNO_2$ (MNH_4^+) requires 262.15738. $\nu_{max.}$ (thin film) 3047 (w), 2927 (s), 2856 (m), 1708 (s), 1409 (w), 1282 (w), 1205 (w), 941 (w), 743 (w), 652 (w); δ_H (500 MHz, $CDCl_3$) 1.30-1.40 (6H, m), 1.40-1.51 (2H, m), 1.74-1.85 (4H, m), 2.37 (1H, dd, *J* 15.5, 8.0), 2.46 (1H, dd, *J* 15.5, 7.0), 2.68-2.73 (1H, m), 3.09-3.15 (1H, m), 3.58 (2H, t, *J* 7.0), 5.68 (1H, dt, *J* 5.5, 2.0), 5.74 (1H, dt, *J* 5.5, 2.0); δ_C (125 MHz, $CDCl_3$) 26.9, 27.7, 29.1, 32.6, 35.6, 36.4, 40.0, 41.1, 44.6, 45.1, 132.8, 136.3, 178.8; *m/z* (C.I., NH_3) 264 ($M(^{37}Cl)NH_4^+$, 35), 262 ($M(^{35}Cl)NH_4^+$, 100), 226 (MNH_4^+–HCl, 12), 201 (25), 199 (82), 187 (20), 185 (70), 121 (16), 94 (18), 80 (52), 67 (17), 58 (30%).

(1SR, 5RS, 7SR, 8SR)-7-(6-Chlorohexyl)-8-iodo-2-oxabicyclo[3.3.0]octan-3-one

To a vigorously stirred solution of acid 7 (550 mg, 2.20 mmol) in water (30 ml) was added successively $KHCO_3$ (1.46 g, 13.3 mmol), KI (2.25 g, 13.3 mmol) and, after 5 min, I_2 (1.15 g, 2.53 mmol) followed by ether (15 ml). After 13 h concentrated hydrochloric acid was added dropwise until the pH fell below 7 at which point the mixture was diluted with ether (30 ml) and the organic layer separated. The ether layer was washed successively with a sat. aq. solution of $Na_2S_2O_3$ (5 ml), water (10 ml) and brine (20 ml), then dried ($MgSO_4$) and concentrated. Flash column chromatography (3:1, petrol:ether) afforded the title iodolactone (820 mg, 89%) as a colourless oil. R_f (1:1, petrol:ether) 0.32; Accurate Mass: Found: 243.1165, $C_{13}H_{20}ClO_2$ (MH^+–HI) requires 243.11518; $\nu_{max.}$ (thin film) 2929 (s), 2855 (s), 1780 (s), 1455 (m), 1342 (w), 1298 (m), 1215 (m), 1160 (s), 995 (s), 871 (m), 725 (w), 650 (m); δ_H (500 MHz, $CDCl_3$) 1.20-1.30 (3H, m), 1.32-1.37 (4H, m), 1.43-1.47 (2H, m), 1.56 (1H, dd, *J* 13.0, 6.5), 1.74-1.80 (2H, m), 1.91 (1H, ddd, *J* 13.0, 12.0, 10.0), 2.37 (1H, dd, *J* 18.5, 2.0), 2.90 (1H, dd, *J* 18.5, 10.5), 3.17 (1H, dddd, *J* 10.0, 10.0, 6.0, 2.0), 3.54 (2H, t, *J* 6.5), 4.53 (1H, d, 4.0), 5.30 (1H, d, *J* 6.0); δ_C (125 MHz, $CDCl_3$) 26.6, 27.5, 28.8, 32.4, 35.0, 35.1, 36.4, 38.3, 41.4, 41.8, 45.0, 92.2, 177.1; *m/z* (A.P.C.I., +ve) 243 ($M(^{35}Cl)H^+$–HI, 10), 189 (20), 173 (100%).

7-(6-Chlorohexyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one (**8**)

To a stirred solution of the iodolactone (750 mg, 2.02 mmol) in benzene (20 ml) was added DBU (333 μl, 2.23 mmol) and the mixture heated at reflux. After 1 h the reaction mixture was diluted with 1.0 M hydrochloric acid (20 ml) and extracted with ether (2 x 15 ml). The combined organic portions were washed with brine (20 ml), then dried ($MgSO_4$), concentrated and purified by flash column chromatography (1:1, petrol:ether) to give lactone **8** (471 mg, 96%) as an oil. R_f (1:1, petrol:ether) 0.18; Accurate Mass: Found: 243.1156, $C_{13}H_{20}ClO_2$ (MH^+) requires 243.11518; $\nu_{max.}$ (thin film) 2932 (s), 2857 (m), 1771 (s), 1649 (w), 1446 (w), 1348 (w), 1307 (m), 1172 (s), 1004 (s), 931 (m); δ_H (500 MHz, $CDCl_3$) 1.32-1.37 (2H, m), 1.43-1.52 (4H, m), 1.75-1.80 (2H, m), 2.12 (2H, t, *J* 7.5), 2.20 (1H, dd, *J* 17.0, 1.5), 2.32 (1H, dd, *J* 18.5, 5.5), 2.67 (1H, ddd, *J* 17.0, 8.5, 1.0), 2.82 (1H, dd, *J* 18.5, 10.5), 3.09-3.16 (1H, m), 3.53 (2H, t, *J* 6.5), 5.48 (1H, d, *J* 8.0), 5.53 (1H, ddd, *J* 3.5, 3.5, 1.5); δ_C (50.3 MHz, $CDCl_3$) 26.5, 27.0, 28.5, 30.8, 32.3, 35.4, 36.3, 42.0, 45.0, 90.2, 122.3, 152.5, 177.8; *m/z* (A.P.C.I., +ve) 259 (40), 257 (95), 245 ($M(^{37}Cl)H^+$, 45), 243 ($M(^{35}Cl)H^+$, 100), 227 (15), 225 (40), 199 (50), 183 (77), 153 (96), 125 (47) 107 (20%).

cis-*4-(6-Chlorohexyl)cyclopent-2-ene-1-acetic acid* (**10**)

