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A convergent approach to the marine natural product eleutherobin: synthesis of key intermediates and attempts to produce the basic skeleton

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Synthesis of (1*R*,5*R*,6*R*)-2-(6-hydroxymethyl-5-isopropyl-2-methylcyclohex-2-enyl)-*N*-methoxy-*N*-methylacetamide **8** from *R*-(−)-phellandrene in six steps, and (3a*R**,4*S**,6*R**,6a*S**)-(6-hydroxymethyl-4-methoxy-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)acetic acid methyl ester **17** from tetrabromoacetone and 2-methoxy-5-methylfuran in six steps, provided two key fragments which have been combined to produce intermediates for attempted construction of the basic skeleton of eleutherobin.

Introduction

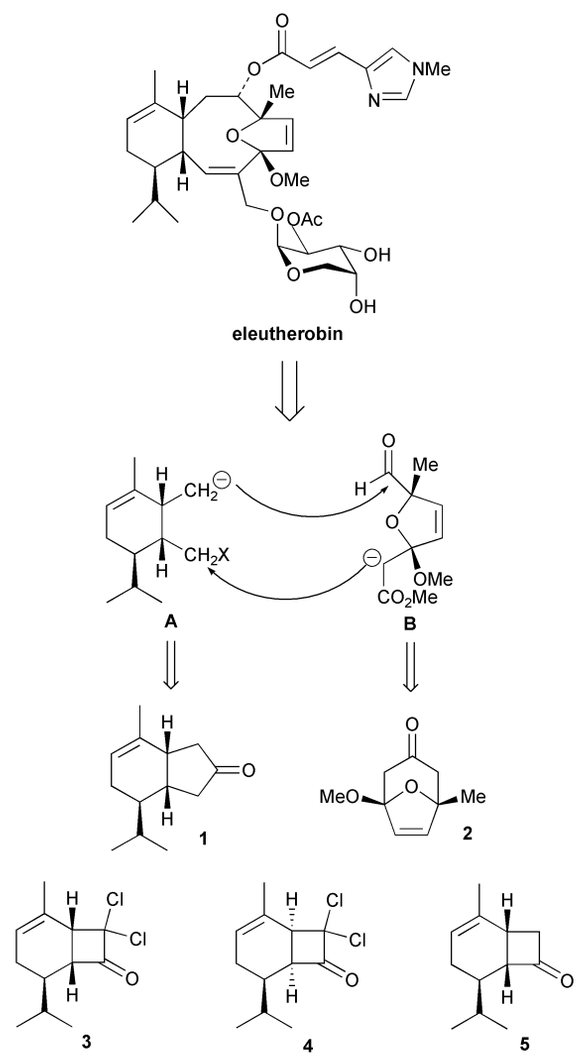
Eleutherobin, from a marine soft coral of the *Eleutherobia* species, was first reported in 1995 by the group of Fenical.[1] It was immediately shown to possess activity as an inhibitor of microtubule depolymerisation with a mean cytotoxicity that was greater than that exhibited by taxol or the epothilones,[2] all of which apparently share a similar mode of action. However, eleutherobin is only available in tiny amounts from the coral and total synthesis will be necessary if the full potential of this interesting compound is to be realised. It has already been the subject of two total syntheses by Nicolaou[3] and Danishefsky,[4] and Gennari has produced a potential advanced intermediate[5] and an analogue with a simplified skeleton.[6]

However, all of these syntheses were linear and multi-stage rather than convergent and only Magnus has reported a convergent strategy,[7] though he claims to have abandoned his approach. Our approach is genuinely convergent (as shown in the analysis), and we now wish to report not only the synthesis of the left- and right-hand fragments, but also their combination to yield several advanced intermediates that include most of the skeleton of the natural product.

Results and discussion

We have already described[8] in outline the synthesis of the two key fragments **1** and **2**, the former in stereochemically pure form from (*R*)-(−)-α-phellandrene, and the latter in racemic form from an oxyallyl cycloaddition[9] between 2-methoxy-5-methylfuran and tetrabromoacetone, but we provide now full details of this chemistry together with methods for their conversion into more advanced intermediates.

Phellandrene can be purchased from Fluka as a mixture of monoterpenes which contains about 50% of the (−)-enantiomer, but apparently none of the (+)-enantiomer. Reaction of this mixture with dichloroacetyl chloride and triethylamine, or with trichloroacetyl chloride and zinc dust under irradiation with ultrasound, provided up to 80% of the dichlorocyclobutanone **3** as the major product, with a small amount (ratio of 9 : 1) of the stereoisomer **4** (details provided in reference 8). The yield is based upon the assumption that (*R*)-(−)-α-phellandrene comprised 50% of the starting material. We never observed formation of the other regioisomers. Proof of the absolute stereochemistry of adduct **3** was achieved by removal of the chlorine atoms with zinc and acetic acid which provided the cyclobutanone **5**. This had been used by Danishefsky in his synthesis,[4] and our product had $[\alpha]_D^{24} = -170$ (*c*. 0.4, $CHCl_3$) in comparison with $[\alpha]_D^{23} = -159$ (*c*. 0.96, $CHCl_3$) reported in his paper.



Reaction of **3** with excess diazomethane (typically three equivalents) followed by removal of the chlorine atoms using zinc and acetic acid yielded the desired ring-expanded product **1**. This bicyclic ketone **1** was treated with six equivalents of MCPBA in dichloromethane to produce the epoxylactones **6a**,**b** (Scheme 1). Initial experiments showed that stoichiometric

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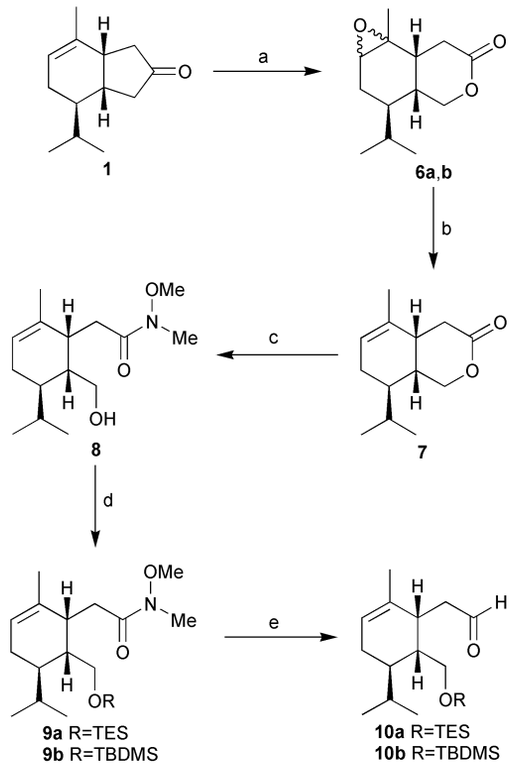


1 6a,b 8 7

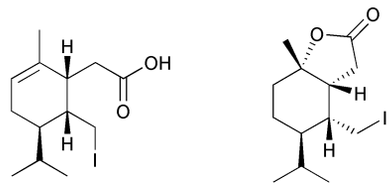
Scheme 1 *Reagents and conditions*: a) MCPBA, CH_2Cl_2, rt, 3 d, 74%; b) Zn, NaI, NaOAc, HOAc, CH_2Cl_2, rt, 4 d, 86%; c) $AlMe_3$, MeNHOMe, toluene, 0 °C–rt, 2 h, 94%; d) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C–0 °C, 2 h, 72% or TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C–0 °C, 1 h, 91%; e) DIBAL-H, CH_2Cl_2, −78 °C–0 °C, 3 h, 52% or 62%.

quantities of the peracid only yielded the epoxides, while an excess of reagent and a long reaction time at room temperature were required to produce a good yield of **6** (up to 89%). Removal of the epoxide group was then effected using a mixture of zinc and sodium iodide in dichloromethane and acetic acid[10] to provide the lactone **7**. The regioselectivity of the Bayer–Villiger reaction is remarkable since the other regioisomer was not observed, and we believe that this must be due to electronic effects once the epoxide has been formed.