To a solution of lactone **8** (0.57 g, 2.35 mmol) in THF (50 ml) was added dropwise BH_3.THF (1.2 ml of a 1.0 M solution in THF, 1.20 mmol) and, after a further 14 h, tetra-*n*-butylammonium fluoride (2.4 ml of a 1.0 M solution in THF, 2.40 mmol). After 1 h the reaction mixture was diluted with water (20 ml) and 1.0 M hydrochloric acid (20 ml) then extracted with ether (30 ml). The organic extract was washed with brine (30 ml), then dried ($MgSO_4$), concentrated and purified by flash column chromatography (CH_2Cl_2) to return the starting lactone **8** (0.28 g) and the title compound **10** (0.27 g, 92% based on recovered **8**) as an oil. R_f (1:1, petrol:ether) 0.28; Accurate Mass: Found: 262.1572, $C_{13}H_{25}ClNO_2$ (MNH_4^+) requires 262.15738; $\nu_{max.}$ (thin film) 3054 (w), 2929 (s), 2862 (m), 1706 (s), 1545 (w), 1530 (w), 1380 (w), 1331 (w), 1261 (w), 1134 (w), 1092 (w); δ_H (500 MHz, $CDCl_3$) 1.00 (1H, dt, *J* 13.0, 7.5), 1.20-1.39 (6H, m), 1.41-1.49 (2H, m), 1.72-1.81 (2H, m), 2.35 (1H, dd, *J* 15.5, 8.0), 2.37 (1H, dt, *J* 13.0, 8.0), 2.49 (1H, dd, *J* 15.5, 7.0), 2.61-2.68 (1H, m), 3.03-3.09 (1H, m), 3.54 (2H, t, *J* 6.5), 5.65 (1H, dt, *J* 5.5, 2.0), 5.72 (1H, dt, *J* 5.5, 2.0); δ_C (125 MHz, $CDCl_3$) 26.8, 27.7, 29.0, 32.6, 36.5, 37.1, 40.9, 41.7, 45.2, 45.7, 132.8, 136.3, 178.7; *m/z* (C.I., NH_3) 264 ($M(^{37}Cl)NH_4^+$, 35), 262 ($M(^{35}Cl)NH_4^+$, 90), 247 ($M(^{37}Cl)H^+$, 30), 245 ($M(^{35}Cl)H^+$, 80), 211 (35), 209 (25), 187 (11), 185 (40), 151 (32), 149 (40), 140 (100), 107 (28), 94 (32), 81 (50), 67 (33), 55 (48%).

cis-*3-(6-Chlorohexyl)-5-(2-hydroxyethyl)cyclopentene*

To a cooled (0°C) suspension of $LiAlH_4$ (22 mg, 0.57 mmol) in THF (5 ml) was added a solution of acid **10** (70 mg, 0.29 mmol) in THF (1.0 ml). After 15 h sat. aq. potassium sodium tartrate solution (1.0 ml) was added with vigorous stirring. After a further 1 h the reaction mixture was diluted with more sat. aq. potassium sodium tartrate solution (3 ml) and ether (5 ml) and the layers separated. The organic layer was washed successively with 1.0 M aq. NaOH solution (5 ml), water (5 ml) and brine (5 ml), then dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the title compound (65 mg, 92%) as an oil. R_f (1:1, petrol:ether) 0.25; Accurate Mass: Found: 248.1781, $C_{13}H_{27}ClNO$ (MNH_4^+) requires 248.17812. $\nu_{max.}$ (thin film) 3368 (br m), 3045 (w), 2927 (s), 2855 (w), 1446 (m), 1051 (m), 737 (w), 669 (m); δ_H (500 MHz, $CDCl_3$) 0.95 (1H, dt, *J* 12.5, 8.0), 1.26-1.40 (5H, m), 1.41-1.49 (3H, m), 1.54-1.61 (1H, dddd, *J* 14.0, 14.0, 7.0, 7.0), 1.71-1.81 (3H, m), 2.28 (1H, dt, *J* 12.5, 8.0), 2.58-2.64 (1H, m), 2.70-2.76 (1H, m), 3.54 (2H, t, *J* 6.5), 3.69 (1H, dt, *J* 10.5, 7.0), 3.73 (1H, dt, *J* 10.5, 6.5), 5.66 (1H, dt, *J* 5.5, 2.0), 5.67 (1H, dt, *J* 5.5, 2.0); δ_C (125 MHz, $CDCl_3$) 26.8, 27.8, 29.0, 32.5, 36.6, 37.3, 39.6, 42.2, 45.1, 45.6, 61.7, 134.3, 135.4; *m/z* (C.I., NH_3) 250 ($M(^{37}Cl)NH_4^+$, 25), 248 ($M(^{35}Cl)NH_4^+$, 90), 212 (50), 195 (65), 177 (19), 165 (25), 111 (27), 93 (100), 81 (21%).

cis-*3-(6-Chlorohexyl)-5-(2-oxoethyl)cyclopentene* (15)

A suspension of *cis*-3-(6-chlorohexyl)-5-(2-hydroxyethyl)cyclopentene (60 mg, 0.26 mmol), molecular sieves (0.15 g, 4Å powdered) and pyridinium dichromate (0.11 g, 0.31 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature. After 4 h the solution was diluted with ether (5 ml) and filtered through a short plug of Celite®. The filtrate was washed successively with sat. aq. $CuSO_4$ solution (5 ml), 1.0 M hydrochloric acid (5 ml) and brine (5 ml) then dried ($MgSO_4$) and concentrated to give the title aldehyde **15** (50 mg, 84%) as an oil. R_f (1:1, petrol:ether) 0.50; Found: C, 68.18; H, 9.29%. $C_{13}H_{21}ClO$ requires C, 68.26; H, 9.25%; $\nu_{max.}$ (thin film) 2928 (CH, s), 2856 (CH, m), 1725 (s), 1458 (w); δ_H (500 MHz, $CDCl_3$) 0.95 (1H, dt, *J* 13.0, 7.5), 1.25-1.37 (5H, m), 1.39-1.44 (3H, m), 1.74-1.80 (2H, m), 2.37 (1H, dt, *J* 13.0, 8.0), 2.45 (1H, ddd, *J* 16.5, 8.0, 2.0), 2.58 (1H, ddd, *J* 16.5, 6.5, 2.0), 2.63-2.66 (1H, m), 3.10-3.13 (1H, m), 3.53 (2H, t, *J* 7.0), 5.61 (1H, dt, *J* 5.5, 2.0), 5.71 (1H, dt, *J* 5.5, 2.0), 9.79 (1H, t, *J* 2.0); δ_C (125 MHz, $CDCl_3$) 26.9, 27.7, 29.0, 32.5, 36.5, 37.3, 39.6, 45.1, 45.7, 50.8, 132.6, 136.2, 202.2; *m/z* (C.I., NH_3) 248 ($M(^{37}Cl)NH_4^+$, 25), 246 ($M(^{35}Cl)NH_4^+$, 92), 218 (30), 201 (33), 187 (25), 185 (100), 109 (60), 101 (45), 81 (73), 80 (90%).