Attempts to open the lactone ring with sodium methoxide were successful but the ring closed spontaneously during work-up. However, synthesis of the corresponding Weinreb amide **8** could be effected using two equivalents of Me_3Al in the presence of methoxymethylamine in benzene,[11] and the hydroxy group was protected as its TES ether **9a** or TBDMS ether **9b**. The amides were also converted into the corresponding aldehydes **10a**,**b** for potential intermolecular aldol reactions. Attempted reactions between the amides **9a**,**b** and several model aldehydes using either LDA in THF or dibutylboron triflate were non-productive, the former conditions providing no reaction and the latter leading to cleavage of the silyl ethers. Similarly, there was no apparent reaction between the aldehydes **10a**,**b** and several model aldehydes using a variety of bases, possibly because the retro-aldol reaction was favoured. These results suggested that formation of the 'northern' C–C bond using an aldol-type approach were doomed to failure.

Interestingly, when the lactone **7** was treated with trimethylsilyl iodide in order to prepare the iodoacid **11** as a precursor for the 'southern' C–C bond, the fused butyrolactone **12** was obtained instead, and this structure was clearly evident both from the IR spectrum (carbonyl at 1776 cm^{-1}) and the ^1H (δ 0.54, C*H*CH_2I) and ^{13}C NMR (δ 13.8, CH_2I) spectra.

The other key fragment **2** was prepared using oxyallyl technology[9] (full details of this preparation were included in reference 8). When oxabicyclo[3.2.1]oct-6-en-3-one **2** was treated with various peracids to attempt a Bayer–Villiger reaction to



11 12

produce lactone(s), epoxide **13** was produced but none of the required lactone(s), and there was considerable decomposition in some cases (Scheme 2). To avoid reaction of the double bond, we converted the alkene **2** into the *cis*-diol, and thence the acetonide **14**. At this point in the synthesis, a kinetic resolution might be effected on the racemic diol through use of the Sharpless asymmetric dihydroxylation protocol,[12] but this has not yet been explored, and we continued with the racemic acetonide. The keto acetonide **14** could be converted into a mixture of enol silylethers **15a** and **15b**, and with DBU as base the ratio of **15a** : **15b** was 1 : 10, while with LDA or lithium cyclohexylamide the ratio was 5 : 8 and 1 : 2. However, an attempt at selective ozonolysis of the desired regioisomer **15a** to provide an intermediate with the required substitution pattern **B** was unsuccessful.

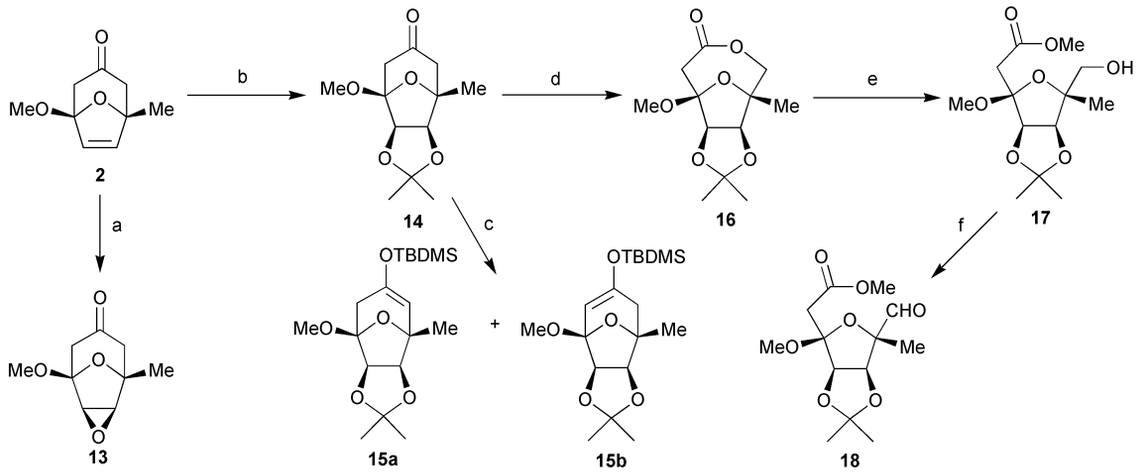
We were, however, very pleased to find that the acetonide **14** reacted with MCPBA to yield the lactone **16** (as the major product), and thence the hydroxyester **17** by treatment with K_2CO_3–MeOH. This was also converted into the corresponding aldehyde **18** for an intermolecular aldol reaction with aldehydes **10a**,**b**, but this also failed.

Then our attention was turned to attempts to construct the 'southern' carbon–carbon bond (Scheme 3). We explored the viability of an intermolecular aldol reaction between the aldehyde **19** prepared from the amide **8** (Swern oxidation) and the aldehyde **22** synthesised in three steps from alcohol **17** (protection with TBDMSCl, reduction of the ester with $LiAlH_4$ and Swern oxidation). With piperidine as base the only 'products' isolated from the reaction mixture were unreacted aldehyde **19** and two geometrical isomers of the des-methoxy product **23a**,**b**. This result was not wholly unexpected because we anticipated that the acetal grouping within compound **22** was making the methoxy group sensitive to base-catalysed elimination. It did, however, introduce a serious limitation of our options since it eliminated any base-catalysed reactions of either aldehyde **22** or ester **18**.

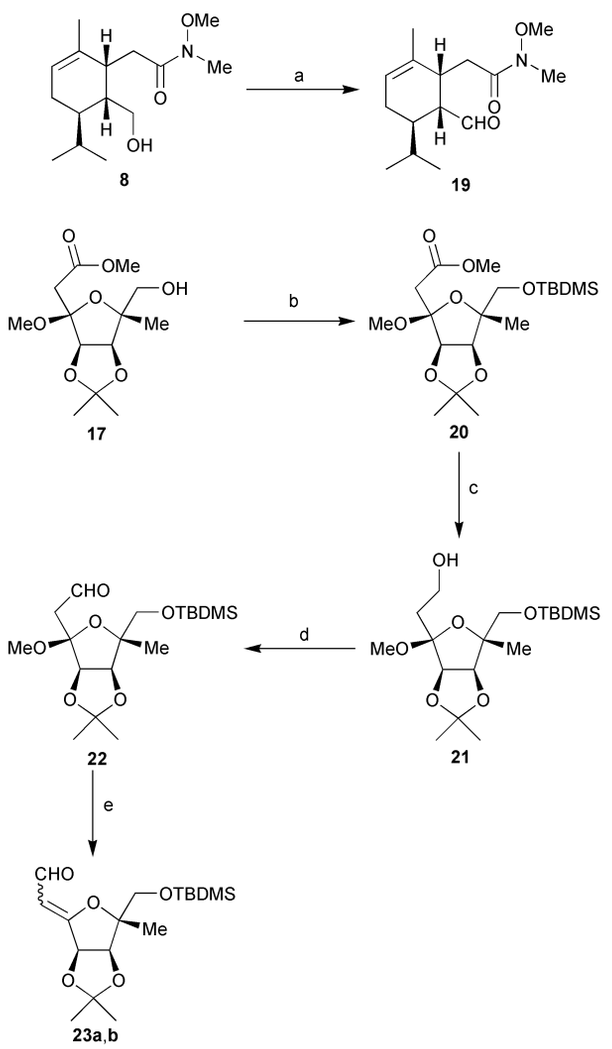
Thus far all of our efforts had been directed towards effecting *intermolecular* C–C bond formation, so we turned our attentions towards effecting *intramolecular* bond formation. We explored the possibility of preparing the key 'southern' *cis*-alkene through a RCM reaction carried out on the tethered molecule **30a**,**b**. This was synthesised from the aldehyde **19** and the alcohol **21** as shown in Scheme 4. The vinyl acid **26** was prepared by means of a Wittig reaction, followed by reduction of the amide to the aldehyde **25** and reoxidation to yield **26**. The vinyl species **29** required formation of the phenylselenide[13] **27**, followed by elimination[14] to provide the vinyl group and deprotection of the TBDMS ether with fluoride to produce **29**. Combination of these vinyl species **26** and **29** to form the esters **30a**,**b** was carried out using DCC as dehydrating reagent in the presence of catalytic DMAP.[15] Unfortunately, reaction of this tethered divinyl species **30a**,**b** with either the standard Grubb's catalyst or the second generation catalyst[16] failed to produce any evidence of a ring-closing metathesis, but other catalysts and reactions conditions are being explored.

Conclusion

These initial investigations have identified some limitations but also provided a number of potentially useful intermediates for our convergent approach to eleutherobin. In particular, we have

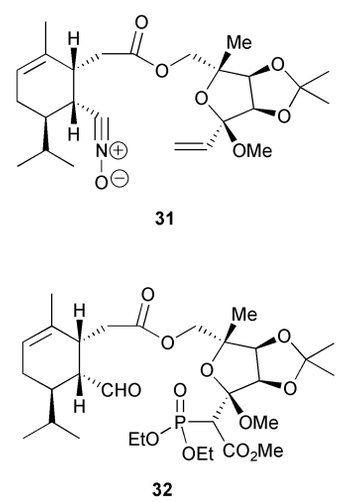


Scheme 2 *Reagents and conditions*: a) MCPBA, CH_2Cl_2, reflux, 5 d, 64%; b) i, NMO, OsO_4, THF–H_2O, rt, 5 d, ii, 2,2-dimethoxypropane, *p*-TSA, rt, 3 h, 84%; overall; c) LDA, TBDMSOTf, THF, −78 °C–rt, 3 h, 23%; d) MCPBA, dichloroethane, reflux, 20 h, 38%; e) K_2CO_3, MeOH, rt, 1 h, 89%; f) DMSO, $(CO)_2Cl_2$, Et_3N, CH_2Cl_2, −78 °C–rt, *ca.* 1.5 h, 52%.



Scheme 3 *Reagents and conditions*: a) DMSO, $(CO)_2Cl_2$, Et_3N, CH_2Cl_2, −78 °C–rt, ~1.5 h, 75%; b) TBDMSCl, imidazole, DMF, rt, 18 h, 93%; c) $LiAlH_4$, THF, 0 °C, 1 h, 95%; d) DMSO, $(CO)_2Cl_2$, Et_3N, CH_2Cl_2, −78 °C–rt, ~1.5 h, 81%; e) **19**, piperidine, HOAc, benzene, rt, 3 h, 28%.

devised very concise routes to intermediates **10** and **18** which are appropriately functionalised for conversion into the basic skeleton of eleutherobin. At present, approaches that involve an intramolecular nitrile oxide cycloaddition[17] of the tethered molecule **31** and an intramolecular Horner–Emmons reaction of an intermediate like **32** are being explored.



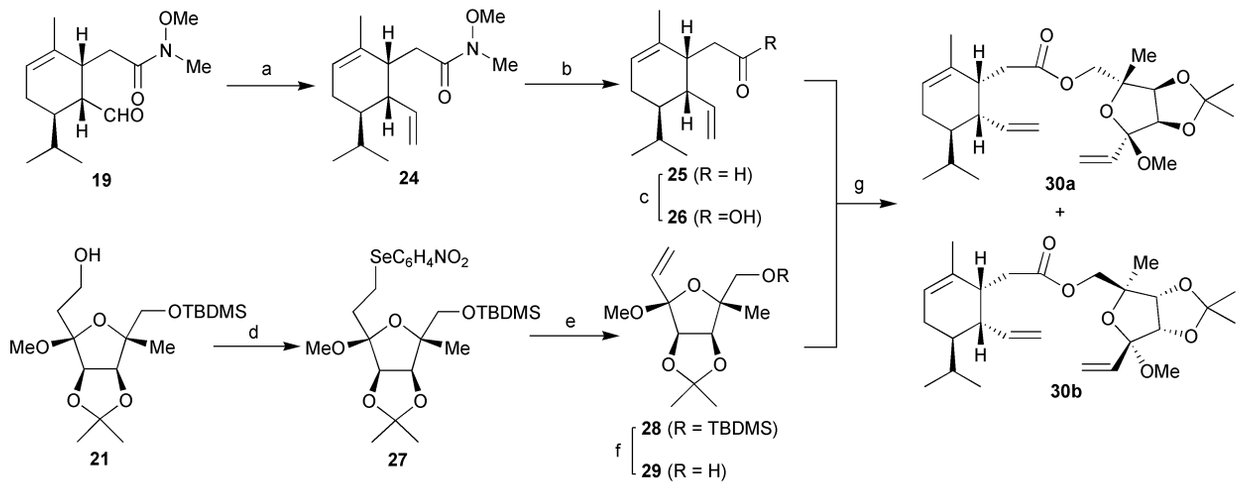
Another key task is to resolve the right hand fragment **2**, perhaps by means of a kinetic Sharpless *cis*-hydroxylation. Success in these new investigations should provide access to gram quantities of the basic skeleton of eleutherobin for further elaboration into the natural product and analogues for biological evaluation.

Experimental

All the reactions were performed under an inert atmosphere of nitrogen and the solvents for reactions were dried and distilled under nitrogen prior to use. Melting points were determined on an IA 9100 electrothermal melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. Microanalyses were carried out on a Perkin Elmer 2400 CHN elemental analyzer. IR spectra were measured as films or KBr plates on Perkin Elmer FT-IR instrument. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 or a Bruker DRX 500 spectrometer. Mass spectra were recorded on a VG Autospec spectrometer or a VG QUATTRO triple quadrupole mass spectrometer.

(1*S**,5*R**)-1-Methoxy-5-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2)[8]

IR (ν_{max}/cm^{-1}): 2973, 2935, 1717, 1445, 1338, 1268, 1156, 850; ^1H NMR (500 MHz, $CDCl_3$): δ 6.11 and 6.03 (2H, 2d, J = 5.8 Hz, H-6 and H-7), 3.43 (3H, s, OCH_3), 2.64 and 2.56 (2H, 2d, J = 16.2Hz, H-2 and H-2′), 2.47 and 2.33 (2H, 2d, J = 16.5 Hz, H-4 and H-4′), 1.52 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.0 (C-3), 139.4 and 132.4 (C-6 and C-7),



Scheme 4 *Reagents and conditions*: a) CH_3PPh_3Br, *n*-BuLi, THF, rt, 1 h, 72%; b) DIBAL-H, CH_2Cl_2, −78 °C–0°C, 3 h, 55%; c) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O, rt, 2.5 h, 85%; d) *o*-$NO_2C_6H_4CN$, *n*–Bu_3P, THF, rt, 1 h, 78%; e) H_2O_2, THF, rt, 5 h, 80%; f) TBAF, THF, rt, 30 min, 80%; g) DCC, DMAP, CH_2Cl_2, rt, 5 h, 62%.

109.6 (C-1), 80.7 (C-5), 51.6 (OCH_3), 50.12 and 50.10 (C-2 and C-4), 23.1 (CH_3); HRMS (CI): calcd for $C_9H_{13}O_3$ ($[M + H]^+$) 169.0864, found 169.0862.

(1*R*,5*R*,6*R*)-8,8-Dichloro-5-isopropyl-2-methylbicyclo[4.2.0]oct-2-en-7-one (3)[8]

$[\alpha]_D^{24}$: −146.7 (*c*. 0.3, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2961, 2875, 1804, 1464, 1370, 1070, 796; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (1H, br s, H-3), 3.65 (1H, dd, J = 8.1, 10.2 Hz, H-6), 3.28 (1H, d, J = 10.2 Hz, H-1), 2.07 (1H, m, H-4), 1.92–1.78 (5H, m, H-5, 2-CH_3 and H-4′), 1.67 (1H, m, C*H*(CH_3)$_2$), 0.95 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.88 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.1 (C-7), 129.6 (C-2), 125.8 (C-3), 87.3 (C-8), 56.9 (C-6), 49.7 (C-1), 38.3 (C-5), 30.5 (*C*H(CH_3)$_2$), 24.7 (C-4), 22.4 (2-CH_3), 20.7 and 19.4 (CH(*C*H$_3$)$_2$); EIMS (*m*/*z*, %): 246 (M^+, 9), 203 (10), 176 (14), 139 (18), 97 (100), 77 (53), 55 (28), 43 (79); HRMS (EI): calcd for $C_{12}H_{16}OCl_2$ 246.0578, found 246.0579.