cis-*3-(6-Chlorohexyl)-5-(2-hydroxybut-3-enyl)cyclopentene*

To a cooled (−78°C) solution of aldehyde **15** (30 mg, 0.13 mmol) in THF (2 ml) was added vinylmagnesium bromide (160 μl of a 1.0 M solution in THF, 0.16 mmol). The reaction mixture was allowed to reach ambient temperature over 15 h then was diluted with 1.0 M hydrochloric acid (2 ml) and extracted with ether (2 x 5 ml). The combined extracts were washed with brine (5 ml), then dried ($MgSO_4$) and concentrated to give the title compound (30 mg, 89%) as an inseparable mixture (ratio 1:1) of oils. R_f (1:1, petrol:ether) 0.43; $\nu_{max.}$ (thin film) 3407 (br m), 2927 (s), 2855 (m), 1446 (w), 1070 (w), 736 (w); δ_H (500 MHz, $CDCl_3$) 0.92-1.00 (1H, m), 1.20-1.38 (5H, m), 1.41-1.51 (3H, m), 1.51–1.69 (2H, m), 1.69-1.81 (2H, m), 2.25-2.34 (1H, m), 2.59-2.62 (1H, m), 2.74-2.82 (1H, m), 3.54 (2H, t, *J* 6.5), 4.18-4.22 (1H, m), 5.10-5.13 (1H, m), 5.25 (1H, *ca.* d, *J* 17.0), 5.66-5.69 (2H, m), 5.85-5.93 (1H, m); δ_C (125 MHz, $CDCl_3$) 26.9, 27.8, 29.1, 32.6, 36.7, 37.8/37.9, 42.1, 44.1/44.4, 45.1, 45.6/45.7, 72.1/72.4, 114.4/114.8, 134.1/134.5, 135.1/135.2, 141.2/141.6; *m/z*

(C.I., NH_3) 276 ($M(^{37}Cl)NH_4^+$, 15), 274 ($M(^{35}Cl)NH_4^+$, 45), 258 ($M(^{37}Cl)H^+-H_2O$, 12), 256 ($M(^{35}Cl)H^+-H_2O$, 30), 238 (28), 202 (20), 185 (60), 134 (20), 119 (100%).

cis-3-(6-Chlorohexyl)-5-(2-oxobut-3-enyl)cyclopentene

To a stirred solution of *cis*-3-(6-chlorohexyl)-5-(2-hydroxybut-3-enyl)cyclopentene (90 mg, 0.35 mmol) in acetone (3 ml) was added dropwise Jones' reagent[17] (0.20 ml of a 2.0 M aq. solution, 0.4 mmol). After 10 min MeOH (0.5 ml) was added and the resulting green solution diluted with water (5 ml). The mixture was extracted with ether (2 x 10 ml) and the combined extracts washed with brine (10 ml), then dried ($MgSO_4$) and concentrated to give the title compound (73 mg, 82%) as an oil. R_f (1:1, petrol:ether) 0.55; Found: C, 70.67; H, 9.06%. $C_{15}H_{23}ClO$ requires C, 70.71; H, 9.10%; $\nu_{max.}$ (thin film) 2927 (CH, s), 2855 (CH, s), 1705 (sh), 1684 (s), 1446 (w), 1401 (m), 1368 (w), 987 (w); δ_H (500 MHz, $CDCl_3$) 0.91 (1H, dt, *J* 13.0, 7.5), 1.24-1.45 (8H, m), 1.74-1.80 (2H, m), 2.35 (1H, dt, *J* 13.0, 8.0), 2.58 (1H, dd, *J* 16.0, 8.0), 2.62-2.64 (1H, m), 2.72 (1H, dd, *J* 16.0, 6.5), 3.09-3.12 (1H, m), 3.53 (2H, t, *J* 6.5), 5.60-5.61 (1H, m), 5.67-5.69 (1H, m), 5.82 (1H, dd, *J* 10.5, 0.5), 6.21 (1H, dd, *J* 17.5, 0.5), 6.36 (1H, dd, *J* 17.5, 10.5); δ_C (125 MHz, $CDCl_3$) 26.8, 27.7, 29.0, 32.4, 36.7, 37.5, 41.1, 45.1, 45.6, 46.7, 127.9, 133.4, 135.8, 136.8, 200.1; *m/z* (C.I., NH_3) 272 ($M(^{35}Cl)NH_4^+$, 15), 257 ($M(^{37}Cl)H^+$, 28), 255 ($M(^{35}Cl)H^+$, 100), 185 (22), 135 (20), 93 (20), 80 (22%).

cis-3-(6-Iodohexyl)-5-(2-oxobut-3-enyl)cyclopentene (4)

To a stirred solution of *cis*-3-(6-chlorohexyl)-5-(2-oxobut-3-enyl)cyclopentene (29 mg, 0.11 mmol) in 2-butanone (3 ml) was added NaI (51 mg, 0.34 mmol) and the mixture heated at reflux. After 15 h the reaction mixture was diluted with water (5 ml) and extracted with ether (2 x 10 ml). The combined extracts were washed with brine (5 ml), then dried ($MgSO_4$), concentrated and purified by flash column chromatography (20:1, petrol:ether) to give the title compound 4 (34 mg, 86%) as an oil. R_f (1:1, petrol:ether) 0.60; Accurate mass: Found: 347.0877, $C_{15}H_{24}IO$ (MH^+) requires 347.08772; $\nu_{max.}$ (thin film) 2925 (CH, s), 2853 (CH, s), 1702 (sh), 1682 (s), 1401 (m); δ_H (500 MHz, $CDCl_3$) 0.92 (1H, dt, *J* 13.0, 7.5), 1.19-1.45 (8H, m), 1.79-1.85 (2H, m), 2.35 (1H, dt, *J* 13.0, 8.0), 2.59 (1H, dd, *J* 16.0, 8.0), 2.62-2.64 (1H, m), 2.72 (1H, dd, *J* 16.0, 6.5), 3.09-3.12 (1H, m), 3.19 (2H, t, *J* 7.0), 5.61 (1H, dt, *J* 5.5, 2.0), 5.68 (1H, dt, *J* 5.5, 2.0), 5.82 (1H, dd, *J* 10.5, 1.0), 6.21 (1H, dd, *J* 17.5, 1.0), 6.36 (1H, dd, *J* 17.5, 10.5); δ_C (125 MHz, $CDCl_3$) 7.2, 27.7, 28.7, 30.4, 33.5, 36.7, 37.5, 41.1, 45.6, 46.6, 128.0, 133.4, 135.8, 136.8, 200.1; *m/z* (C.I., NH_3) 364 (MNH_4^+, 18), 347 (MH^+, 100), 277 (29), 149 (23), 93 (28), 80 (54), 55 (64%).

trans-3-(6-Chlorohexyl)-5-(2-hydroxyethyl)cyclopentene

To a cooled (0°C) suspension of $LiAlH_4$ (62 mg, 1.64 mmol) in THF (9 ml) was added dropwise a solution of acid 7 (0.2 g, 0.82 mmol) in THF (1.0 ml). After 15 h sat. aq. potassium sodium tartrate solution (2.0 ml) was added with vigorous stirring. After a further 1 h the reaction mixture was diluted with more sat. aq. potassium sodium tartrate solution (5 ml) and ether (10 ml) and the layers separated. The organic layer was washed successively with 1.0 M aq. NaOH solution (5 ml), water (5 ml) and brine (10 ml), then dried ($MgSO_4$), concentrated and purified by flash column chromatography (4:1, petrol:ether) to give the alcohol (0.15 g, 80%) as a colourless oil. R_f (1:1, petrol:ether) 0.25; Accurate Mass: Found: 248.1781, $C_{13}H_{27}ClNO$ (MNH_4^+) requires 248.17812. $\nu_{max.}$ (thin film) 3355 (br m), 3043 (w), 2927 (s), 2855 (m), 1446 (m), 1367 (w), 1310 (w), 1051 (m), 737 (m), 651 (m); δ_H (500 MHz, $CDCl_3$) 1.23-1.39 (6H, m), 1.40-1.50 (2H, m), 1.53-1.61 (1H, m), 1.62-1.70 (3H, m), 1.71-1.82 (3H, m), 2.65-2.70 (1H, m), 2.77-2.83 (1H, m), 3.54 (2H, t, *J* 6.5), 3.68 (1H, dt, *J* 10.5, 7.0), 3.72 (1H, dt, *J* 10.5, 6.5), 5.68 (1H, dt, *J* 5.5, 1.5), 5.69 (1H, dt, *J* 5.5, 1.5); δ_C (125 MHz, $CDCl_3$) 26.7, 27.6, 28.9, 32.4, 35.7, 36.6, 38.7, 41.2, 44.5, 45.0, 61.3, 134.3, 135.1; *m/z* (A.P.C.I., +ve) 247 ($M(^{37}Cl-OH+OMe)H^+$, 30), 245 ($M(^{35}Cl-OH+OMe)H^+$, 100), 233 ($M(^{37}Cl)H^+$, 6), 231 ($M(^{35}Cl)H^+$, 18), 227 ($M(-Cl+OMe)H^+$, 85), 213 (10), 211 (20), 144 (22), 122 (26%).

trans-*3-(6-Chlorohexyl)-5-(2-oxoethyl)cyclopentene* **(16)**

A suspension of *trans*-3-(6-chlorohexyl)-5-(2-hydroxyethyl)cyclopentene (0.15 g, 0.65 mmol), molecular sieves (0.4 g, 4 Å powdered) and pyridinium dichromate (0.34 g, 0.98 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature. After 4 h the mixture was diluted with ether (10 ml) and filtered through a short plug of Celite®. The filtrate was washed successively with sat. aq. $CuSO_4$ solution (5 ml), 1.0 M hydrochloric acid (5 ml) and brine (10 ml), then dried ($MgSO_4$) and concentrated to give aldehyde **16** (0.14 g, 94%) as an oil. R_f (1:1, petrol:ether) 0.50; $\nu_{max.}$ (thin film) 2928 (s), 2856 (m), 1725 (s), 1463 (w), 1071 (w), 733 (w); δ_H (500 MHz, $CDCl_3$) 1.26-1.59 (8H, m), 1.64-1.70 (1H, m), 1.73-1.81 (3H, m), 2.42 (1H, ddd, *J* 16.5, 8.0, 2.0), 2.50 (1H, ddd, *J* 16.5, 6.5, 2.0), 2.67-2.71 (1H, m), 3.16-3.49 (1H, m), 3.53 (2H, t, *J* 7.0), 5.66 (1H, dt, *J* 5.5, 2.0), 5.74 (1H, dt, *J* 5.5, 2.0), 9.78 (1H, t, *J* 2.0); δ_C (125 MHz, $CDCl_3$) 26.8, 27.6, 29.0, 32.6, 35.6, 36.4, 39.0, 44.7, 45.1, 49.8, 132.6, 136.2, 202.3; *m/z* (C.I., NH_3) 246 ($M(^{35}Cl)NH_4^+$, 20), 185 (20), 109 (25), 81 (50), 80 (100%).