(3a*R*,4*R*,7a*R*)-4-Isopropyl-7-methyl-1,3,3a,4,5,7a-hexahydroinden-2-one (1)

Freshly prepared CH_2N_2–Et_2O solution (0.205 mol) was poured slowly into a solution of **3** (16.9 g, 0.0684 mol) in diethyl ether (684 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temperature and quenched with acetic acid (17.4 mL). The solvent was evaporated under reduced pressure and the crude intermediate was ready to undergo dechlorination. It was dissolved in acetic acid (342.7 mL) and zinc dust (26.7 g, 0.42 mol) was added at room temperature. The mixture was stirred at room temperature for 1 h, then cooled to 0 °C, water was added followed by DCM and the two layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine successively. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (9 : 1 petroleum ether : diethyl ether) to give **1** as a colourless oil (7.35 g, 56% yield for the two steps). $[\alpha]_D^{24}$: −45.4 (*c*. 0.9, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2960, 2925, 1743, 1465, 1407, 1367, 1155; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.47 (1H, br s, H-6), 2.68 (1H, m, H-7a), 2.49 (1H, ddd, J = 0.9, 8.5, 18.6 Hz, H-1), 2.35 (3H, m, H-3a, H-3 and H-3′), 2.02 (1H, ddd, J = 1.5, 10.4, 18.6 Hz, H-1′), 1.96 (1H, m, H-5), 1.85 (2H, m, H-5′ and C*H*(CH_3)$_2$), 1.67 (3H, s, 7-CH_3), 1.31 (1H, m, H-4), 0.93 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.79 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.1 (C-2), 134.4 (C-7), 121.7 (C-6), 42.5 (C-1 and C-3), 40.7 (C-7a), 37.8 (C-4), 37.4 (C-3a), 26.9 (*C*H(CH_3)$_2$), 23.5 (C-5), 22.2 (7-CH_3), 21.3 and 16.1 (*C*H(*C*H$_3$)$_2$); EIMS (*m*/*z*, %): 192 (M^+, 82), 177 (17), 149 (93), 135 (39), 121 (61), 107 (100), 93 (87), 79 (86), 55 (75), 41 (88); HRMS (EI): calcd for $C_{13}H_{20}O$ 192.1514, found 192.1508; Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.90; H, 10.19%.

(1*R*,3*R*,3a *R*,7a*R*,7b*S*)-3-Isopropyl-7b-methyloctahydro-1,5-dioxacyclopropa[α]naphthalen-6-one (6a) and (1*S*,3*R*,3a*R*,7a*R*,7b*R*)-3-Isopropyl-7b-methyloctahydro-1,5-dioxacyclopropa[α]-naphthalen-6-one (6b)

m-CPBA (25.4 g, 147.2 mmol) was added to a stirred solution of **1** (4.71 g, 24.53 mmol) in DCM (122.5 mL) at room temperature. The mixture was stirred at room temperature for 3 days, then it was cooled to 0 °C and 10% aqueous Na_2SO_3 solution was added. The two layers were separated and the aqueous layer was extracted with DCM and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine successively. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 8 petroleum ether : diethyl ether) to give products **6a** and **6b** (*ca*. 1 : 1) as white solids (4.04 g, 74%). **6a**, Mp: 33–34 °C; IR (ν_{max}/cm^{-1}): 2960, 1748, 1558, 1458, 1388, 1084; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 (1H, dd, J = 5.3, 11.8 Hz, H-4), 4.03 (1H, dd, J = 7.9, 11.8 Hz, H-4′), 3.18 (1H, d, J = 2.8 Hz, H-1), 2.70 (1H, dd, J = 6.4, 16.3 Hz, H-7), 2.64 (1H, dd, J = 10.8, 16.3 Hz, H-7′), 2.39 (1H, m, H-7a), 2.05 (1H, m, H-2), 1.83 (1H, m, H-3a), 1.73 (1H, m, C*H*(CH_3)$_2$), 1.57 (2H, m, H-3 and H-2′), 1.32 (3H, s, 7b-CH_3), 0.93 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.79 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz,$CDCl_3$): δ 173.2 (C-6), 69.2 (C-4), 61.3 (C-1), 58.1 (C-7b), 34.1 (C-7a), 33.2 (C-3), 32.9 (C-3a), 29.3 (C-7), 26.6 (*C*H(CH_3)$_2$), 23.0 (C-2), 22.3 (7b-CH_3), 21.0 and 15.5 (CH(*C*H$_3$)$_2$); EIMS (*m*/*z*, %): 224 (M^+, 21), 209 (20), 182 (82), 153 (71), 125 (79), 107 (80), 77 (82), 67 (72), 53 (72), 29 (100); HRMS (EI): calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1411. **6b**, Mp: 34–35 °C; IR (ν_{max}/cm^{-1}): 2960, 1735, 1558, 1458, 1398, 1192, 1081; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.47 (1H, dd, J = 1.8, 11.9 Hz, H-4), 4.14 (1H, dd, J = 2.5, 11.9 Hz, H-4′), 3.05 (1H, d, J = 4.8 Hz, H-1), 2.79 (1H, dd, J = 6.3, 17.6 Hz, H-7), 2.53 (1H, m, H-7a), 2.48 (1H, dd, J = 11.8, 17.6 Hz, H-7′), 1.93 (3H, m, C*H*(CH_3)$_2$, H-2 and H-3a), 1.72 (1H, dd, J = 11.1, 15.6 Hz, H-2′), 1.50 (1H, m, H-3), 1.28 (3H, s, 7b-CH_3), 0.91 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.77 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz,$CDCl_3$): δ 169.8 (C-6), 70.1 (C-4), 59.9 (C-1), 59.1 (C-7b), 37.2 (C-7a), 30.8 and 30.7 (C-3 and C-3a), 30.5 (C-7), 26.4 (*C*H(CH_3)$_2$), 21.9 (C-2), 20.7 and 14.4 (CH(*C*H$_3$)$_2$), 19.8 (7b-CH_3); EIMS (*m*/*z*,

%): 224 (M^+, 12), 209 (20), 181 (70), 153 (81), 141 (73), 123 (82), 95 (81), 81 (100), 69 (90), 56 (82); HRMS (EI): calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1414.

(4a*R*,8*R*,8a*R*)-8-Isopropyl-5-methyl-1,4,4a,7,8,8a-hexahydroisochromen-3-one (7)

A solution of epoxylactones **6a** and **6b** (4.04 g, 18.0 mmol) in DCM (150 mL) was added to a slurry mixture of zinc dust (6.60 g, 100.8 mmol), sodium iodide (21.60 g, 144.0 mmol), anhydrous sodium acetate (7.38 g, 90.0 mmol) and acetic acid (20.1 mL) in DCM (75 mL). The reaction mixture was stirred at room temperature for 4 days before filtration through a pad of Celite. The filtrate was in part evaporated and taken up in DCM, then washed with a saturated aqueous solution of $NaHCO_3$. The organic extract was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (7 : 3 petroleum ether : ethyl acetate) to give the product **7** as a colourless oil (3.24 g, 86%). $[\alpha]_D^{24}$ +38.4 (*c*. 1.0, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2960, 2914, 1739, 1464, 1388, 1252, 1069; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.48 (1H, br s, H-6), 4.33 (1H, dd, J = 5.2, 11.7 Hz, H-1), 4.28 (1H, dd, J = 4.1, 11.7 Hz, H-1′), 2.84 (1H, dd, J = 7.2, 17.2 Hz, H-4), 2.48 (1H, m, H-4a), 2.34 (1H, dd, J = 9.9, 17.2 Hz, H-4′), 2.01 (1H, m, H-8a), 1.96 (1H, m, H-7), 1.88 (2H, m, H-7′ and C*H*(CH_3)$_2$), 1.67 (3H, s, 5-CH_3), 1.52 (1H, m, H-8), 0.95 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.82 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4 (C-3), 134.2 (C-5), 122.3 (C-6), 69.9 (C-1), 35.9 (C-8), 35.7 (C-4a), 34.3 (C-8a), 33.3 (C-4), 26.6 (*C*H(CH_3)$_2$), 23.6 (C-7), 21.11, 21.09 and 16.0 (5-CH_3 and CH(*C*H$_3$)$_2$); HRMS (EI): calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1457; Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.44; H, 9.73%.