trans-*3-(6-Chlorohexyl)-5-(2-hydroxybut-3-enyl)cyclopentene*

To a cooled (–78°C) solution of aldehyde **16** (0.14 g, 0.61 mmol) in THF (10 ml) was added dropwise vinylmagnesium bromide (0.8 ml of a 1.0 M solution in THF, 0.80 mmol). The mixture was allowed to achieve ambient temperature over 14 h then diluted with 1.0 M hydrochloric acid (10 ml) and extracted with ether (2 x 15 ml). The combined extracts were washed with brine (20 ml), then dried ($MgSO_4$) and concentrated to give the title compound (0.15 g, 95%) as an inseparable mixture (ratio 1:1) of oils. R_f (1:1, petrol:ether) 0.43; $\nu_{max.}$ (thin film) 3392 (br m), 3045 (w), 2927 (s), 2855 (m), 1446 (w), 1061 (w), 993 (w), 739 (w), 651 (w); δ_H (500 MHz, $CDCl_3$) 1.22-1.40 (5H, m), 1.41–1.51 (2H, m), 1.51–1.59 (2H, m), 1.60-1.73 (2H, m), 1.74-1.81 (2H, m), 2.18-2.34 (1H, m), 2.65-2.70 (1H, m), 2.82-2.87 (1H, m), 3.54 (2H, t, *J* 7.0), 4.17-4.20 (1H, m), 5.10-5.15 (1H, m), 5.22-5.27 (1H, m), 5.66-5.74 (2H, m), 5.85-5.94 (1H, m); δ_C (125 MHz, $CDCl_3$) 26.8, 27.7/27.7, 29.1, 32.6, 35.8, 36.7/36.9, 41.1/41.2, 43.3 (2), 44.5/44.6, 45.1, 72.3/72.4, 114.4/114.6, 134.0/134.3, 135.0/135.3, 141.3/141.5; *m/z* (C.I., NH_3) 274 ($M(^{35}Cl)NH_4^+$, 30), 257 ($M(^{35}Cl)H^+$, 10), 256 ($M(^{35}Cl)NH_4^+–H_2O$, 22), 241 ($M(^{37}Cl)H^+–H_2O$, 22), 239 ($M(^{35}Cl)H^+–H_2O$, 22), 185 (60), 119 (100), 91 (58), 80 (60%).

trans-*3-(6-Chlorohexyl)-5-(2-oxobut-3-enyl)cyclopentene*

To a stirred solution of *trans*-3-(6-chlorohexyl)-5-(2-hydroxybut-3-enyl)cyclopentene (0.14 g, 0.55 mmol) in acetone (5 ml) was added dropwise Jones' reagent[17] (0.33 ml of a 2.0 M aq. solution, 0.66 mmol). After 10 min MeOH (1.0 ml) was added and the resulting green solution diluted with water (15 ml). The mixture was extracted with ether (2 x 20 ml) and the combined extracts washed with brine (15 ml), then dried ($MgSO_4$) and concentrated to give the title enone (0.11 g, 80%) as an oil. R_f (1:1, petrol:ether) 0.55; $\nu_{max.}$ (thin film) 3047 (w), 2927 (s), 2856 (s), 1705 (s), 1683 (sh s), 1616 (s), 1447 (m), 1402 (w), 1365 (w), 1160 (m), 986 (w), 741 (m), 651 (m); δ_H (500 MHz, $CDCl_3$) 1.91-1.51 (8H, m), 1.62 (1H, ddd, *J* 13.0, 8.5, 5.0), 1.70-1.79 (3H, m), 2.56 (1H, dd, *J* 16.0, 8.0), 2.65 (1H, dd, *J* 16.0, 6.5), 2.65-2.69 (1H, m), 3.15-3.18 (1H, m), 3.53 (2H, t, *J* 7.0), 5.63-5.65 (1H, m), 5.69-5.71 (1H, m), 5.83 (1H, dd, *J* 10.5, 1.0), 6.20 (1H, dd, *J* 17.5, 1.0), 6.35 (1H, dd, *J* 17.5, 10.5); δ_C (125 MHz, $CDCl_3$) 26.8, 27.7, 29.0, 32.6, 35.7, 36.5, 40.4, 44.5, 45.1, 45.6, 128.1, 133.4, 135.8, 136.8, 200.4; *m/z* (C.I., NH_3) 274 ($M(^{37}Cl)NH_4^+$, 30), 272 ($M(^{35}Cl)NH_4^+$, 12), 257 (40), 255 ($M(^{35}Cl)H^+$, 42), 238 (50), 221 (100), 219 (20), 185 (25), 149 (38), 80 (39%).

trans-*3-(6-Iodohexyl)-5-(2-oxobut-3-enyl)cyclopentene* **(11)**

To a stirred solution of *trans*-3-(6-chlorohexyl)-5-(2-oxobut-3-enyl)cyclopentene (60 mg, 0.24 mmol) in 2-butanone (5 ml) was added NaI (105 mg, 0.71 mmol) and the mixture heated at reflux. After 15 h the reaction mixture was diluted with water (10 ml) and extracted with ether (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), then dried ($MgSO_4$), concentrated and purified by flash column chromatography (20:1, petrol:ether) to give enone **11** (68 mg, 82%) as an oil. R_f (1:1, petrol:ether) 0.60; Accurate Mass: Found: 364.1143, $C_{15}H_{27}INO$ (MNH_4^+) requires 364.11426; $\nu_{max.}$ (thin film) 3045 (w), 2926 (s), 2854 (m), 1708 (sh s), 1615 (m), 1462 (w), 1402 (w), 1367 (w), 1168 (w), 912 (w), 735 (m); δ_H (500 MHz, $CDCl_3$) 1.27-1.41 (8H, m), 1.63 (1H, ddd, *J* 13.0, 8.0, 5.0), 1.74 (1H, ddd, *J* 13.0, 8.5, 5.5), 1.80-1.86 (2H, m), 2.57 (1H, dd, *J* 16.0, 8.0), 2.65 (1H, dd, *J* 16.0, 6.5), 2.65-2.71 (1H, m), 3.12-3.20 (1H, m), 3.19 (2H, t, *J* 7.0), 5.65 (1H, dt, *J* 5.5, 2.0), 5.71 (1H, dt, *J* 5.5, 2.0), 5.83 (1H, dd, *J* 10.5, 1.0), 6.21 (1H, dd, *J* 17.5, 1.0), 6.36 (1H, dd, *J* 17.5, 10.5); δ_C (125 MHz, $CDCl_3$) 7.2, 27.7, 28.7, 30.5, 33.5, 35.7, 36.6, 40.5, 44.6, 45.7, 128.0, 133.4, 135.8, 136.8, 200.4; *m/z* (C.I., NH_3) 364 (MNH_4^+, 30), 347 (MH^+, 100), 219 (MH^+–HI, 60), 149 (44), 108 (40), 93 (55), 80 (88), 55 (17%).