(1*R*,5*R*,6*R*)-2-(6-Hydroxymethyl-5-isopropyl-2-methylcyclohex-2-enyl)-*N*-methoxy-*N*-methylacetamide (8)

Trimethylaluminium (2.0 M solution in hexanes) (2.45 mL, 4.90 mmol) was added dropwise to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (478 mg, 4.90 mmol) in toluene (5.88 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. It was cooled to 0 °C and a solution of **7** (0.51 g, 2.45 mmol) in toluene (3.92 mL) was added dropwise. The reaction mixture was once more allowed to warm to room temperature and stirred for 2 h, then cooled to 0 °C and quenched by dropwise addition of a saturated aqueous solution of $NaHCO_3$, followed by ethyl acetate. The precipitate was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was separated and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the product **8** as a colourless oil (0.62 g, 94%), which was used directly without further purification.

(1*R*,5*R*,6*R*)-2-(5-Isopropyl-2-methyl-6-triethylsilanyloxymethylcyclohex-2-enyl)-*N*-methoxy-*N*-methylacetamide (9a)

2,6-Lutidine (1.28 mL, 10.98 mmol) was added dropwise to a stirred solution of **8** (0.986 g, 3.66 mmol) in DCM (18.3 mL) at −78 °C, then triethylsilyl trifluoromethanesulfonate (1.66 mL, 7.32 mmol) was added dropwise. The mixture was allowed to warm to 0 °C and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the two layers formed were separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 2 petroleum ether : ethyl acetate) to give the product **9a** as a colourless oil (1.01 g, 72%). IR (ν_{max}/cm^{-1}): 2957, 2877, 1671, 1460, 1383, 1084, 1007, 816, 744; ^{1}H NMR (500 MHz, C_6D_6): δ 5.38 (1H, br s, H-3), 3.81 (2H, d, J = 6.4 Hz, 6-CH_2), 3.31 (1H, m, H-1), 3.13 (3H, s, OCH_3), 2.95 (3H, s, NCH_3), 2.81 (1H, dd, J = 6.4, 16.0 Hz, 1-CH_2), 2.53 (1H, dd, J = 6.0, 16.0 Hz, 1-CH_2), 2.11 (1H, m, H-6), 2.02 (1H, m, H-4), 1.87 (2H, m, H-4′ and C*H*(CH_3)$_2$), 1.77 (3H, s, 2-CH_3), 1.70 (1H, m, H-5), 1.05 (9H, t, J = 7.9 Hz, Si(CH_2C*H*$_3$)$_3$), 1.00 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)$_2$), 0.87 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)$_2$), 0.65 (6H, q, J = 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$); ^{13}C NMR (75 MHz, C_6D_6): δ 174.4 (C=O), 136.8 (C-2), 121.8 (C-3), 63.2 (6-CH_2), 60.6 (OCH_3), 41.2 (C-6), 37.9 (C-5), 35.7 (C-1), 32.8 (1-CH_2), 32.4 (NCH_3), 27.5 (*C*H(CH_3)$_2$), 24.7 (C-4), 22.5 (2-CH_3), 21.2 and 17.8 (CH(*C*H$_3$)$_2$), 7.2 (Si(CH_2C*H*$_3$)$_3$), 4.8 (Si(*C*H$_2$CH$_3$)$_3$); EIMS (*m*/*z*, %): 383 (M^+, 45), 355 (72), 323 (41), 251 (87), 149 (100), 117 (85), 89 (85), 59 (90), 43 (74); HRMS (EI): calcd for $C_{21}H_{41}NO_3Si$ 383.2856, found 383.2871.

(1*R*,5*R*,6*R*)-2-[6-(*tert*-Butyldimethylsilanyloxymethyl)-5-isopropyl-2-methylcyclohex-2-enyl]-*N*-methoxy-*N*-methylacetamide (9b)

To a solution of **8** (1.48 g, 5.5 mmol) in DCM (27.5 mL) at −78 °C, 2,6-lutidine (1.92 mL, 16.5 mmol) was added dropwise, followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.52 mL, 11.0 mmol) dropwise. The mixture was allowed to warm to 0 °C and stirred for 1 h. Saturated aqueous $NaHCO_3$ solution was added to quench the reaction and the two layers formed were separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 2 petroleum ether : ethyl acetate) to give the product **9b** as a colourless oil (1.92 g, 91%). $[\alpha]_D^{24}$ +92.0 (*c*. 0.3, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2957, 2931, 1671, 1471, 1384, 1254, 1099, 838, 776; ^{1}H NMR (500 MHz, C_6D_6): δ 5.37 (1H, br s, H-3), 3.80 (2H, m, 6-CH_2), 3.28 (1H, m, H-1), 3.12 (3H, s, OCH_3), 2.94 (3H, s, NCH_3), 2.79 (1H, dd, J = 6.2, 16.0 Hz, 1-CH_2), 2.53 (1H, dd, J = 6.5, 16.0 Hz, 1-CH_2), 2.08 (1H, m, H-6), 2.01 (1H, m, H-4), 1.87 (2H, m, H-4′ and C*H*(CH_3)$_2$), 1.77 (3H, s, 2-CH_3), 1.68 (1H, m, H-5), 1.01 (9H, s, SiC(CH_3)$_3$), 0.98 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.85 (3H, d, J = 6.7 Hz, CH(C*H*$_3$)$_2$), 0.11 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, C_6D_6): δ 174.4 (C=O), 136.9 (C-2), 121.7 (C-3), 63.5 (6-CH_2), 60.6 (OCH_3), 41.2 (C-6), 37.8 (C-5), 35.9 (C-1), 32.8 (1-CH_2), 32.4 (NCH_3), 27.4 (*C*H(CH_3)$_2$), 26.2 (SiC(*C*H$_3$)$_3$), 24.6 (C-4), 22.5 (2-CH_3), 21.2 and 17.6 (CH(*C*H$_3$)$_2$), 18.5 (Si*C*(CH_3)$_3$), −5.26 and −5.32 (Si(CH_3)$_2$); EIMS (*m*/*z*, %): 383 (M^+, 12), 368 (7), 326 (100), 251 (16), 220 (26), 208 (37), 149 (16), 119 (24), 103 (34), 89 (39), 73 (64), 43 (41); HRMS (EI): calcd for $C_{21}H_{41}NO_3Si$ 383.2856, found 383.2839.

(1*R*,5*R*,6*R*)-(5-Isopropyl-2-methyl-6-triethylsilanyloxymethylcyclohex-2-enyl)acetaldehyde (10a)

DIBAL-H (1.0 M solution in hexanes) (5.54 mL, 5.54 mmol) was added dropwise to a stirred solution of **9a** (1.06 g, 2.77 mmol) in DCM (18.5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and then it was allowed to warm to 0 °C and stirred for 1 h. A large excess of MeOH was added at 0 °C and the aluminium salts that precipitated were filtered though a pad of Celite under reduced pressure. The solid was washed with diethyl ether and the combined filtrate and washings were concentrated to give the crude product, which was purified by flash column chromatography on silica gel (30 : 1 petroleum ether : diethyl ether) to give **10a** as a colourless oil (470 mg, 52%). IR (ν_{max}/cm^{-1}): 2958, 2878, 1727, 1460, 1240, 1080, 1013, 810, 743; ^{1}H NMR (500 MHz, C_6D_6): δ 9.70 (1H, dd, J = 1.8, 2.8 Hz, CHO), 5.29 (1H, br s, H-3), 3.69 (1H, dd, J = 4.8, 10.4 Hz, 6-CH_2), 3.46 (1H, dd, J = 9.4, 10.4 Hz, 6-CH_2), 2.90 (1H, m, H-1), 2.45 (1H, ddd, J = 2.8, 7.4, 16.6 Hz, 1-CH_2), 2.06 (1H, ddd, J = 1.8, 4.5, 16.6 Hz, 1-CH_2), 1.86 (1H, m, H-6),

1.79 (1H, m, H-4), 1.66 (2H, m, H-4′ and C*H*(CH_3)$_2$), 1.56 (3H, s, 2-CH_3), 1.38 (1H, m, H-5), 1.00 (9H, t, J = 7.9 Hz, Si(CH_2CH_3)$_3$), 0.83 (3H, d, J = 6.9 Hz, CH(CH_3)$_2$), 0.73 (3H, d, J = 6.8 Hz, CH(CH_3)$_2$), 0.59 (6H, q, J = 7.9 Hz, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, C_6D_6): δ 201.1 (CHO), 135.5 (C-2), 122.3 (C-3), 62.3 (6-CH_2), 44.5 (1-CH_2), 41.3 (C-6), 36.6 (C-5), 34.9 (C-1), 26.9 (*C*H(CH_3)$_2$), 24.5 (C-4), 22.2 (2-CH_3), 21.2 and 16.0 (CH(*C*H_3)$_2$), 7.1 (Si(CH_2CH_3)$_3$), 4.7 (Si(CH_2CH_3)$_3$); EIMS (*m*/*z*, %): 324 (M^+, 15), 295 (72), 280 (67), 192 (73), 150 (82), 123 (77), 94 (87), 57 (94), 45 (100); HRMS (EI): calcd for $C_{19}H_{36}O_2Si$ 324.2485, found 324.2487.

(1*R*,5*R*,6*R*)-2-[6-(*tert*-Butyldimethylsilanyloxymethyl)-5-isopropyl-2-methylcyclohex-2-enyl]acetaldehyde (10b)

DIBAL-H (1.0 M solution in hexanes) (17.1 mL, 17.1 mmol) was added dropwise to a stirred solution of **9b** (3.27 g, 8.54 mmol) in DCM (56.9 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and then it was allowed to warm to 0 °C and stirred for 1 h. A large excess of MeOH was added at 0 °C and the aluminium salts that precipitated were filtered through a pad of Celite. The solid was washed with diethyl ether and the combined filtrates and washings were concentrated to give the crude product. It was purified by flash column chromatography on silica gel (30 : 1 petroleum ether : diethyl ether) to give **10b** as a white solid (1.72 g, 62%). Mp: 40–42 °C; $[\alpha]_D^{24}$ +110.6 (*c*. 0.5, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2957, 2930, 1728, 1471, 1255, 1104, 1080, 838, 776; ^{1}H NMR (500 MHz, C_6D_6): δ 9.70 (1H, dd, J = 1.8, 2.7 Hz, CHO), 5.29 (1H, br s, H-3), 3.66 (1H, dd, J = 4.6, 10.5 Hz, 6-CH_2), 3.43 (1H, dd, J = 9.2, 10.5 Hz, 6-CH_2), 2.87 (1H, m, H-1), 2.45 (1H, ddd, J = 2.7, 7.3, 16.7 Hz, 1-CH_2), 2.04 (1H, ddd, J = 1.8, 4.5, 16.7 Hz, 1-CH_2), 1.80 (2H, m, H-4 and H-6), 1.64 (2H, m, H-4′ and C*H*(CH_3)$_2$), 1.56 (3H, s, 2-CH_3), 1.38 (1H, m, H-5), 0.95 (9H, s, SiCH(CH_3)$_3$), 0.82 (3H, d, J = 6.9 Hz, CH(CH_3)$_2$), 0.71 (3H, d, J = 6.8 Hz, CH(CH_3)$_2$), 0.051 and 0.047 (6H, 2s, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, C_6D_6): δ 200.9 (CHO), 135.4 (C-2), 122.1 (C-3), 62.4 (6-CH_2), 44.3 (1-CH_2), 41.1 (C-6), 36.1 (C-5), 34.8 (C-1), 26.7 (*C*H(CH_3)$_2$), 25.9 (SiC(*C*H_3)$_3$), 24.2 (C-4), 22.0 (2-CH_3), 21.0 and 15.7 (CH(*C*H_3)$_2$), 18.2 (Si*C*(CH_3)$_3$), −5.6 and −5.7 (Si(CH_3)$_2$); EIMS (*m*/*z*, %): 324 (M^+, 1), 267 (38), 175 (62), 149 (95), 131 (62), 107 (61), 101 (80), 93 (100), 75 (81); HRMS (EI): calcd for $C_{19}H_{36}O_2Si$ 324.2485, found 324.2469.

(3a*R*,4*R*,5*R*,7a*S*)-4-Iodomethyl-5-isopropyl-7a-methylhexahydrobenzofuran-2-one (12)

Hexamethyldisilane (0.1 mL, 0.49 mmol) was added to a stirred solution of lactone **7** (60 mg, 0.29 mmol) in chloroform (3 mL). Iodine (55 mg, 0.22 mmol) was added and the reaction mixture was heated under refluxing for 2 days. Water and DCM were added and the two layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were washed with an aqueous solution of $Na_2S_2O_3$ (10%). They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (9 : 1 petroleum ether : ethyl acetate) to give the product **12** as a colourless oil (82 mg, 84%). IR (ν_{max}/cm^{-1}): 2958, 2872, 1776, 1260, 1170, 934; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.44 (1H, dd, J = 3.4, 10.8 Hz, 4-CH_2), 3.20 (1H, dd, J = 2.0, 10.8 Hz, 4-CH_2), 2.95 (1H, dd, J = 7.1, 17.6 Hz, H-3), 2.24 (2H, m, H-3′ and H-7), 2.08 (1H, dd, J = 7.1, 10.1 Hz, H-3a), 1.84 (1H, m, C*H*(CH_3)$_2$), 1.50 (2H, m, H-7′ and H-6), 1.39 (3H, s, 7a-CH_3), 1.28 (1H, m, H-6′), 1.15 (1H, m, H-5), 0.96 (3H, d, J = 6.9 Hz, CH(CH_3)$_2$), 0.74 (3H, d, J = 7.0 Hz, CH(CH_3)$_2$), 0.54 (1H, m, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4 (C-2), 85.4 (C-7a), 45.1 (C-3a), 44.2 (C-5), 40.4 (C-4), 36.9 (C-3), 34.8 (C-7), 27.6 (7a-CH_3), 26.1 (*C*H(CH_3)$_2$), 21.3 and 14.8 (CH(*C*H_3)$_2$), 17.9 (C-6), 13.8 (4-CH_2); EIMS (*m*/*z*, %): 337 (M^++1, 68), 336 (M^+, 42), 321 (77), 209 (86), 153 (89), 109 (87), 83 (100), 69 (87); HRMS(EI): calcd for $C_{13}H_{21}O_2I$ 336.0586, found 336.0597.

(1*S,2*R**,4*S**,5*R**)-1-Methoxy-5-methyl-3,9-dioxatricyclo-[3.3.1.0^{2,4}]nonan-7-one (13)**

m-CPBA (1.23 g, 7.13 mmol) was added to a solution of **2** (200 mg, 1.19 mmol) in DCM (6.1 mL), then the reaction mixture was heated under refluxing for 5 days. An aqueous solution of Na_2SO_3 (10%) was added to quench the reaction, followed by DCM. The two layers formed were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with an aqueous solution of Na_2SO_3 (10%), followed by saturated aqueous $NaHCO_3$ solution and brine. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1 petroleum ether : diethyl ether) to give product **13** as a colourless oil (140 mg, 64%). IR (ν_{max}/cm^{-1}): 2963, 2853, 1717, 1312, 1261, 1089, 803; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.59 (3H, s, OCH_3), 3.44 and 3.30 (2H, 2d, J = 3.0 Hz, H-2 and H-4), 2.63 and 2.58 (2H, 2d, J = 17.0 Hz, H-8 and H-8′), 2.48 and 2.35 (2H, 2d, J = 17.0 Hz, H-6 and H-6′), 1.46 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.6 (C-7), 102.3 (C-1), 74.8 (C-5), 54.6 (C-4), 53.6 (C-2), 52.9 (OCH_3), 48.0 (C-8), 47.6 (C-6), 19.9 (CH_3).