2-(6-Chlorohexyl)-2-ethoxycarbonylcyclopentanone

To a stirred suspension of sodium hydride (1.0 g of a 60% dispersion in mineral oil, 25 mmol) in dry xylene (100 ml) was added dropwise diethyl adipate (5.0 ml, 25 mmol). The mixture was heated to 140°C to distil out the volatile components (b.p. <120°C) and then allowed to cool to room temperature before being diluted with dry THF (60 ml). 1-Chloro-6-iodohexane (4.70 ml, 30 mmol) was added via syringe and the solution was heated at reflux for 15 h. The mixture was diluted with water (100 ml) and extracted with ether (3 x 50 ml). The organic portions were combined and washed with brine (50 ml), then dried ($MgSO_4$) and concentrated to yield an oil which was purified by flash column chromatography (6:1→3:1, petrol:ether) to yield the title compound (4.90 g, 71%). R_f (2:1, petrol:ether) 0.34; Accurate mass: Found: 292.1679, $C_{14}H_{27}ClNO_2$ (MNH_4^+) requires 292.16795; $\nu_{max.}$ (thin film) 2936 (CH, m), 2861 (CH, w), 1752 (s), 1724 (s), 1226 (m), 1157 (m); δ_H (200 MHz, $CDCl_3$) 1.17-2.53 (16H, m), 1.23 (3H, t, *J* 7.0), 3.53 (2H, t, *J* 6.5), 4.17 (2H, q, *J* 7.0); δ_C (50.3 MHz, $CDCl_3$) 13.8, 19.3, 24.3, 26.3, 28.8, 32.2, 32.5, 33.3, 37.6, 44.7, 60.2, 61.0, 171.1, 216.3; *m/z* (C.I., NH_3) 292 ($M(^{35}Cl)NH_4^+$, 31), 275 ($M(^{35}Cl)H^+$, 46), 256 (39), 239 (100), 223 (24), 184 (23), 182 (21), 165 (85), 156 (31), 58 (23%).

2-(6-Chlorohexyl)cyclopentanone[18]

A mixture of 2-(6-chlorohexyl)-2-ethoxycarbonylcyclopentanone (2.00 g, 7.29 mmol), glacial acetic acid (34 ml) and hydrochloric acid (50 ml of a 35% solution) was heated at reflux for 16 h, after which time the mixture was concentrated and diluted with ether (100 ml), then washed successively with water (50 ml), sat. aq. $NaHCO_3$ solution (100 ml) and dried ($MgSO_4$) to yield the title compound as an oil (1.18 g, 80%). R_f (1:1, petrol:ether) 0.42; $\nu_{max.}$ (thin film) 2932 (s), 2958 (s), 1741 (s), 1703 (m), 1464 (m), 1454 (m), 1155 (s); δ_H (500 MHz, $CDCl_3$) 1.20-1.46 (7H, m), 1.47-1.56 (1H, m), 1.72-1.79 (2H, m), 1.72-1.81 (4H, m), 1.97-2.05 (1H, m), 2.07-2.13 (1H, m), 2.26-2.32 (1H, m), 3.52 (2H, t, *J* 6.5); δ_C (125 MHz, $CDCl_3$) 20.7, 26.7, 27.3, 28.8, 29.5, 29.5, 32.5, 38.1, 45.0, 49.1, 221.5; *m/z* (C.I., NH_3) 222 ($M(^{37}Cl)NH_4^+$, 27), 220 ($M(^{35}Cl)NH_4^+$, 100), 201 (13), 184 (14), 167 (15%).

cis- *and* trans-*5-(6-Chlorohexyl)-2-phenylselenylcyclopentanone*

To a stirred solution of diisopropylamine (0.99 ml, 7.58 mmol) in dry THF (8 ml) at −78°C was added *n*-butyllithium (5.34 ml of a 1.42 M solution in hexanes, 7.58 mmol) and, after 0.5 h, was added a solution of 2-(6-chlorohexyl)cyclopentanone (1.02 g, 5.05 mmol) in THF (2 ml) via canula. To a separate solution of diphenyldiselenide (0.95 g, 3.03 mmol) in THF (2 ml) was added dropwise bromine (156 µl, 3.03 mmol) and the mixture agitated to prevent formation of phenylselenyl tribromide. The solution of phenylselenyl bromide was also added to the enolate solution via canula. After 5 min the cold reaction mixture was poured into hydrochloric acid (50 ml of a 0.5 M solution) and this was extracted with ether (2 x 50 ml). The organic extracts were combined and washed successively with water (20 ml), sat. aq. $NaHCO_3$ solution (50 ml), and brine (50 ml), then dried ($MgSO_4$). The solution was concentrated to yield an oil which was purified by flash column

chromatography (10:1, petrol:ether) to give a mixture of the title compounds (1.57 g, 87%, 60:40 *trans-:cis-* ratio) which could be separated by flash column chromatography (20:1, petrol:ether) for analytical purposes. *Trans- isomer*: R_f 0.56 (1:1, petrol:ether); Found: C, 56.48; H, 6.28%. $C_{17}H_{23}ClOSe$ requires C, 57.07; H, 6.48; $\nu_{max.}$ (thin film) 2933 (s), 2858 (m), 1743 (s), 1578 (w), 1477 (m), 1438 (m); δ_H (500 MHz, $CDCl_3$) 1.24-1.38 (7H, m), 1.38-1.55 (1H, m), 1.73-1.79 (2H, m), 1.71-1.79 (1H, m), 1.82-1.90 (1H, m), 2.01-2.09 (1H, m), 2.17-2.23 (1H, m), 2.35-2.41 (1H, m), 3.52 (2H, t, *J* 6.5), 3.68 (1H, t, *J* 8.5), 7.27-7.35 (3H, m), 7.59-7.68 (2H, m); δ_C (125 MHz, $CDCl_3$) 26.6, 27.2, 27.8, 28.7 (2), 29.7, 32.5, 45.0, 46.1, 47.3, 128.3, 129.0, 129.0, 135.4, 216.5; ***m/z*** (C.I., NH_3) 376 ($M(^{35}Cl, ^{80}Se)NH_4^+$, 20), 359 ($M(^{35}Cl, ^{80}Se)H^+$, 20), 220 (51), 201 ($M(^{35}Cl)H^+$–HSePh, 100), 194 (34), 78 (38%). *Cis- isomer*: R_f (1:1, petrol:ether) 0.46; $\nu_{max.}$ (thin film) 2932 (CH, s), 2857 (CH, m), 1727 (C=O, s), 1578 (w), 1477 (w), 1438 (m), 740 (m); δ_H (500 MHz, $CDCl_3$) 1.24-1.50 (7H, m), 1.62-1.86 (4H, m), 1.93-2.09 (2H, m), 2.11-2.03 (2H, m), 3.53 (2H, t, *J* 6.5), 3.87 (1H, d, *J* 6.5), 7.27-7.35 (3H, m), 7.59-7.61 (2H, m); δ_C (125 MHz, $CDCl_3$) 26.63, 27.33, 27.44, 28.61, 28.71, 31.42, 32.48, 44.99, 46.24, 48.10, 128.33, 128.81, 129.04, 135.24, 214.96; ***m/z*** (C.I., NH_3) 376 ($M(^{35}Cl, ^{80}Se)NH_4^+$, 55), 359 ($M(^{35}Cl, ^{80}Se)H^+$, 77), 220 (70), 201 (100), 78 (90%).