(1*S,2*R**,6*S**,7*R**)-1-Methoxy-4,4,7-trimethyl-3,5,11-trioxatricyclo[5.3.1.0^{2,6}]undecan-9-one (14)**

A stirred solution of the ketone **2** (2.94 g, 17.5 mmol) and 4-methylmorpholine *N*-oxide (2.46 g, 21.0 mmol) in a mixture of THF (47.2 mL) and water (5.3 mL) was cooled with a water bath. Osmium tetroxide (2.5 wt% solution in 2-methylpropan-2-ol) (2.8 mL, 0.22 mmol) was added dropwise and after stirring the reaction mixture at room temperature for 5 days, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to give the diol as a colourless oil (3.35 g, 95%). A solution of the diol (3.35 g, 16.58 mmol) in 2,2-dimethoxypropane (41.5 mL) was cooled to 0 °C. *p*-Toluenesulfonic acid monohydrate (21 mg, 0.11 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 3 h, then the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 5 petroleum ether : ethyl acetate) to give the product **14** as a viscous colourless oil (3.53 g, 88%). IR (ν_{max}/cm^{-1}): 2984, 2938, 1721, 1379, 1269, 1211, 1079, 873; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.33 and 4.19 (2H, 2d, J = 5.8 Hz, H-2 and H-6), 3.59 (3H, s, OCH_3), 2.81 (1H, d, J = 14.9 Hz, H-10), 2.49 (1H, dd, J = 1.5, 14.9 Hz, H-10′), 2.46 (1H, d, J = 15.7 Hz, H-8), 2.31 (1H, dd, J = 1.5, 15.7 Hz, H-8′), 1.57 and 1.30 (6H, 2s, 4-(CH_3)$_2$), 1.45 (3H, s, 7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3 (C-9), 113.0 (C-4), 104.4 (C-1), 83.6 (C-6), 83.3 (C-2), 78.8 (C-7), 52.3 (OCH_3), 51.2 (C-8), 48.8 (C-10), 26.0 and 24.9 (4-(CH_3)$_2$), 19.9 (7-CH_3); EIMS (*m*/*z*, %): 243 (M^+ + 1, 17), 227 (38), 184 (57), 166 (72), 141 (85), 124 (86), 100 (83), 85 (85), 69 (74), 55 (71), 41 (87), 29 (100); Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.35; H, 7.31%.

(1*S,2*R**,6*S**,7*R**)-*tert*-Butyl(1-methoxy-4,4,7-trimethyl-3,5,11-trioxatricyclo[5.3.1.0^{2,6}]undec-8-en-9-yloxy)dimethylsilane (15a) and (1*R**,2*S**,6*R**, 7*S**) *tert*-Butyl(7-methoxy-1,4,4-trimethyl-3,5,11-trioxatricyclo[5.3.1.0^{2,6}]undec-8-en-9-yloxy)dimethylsilane (15b)**

A solution of **14** (76 mg, 0.31 mmol) in THF (0.19 mL) was added dropwise to freshly prepared lithium diisopropylamide solution (0.38 mmol) in THF (1.38 mL) at −78 °C. The reaction mixture was stirred for 30 minutes before addition of *tert*-butyldimethylsilyl trifluoromethanesulphonate (79 μL, 0.35 mmol) dropwise. It was allowed to warm to room temperature

and stirred for a further 2.5 h. Saturated aqueous $NaHCO_3$ solution was added to quench the reaction, followed by pentane and the two layers formed were separated. The aqueous layer was extracted with pentane and the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 2 petroleum ether : diethyl ether) to give the product **15a** as a colourless oil (10 mg, 9%) and its isomer **15b** as a white solid (16 mg, 14%), and some starting material was recovered. **15a**, IR (ν_{max}/ cm^{-1}): 2932, 2859, 1655, 1362, 1256, 1178, 1074, 841; ^{1}H NMR (500 MHz, C_6D_6): δ 4.80 (1H, t, J = 0.7 Hz, H-8), 4.25 and 4.18 (2H, 2d, J = 5.7 Hz, H-2 and H-6), 3.59 (3H, s, OCH_3), 2.72 (1H, dd, J = 1.9, 16.8 Hz, H-10), 1.92 (1H, dd, J = 0.8, 16.8 Hz, H-10′), 1.59 and 1.25 (6H, 2s, 4-$(CH_3)_2$), 1.50 (3H, s, 7-CH_3), 0.92 (9H, s, Si$C(CH_3)_3$), 0.047 and 0.043 (6H, 2s, Si$(CH_3)_2$); ^{13}C NMR (125 MHz, C_6D_6): δ 150.2 (C-9), 112.5 (C-4), 109.3 (C-8), 103.6 (C-1), 86.9 and 85.6 (C-2 and C-6), 77.3 (C-7), 51.7 (OCH_3), 38.9 (C-10), 26.5 and 25.7 (4-$(CH_3)_2$), 25.6 (Si$C(CH_3)_3$), 19.2 (7-CH_3), 18.0 (Si$C(CH_3)_3$), −4.5 and −4.7 (Si$(CH_3)_2$); ESIMS (m/z, %): 357 ([M + H]$^+$, 33); **15b**, Mp: 64–65 °C; IR (ν_{max}/ cm^{-1}): 2932, 2858, 1655, 1362, 1255, 1178, 1074, 840; ^{1}H NMR (500 MHz, C_6D_6): δ 5.00 (1H, t, J = 0.9 Hz, H-8), 4.46 and 3.97 (2H, 2d, J = 5.7 Hz, H-2 and H-6), 3.52 (3H, s, OCH_3), 2.26 (1H, dd, J = 2.0, 17.2 Hz, H-10), 1.57 (1H, d, J = 17.2 Hz, H-10′), 1.58 and 1.23 (6H, 2s, 4-$(CH_3)_2$), 1.40 (3H, s, 1-CH_3), 0.93 (9H, s, Si$C(CH_3)_3$), 0.06 and 0.05 (6H, 2s, Si$(CH_3)_2$); ^{13}C NMR (125 MHz, C_6D_6): δ 152.5 (C-9), 112.5 (C-4), 107.1 (C-8), 104.0 (C-7), 86.2 and 85.7 (C-2 and C-6), 78.5 (C-1), 52.1 (OCH_3), 41.2 (C-10), 26.6 (4-$(CH_3)_2$), 25.6 (4-$(CH_3)_2$ and Si$C(CH_3)_3$), 21.0 (1-CH_3), 18.0 (Si$C(CH_3)_3$), −4.5 and −4.8 (Si$(CH_3)_2$); ESIMS (m/z, %): 357 ([M + H]$^+$,100).

(1*S**,2*R**,6*S**,7*R**)-1-Methoxy-4,4,7-trimethyl-3,5,9,12-tetraoxatricyclo[5.4.1.0^{2,6}]dodecan-10-one (16)

m-CPBA (14.55 g, 84.3 mmol) was added to a stirred solution of acetonide **14** (3.40 g, 14.05 mmol) in DCE (112.4 mL) at room temperature. The reaction mixture was refluxed for 20 h. It was then cooled to 0 °C and quenched with 10% aqueous Na_2SO_3 solution, DCM was added and the two layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine successively. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 7 petroleum ether : ethyl acetate) to give the product **16** as a white solid (1.38 g, 38%). Mp: 101–103 °C; IR (ν_{max}/cm^{-1}): 2988, 2941, 1742, 1377, 1260, 1211, 1084, 875; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.72 and 4.59 (2H, 2d, J = 5.8 Hz, H-2 and H-6), 4.32 and 4.12 (2H, 2d, J = 13.4 Hz, H-8 and H-8′), 3.53 (3H, s, OCH_3), 3.27 (1H, d, J = 15.4 Hz, H-11), 3.10 (1H, d, J = 15.4 Hz, H-11′), 1.55 and 1.37 (6H, 2s, 4-$(CH_3)_2$), 1.33 (3H, s, 7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1 (C-10), 113.2 (C-4), 102.6 (C-1), 83.8 and 82.0 (C-2 and C-6), 81.1 (C-7), 75.7 (C-8), 52.3 (OCH_3), 48.0 (C-11), 25.8 and 24.7 (4-$(CH_3)_2$), 17.8 (7-CH_3); EIMS (m/z, %): 259 (M^++1, 2), 243 (5), 201 (7), 169 (10), 141 (56), 125 (55), 99 (83), 83 (75), 71 (79), 59 (78), 42 (100); Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 56.07; H, 7.01%.