5-(6-Chlorohexyl)cyclopent-2-enone (12)

To a stirred solution of 5-(6-chlorohexyl)-2-phenylselenylcyclopentanone (725 mg, 2.02 mmol) in THF (1 ml) at 0°C was added pyridine (54 µl, 0.67 mmol) and hydrogen peroxide (141 µl of a 60% aqueous solution, 2.48mmol) as a dilute solution in water (0.5 ml). After 1 h the reaction mixture was diluted with water (10 ml) and the aqueous layer extracted with ether (3 x 10 ml). The combined organic portions were washed with brine (15 ml) and dried ($MgSO_4$). The solution was concentrated to yield an oil which was purified by flash column chromatography (5:1, petrol:ether) to give the enone **12** (280 mg, 69%). R_f (1:1, petrol:ether) 0.27; Accurate mass: Found: 201.1046, $C_{11}H_{18}ClO$ (MH^+) requires 201.10462; $\nu_{max.}$ (thin film) 2932 (m), 2857 (w), 1705 (s), 1590 (w), 1345 (w); δ_H (500 MHz, $CDCl_3$) 1.31-1.48 (7H, m), 1.74-1.83 (3H, m), 2.29-2.33 (1H, m), 2.37 (1H, dq, *J* 19.0, 2.0), 2.88 (1H, ddt, *J* 19.0, 6.5, 2.5), 3.53 (2H, t, *J* 6.5), 6.19 (1H, dt, *J* 5.5, 2.0), 7.69 (1H, dt, *J* 5.5, 2.5); δ_C (125 MHz, $CDCl_3$) 26.6, 26.9, 28.7, 31.0, 32.4, 35.6, 44.7, 45.0, 134.1, 163.8, 212.9; ***m/z*** (C.I., NH_3) 218 ($M(^{35}Cl)NH_4^+$, 32), 203 ($M(^{37}Cl)H^+$, 30), 201 ($M(^{35}Cl)H^+$ 100), 165 (35), 82 (30%).

cis- *and* **trans-***5-(6-Chlorohexyl)cyclopent-2-enol* (13) *and* (14)

To a stirred solution of enone **12** (1.0 g, 4.99 mmol) and $CeCl_3.7H_2O$ (1.86 g, 4.99 mmol) in methanol (12 ml) was added sodium borohydride (189 mg, 4.99 mmol). After 5 min the pH was adjusted to 7.0 with 1.0 M hydrochloric acid. The solution was then diluted with water (20 ml) and extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (30 ml), dried ($MgSO_4$) and concentrated to yield a 1:1 mixture of the *cis-* and *trans-* alcohols (938 mg, 93%). Analytical samples of the separate isomers were obtained by flash column chromatography (20:1→3:1, petrol:ether). *Cis- isomer* 13: R_f (1:1 petrol:ether) 0.24; Found: C, 64.88; H, 9.74%. $C_{11}H_{19}ClO$ requires C, 65.17; H, 9.45%); $\nu_{max.}$ (thin film) 3387 (br, m), 2930 (s), 2856 (s), 1464 (m), 1445 (m), 1013 (m); δ_H (500 MHz, $CDCl_3$) 1.35-1.51 (7H, m), 1.60-1.65 (1H, m), 1.76-1.81 (2H, m), 2.03-2.10 (2H, m), 2.35-2.42 (1H, m), 3.54 (2H, t, *J* 6.5), 4.57-4.58 (1H, m), 5.92-5.94 (1H, m), 6.02-6.04 (1H, m); δ_C (125 MHz, $CDCl_3$) 26.8, 28.5, 28.9, 29.2, 32.6, 36.8, 42.7, 45.1, 76.8, 133.2, 136.0; ***m/z*** (C.I., NH_3) 187 ($M(^{37}Cl)H^+$–H_2O, 25), 185 ($M(^{35}Cl)H^+$–H_2O, 100%). *Trans- isomer* 14: R_f (1:1, petrol:ether) 0.23; $\nu_{max.}$ (thin film) 3334 (br, m), 2927 (s), 2855 (s), 1463 (m), 1446(m), 1046 (m); δ_H (500 MHz, $CDCl_3$) 1.31-1.51 (7H, m), 1.55-1.63 (1H, m), 1.74-1.80 (2H, m), 1.88-1.96 (2H, m), 2.56-2.65 (1H, m), 3.53 (2H, t, *J* 7.0), 4.45 (1H, s), 5.72-5.75 (1H, m), 5.87-5.88 (1H, m); δ_C (125 MHz, $CDCl_3$) 26., 279, 29.0, 32.6, 34.2, 37.6, 45.1, 48.2, 83.5, 133.2, 133.7; ***m/z*** (C.I., NH_3) 202 ($M(^{35}Cl)NH_4^+$–H_2O, 12), 187 ($M(^{37}Cl)H^+$–H_2O, 22), 185 ($M(^{35}Cl)H^+$–H_2O, 100%).

cis-*3-(6-Chlorohexyl)-5-(2-oxoethyl)cyclopentene* (15)

A solution of the alcohol **13** (147 mg, 0.73 mmol) and $Hg(OAc)_2$ (23 mg, 0.07 mmol) in *n*-butylvinyl ether (5 ml) was heated at 150°C in a sealed tube for 17 h. The reaction mixture was concentrated to yield an oil which was purified by flash column chromatography (20:1, petrol:ether) to give aldehyde **15** (105 mg, 63%). Data as above.

trans-*3-(6-Chlorohexyl)-5-(2-oxoethyl)cyclopentene* (16)

A mixture of the alcohol **14** (49 mg, 0.24 mmol) and $Hg(OAc)_2$ (8.0 mg, 0.02 mmol) in *n*-butylvinyl ether (2 ml) was heated at reflux for 17 h. The reaction mixture was concentrated to yield an oil which was purified by flash column chromatography (30:1, petrol:ether) to give aldehyde **16** (38mg, 69%). Data as above

Bicyclo[10.2.1]pentadec-13-en-3-one (2)

To a solution of the iodoenone **4** (31 mg, 0.09 mmol) and AIBN (1.0 mg, 6.0 μmol) in degassed benzene (18 ml) at reflux was added, over 6 h (syringe pump), a solution of tri-*n*-butyltin hydride (34 μl, 79% pure by ^1H n.m.r., 0.10 mmol) and AIBN (1.0 mg, 6.0 μmol) in degassed benzene (1 ml). After a further 1 h at reflux the solution was concentrated to yield an oil which was purified by flash column chromatography (200:1, petrol:ether) to give the macrocyclisation product **2** (10 mg, 51%). R_f (1:1, petrol:ether) 0.54; Accurate mass: Found: 221.1905, $C_{15}H_{25}O$ (MH^+) requires 221.19054; $\nu_{max.}$ (thin film) 2926 (s), 2854 (s), 1711 (s), 1462 (w), 1377 (w); δ_H (500 MHz, $CDCl_3$) 1.02-1.86 (15H, m), 2.13 (1H, dt, *J* 14.0, 9.0), 2.29 (1H, ddd, *J* 14.0, 9.5, 4.5), 2.47 (1H, ddd, *J* 14.0, 7.5, 4.5), 2.52 (1H, dd, *J* 17.0, 4.5), 2.57-2.64 (1H, m), 2.65 (1H, dd, *J* 17.0, 10.5), 3.06-3.12 (1H, m), 5.65 (1H, dt, *J* 5.5, 2.0), 5.70 (1H, dt, *J* 5.5, 2.0); δ_C (125 MHz, $CDCl_3$) 24.1, 24.3, 24.9, 26.2, 27.1, 27.6, 32.1, 33.1, 40.5, 43.9, 45.3, 48.2, 133.0, 136.4, 212.1; *m/z* (C.I., NH_3) 238 (MNH_4^+, 7), 221 (MH^+, 100), 220 (10), 80 (17%). Also obtained was the reduced, uncyclised material **17** (6.2 mg, 31%). R_f (1:1, petrol:ether) 0.59; $\nu_{max.}$ (thin film) 2956 (s), 2924 (s), 2854 (s), 1702 (sh), 1685 (m), 1705 (sh), 1458 (w), 1401 (w), 1098 (w), 1073 (w); δ_H (500 MHz, $CDCl_3$) 0.93 (1H, dt, *J* 12.5, 7.5), 0.93 (3H, t, *J* 7.5), 1.22-1.47 (10H, m), 2.36 (1H, dt, *J* 13.0, 8.0), 2.60 (1H, dd, *J* 16.0, 8.0), 2.60-2.67 (1H, m), 2.72 (1H, dd, *J* 16.0, 6.5), 3.08-3.15 (1H, m), 5.61 (1H, dt, *J* 5.5, 2.0), 5.70 (1H, dt, *J* 5.5, 2.0), 5.83 (1H, dd, *J* 10.5, 1.0), 6.22 (1H, dd, *J* 17.5, 1.0), 6.37 (1H, dd, *J* 17.5, 10.5); δ_C (125 MHz, $CDCl_3$) 13.6, 22.6, 27.9, 29.5, 31.9, 36.9, 37.5, 41.1, 45.7, 46.7, 128.0, 133.2, 136.0, 136.9, 200.3; *m/z* (C.I., NH_3) 238 (MNH_4^+, 7), 223 ($MNH_4^+{-}CH_3$, 62), 221 (MH^+, 100), 193 (12), 151 (31), 80 (38), 55 (31%).

Bicyclo[10.2.1]pentadec-12-en-3-one (19)

To a solution of enone **11** (56 mg, 0.16 mmol) and AIBN (2 mg, 0.01 mmol) in degassed benzene (80 ml) at reflux was added, over 10h (syringe pump), a solution of tri-*n*-butyltin hydride (70 μl, 75% pure by ^1H n.m.r., 0.19mmol) in degassed benzene (4ml). After a further 3 h the reaction mixture was concentrated, thiophenol (25 μl, 0.22 mmol) was added[19] and the mixture purified by flash column chromatography (200:1, petrol:ether) to give macrocycle **19** (13 mg, 37%) as an oil. R_f (1:1, petrol:ether) 0.50; Accurate Mass: Found: 238.2171, $C_{15}H_{28}NO$ (MNH_4^+) requires 238.217089. $\nu_{max.}$ (thin film) 2927 (s), 2856 (m), 1718 (s), 1656 (w), 1446 (m), 1127 (m), 1041 (m), 877 (w), 666 (w); δ_H (500 MHz, $CDCl_3$) 1.20-1.33 (8H, m), 1.37-1.44 (2H, m), 1.67-1.74 (2H, m), 1.87-1.93 (1H, m), 2.00 (1H, dddd, *J* 14.0, 8.5, 5.5, 5.5), 2.04 (2H, t, *J* 8.0), 2.21-2.25 (2H, m), 2.31 (1H, dd, *J* 15.5, 7.0), 2.48 (1H, dd, *J* 15.5, 6.0), 2.58 (1H, dd, *J* 16.5, 9.5), 2.81 (1H, tq, *J* 9.5, 6.5), 3.02-3.10 (1H, m), 5.19 (1H, d, *J* 1.5); δ_C (125 MHz, $CDCl_3$) 22.6, 25.9, 27.6, 29.1, 29.7, 30.9, 31.7, 34.3, 37.1, 42.8, 42.9, 43.9, 126.6, 144.9, 214.4; *m/z* (C.I., NH_3) 238 (MNH_4^+, 100), 221 (MH^+, 30), 150 (12%).

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