(3a*R**,4*S**,6*R**,6a*S**)-(6-Hydroxymethyl-4-methoxy-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)acetic acid methyl ester (17)

Potassium carbonate (546 mg, 3.95 mmol) was added to a stirred solution of lactone **16** (2.04 g, 7.90 mmol) in methanol (79.0 mL) and the reaction mixture was stirred at room temperature for 1 h. Water was added and the mixture was extracted with DCM. The combined organic extracts were washed with brine. The extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 7 petroleum ether : ethyl acetate) to give the product **17** as a white solid (2.05 g, 89%). Mp: 48–49 °C; IR (ν_{max}/cm^{-1}): 3482, 2982, 2939, 1733, 1439, 1372, 1215, 1101, 1047, 870; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.84 (2H, 2d, J = 7.1 Hz, H-3a and H-6a), 3.70 (3H, s, CO_2CH_3), 3.63 (2H, m, 6-CH_2 and OH), 3.47 (1H, m, 6-CH_2), 3.33 (3H, s, 4-OCH_3), 3.05 and 2.73 (2H, 2d, J = 16.3 Hz, 4-CH_2), 1.58 and 1.36 (6H, 2s, 2-$(CH_3)_2$), 1.27 (3H, s, 6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6 (C=O), 115.3 (C-2), 102.7 (C-4), 86.3 (C-6), 84.3 and 82.3 (C-3a and C-6a), 69.1 (6-CH_2), 52.2 (CO_2CH_3), 48.6 (4-OCH_3), 37.2 (4-CH_2), 25.8 and 25.5 (2-$(CH_3)_2$), 18.3 (6-CH_3); ESIMS (m/z, %): 313 ([M + Na]$^+$, 100).

(3a*R**,4*S**,6*S**,6a*S**)-(6-Formyl-4-methoxy-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)acetic acid methyl ester (18)

A solution of DMSO (0.74 mL, 10.35 mmol) in DCM (15.0 mL) was cooled at −78 °C, before adding oxalyl chloride (0.60 mL, 6.90 mmol) dropwise. After stirring the reaction mixture for 10 minutes, a solution of **17** (1.00 g, 3.45 mmol) in DCM (8.0 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 30 minutes before addition of triethylamine (1.92 mL, 13.80 mmol) dropwise, then it was stirred for 10 minutes, allowed to warm to room temperature and stirred for a further 30 minutes. Water was added, followed by DCM and the two layers formed were separated. The aqueous layer was extracted with DCM and the combined organic extracts were washed with 5% aqueous citric acid solution, saturated aqueous $NaHCO_3$ solution and brine successively. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1 : 1 petroleum ether : ethyl acetate) to give the product **18** as a colourless oil (516 mg, 52%). IR (ν_{max}/cm^{-1}): 2900, 1735, 1215, 1046; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.50 (1H, s, CHO), 5.01 and 4.84 (2H, 2d, J = 6.9 Hz, H-3a and H-6a), 3.68 (3H, s, CO_2CH_3), 3.43 (3H, s, 4-OCH_3), 2.84 (2H, 2d, J = 15.3 Hz, 4-CH_2), 1.59 and 1.37 (6H, 2s, 2-$(CH_3)_2$), 1.38 (3H, s, 6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8 (CHO), 169.6 (CO_2CH_3), 115.1 (C-2), 104.3 (C-4), 88.1 (C-6), 84.0 and 81.0 (C-3a and C-6a), 51.9 (CO_2CH_3), 49.8 (4-OCH_3), 39.5 (4-CH_2), 25.54 and 25.48 (2-$(CH_3)_2$), 17.4 (6-CH_3); ESIMS (m/z, %): 311 ([M + Na]$^+$, 24).

(1*R*,5*R*,6*R*)-2-(6-Formyl-5-isopropyl-2-methylcyclohex-2-enyl)-*N*-methoxy-*N*-methylacetamide (19)

Oxalyl chloride (2.13 mL, 24.46 mmol) was added dropwise to a stirred solution of DMSO (2.60 mL, 36.69 mmol) in DCM (54.3 mL) at −78 °C. The mixture was stirred for 10 minutes, after which a solution of **8** (3.29 g, 12.23 mmol) in DCM (27.2 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 30 minutes and then triethylamine (6.82 mL, 48.92 mmol) was added dropwise and stirred for 10 minutes. It was allowed to warm to room temperature and stirred for 30 minutes. Water was added and the two layers formed were separated. The aqueous layer was extracted with DCM and the combined organic extracts were washed with 5% aqueous citric acid solution, saturated aqueous $NaHCO_3$ solution and brine successively. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 4 petroleum ether : ethyl acetate) to give **19** as a colourless oil (2.45 g, 75%). $[a]_D^{24}$ +68.0 (*c*. 0.4, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2961, 1718, 1656, 1458, 1386, 1111, 999, 668; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.72 (1H, d, J = 2.7 Hz, CHO), 5.41 (1H, br s, H-3), 3.68 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 3.00 (1H, m, H-1), 2.74 (2H, m, H-6 and 1-CH_2), 2.56 (1H, m, 1-CH_2), 2.08–1.80 (4H, m, H-4, H-4′, H-5 and C$H(CH_3)_2$), 1.71 (3H, s, 2-CH_3), 0.95

(3H, d, J = 6.6 Hz, $CH(CH_3)_2$), 0.82 (3H, d, J = 6.5 Hz, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2 (CHO), 173.4 (amide C=O), 134.6 (C-2), 122.1 (C-3), 61.3 (OCH_3), 52.3 (C-6), 36.2 (C-5), 33.5 (C-1), 32.4 (NCH_3), 31.9 (1-CH_2), 27.5 ($CH(CH_3)_2$), 24.2 (C-4), 21.7 (2-CH_3), 20.7 and 17.6 ($CH(CH_3)_2$); EIMS (m/z, %): 267 (M^+, 26), 239 (14), 206 (33), 147 (31), 135 (62), 121 (47), 103 (87), 93 (93), 81 (82), 61 (67), 43 (100); HRMS (EI): calcd for $C_{15}H_{25}NO_3$ 267.1834, found 267.1821.

(3a*R**,4*S**,6*R**,6a*S**)-[6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxy-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]acetic acid methyl ester (20)

tert-Butyldimethylchlorosilane (1.02 g, 6.79 mmol) and imidazole (0.92 g, 13.58 mmol) were added to a stirred solution of **17** (1.64 g, 5.66 mmol) in DMF (11.3 mL) and the reaction mixture was stirred at room temperature for 18 h. Water and diethyl ether were added and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine. The extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 3 petroleum ether : diethyl ether) to give **20** as a white solid (2.12 g, 93%). Mp: 53–55 °C; IR (ν_{max}/cm^{-1}): 2933, 2859, 1746, 1460, 1378, 1252, 1110, 1049, 840; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 and 4.60 (2H, 2d, J = 6.8 Hz, H-3a and H-6a), 3.68 (3H, s, CO_2CH_3), 3.45 (2H, 2d, J = 10.3 Hz, 6-CH_2), 3.35 (3H, s, 4-OCH_3), 2.91 and 2.65 (2H, 2d, J = 14.4 Hz, 4-CH_2), 1.56 and 1.36 (6H, 2s, 2-$(CH_3)_2$), 1.26 (3H, s, 6-CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.06 and 0.05 (6H, 2s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6 (C=O), 114.4 (C-2), 103.7 (C-4), 85.1 and 82.6 (C-3a and C-6a), 84.7 (C-6), 69.2 (6-CH_2), 51.7 (CO_2CH_3), 48.9 (4-OCH_3), 39.9 (4-CH_2), 25.9, 25.8 and 25.7 (2-$(CH_3)_2$ and $SiC(CH_3)_3$), 18.6 (6-CH_3), 18.3 ($SiC(CH_3)_3$), −5.4 and −5.5 ($Si(CH_3)_2$); ESIMS (m/z, %): 427 ([M + Na]$^+$, 100).

(3a*R**,4*S**,6*R**,6a*S**)-2-[6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxy-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-1-ethanol (21)

A solution of ester **20** (450 mg, 1.11 mmol) in THF (4.4 mL) was added dropwise to a slurry of lithium aluminium hydride (84 mg, 2.22 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then a large excess of methanol was added to quench the reaction and the solid was filtered through a pad of Celite and washed with diethyl ether. The filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10 : 4 petroleum ether : ethyl acetate) to give the product **21** as a white solid (397 mg, 95%). Mp: 60–62 °C; IR (ν_{max}/cm^{-1}): 3446, 2933, 2859, 1458, 1377, 1254, 1102, 1056, 839; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.63 and 4.59 (2H, 2d, J = 6.8 Hz, H-3a and H-6a), 3.71 (2H, m, CH_2OH), 3.52 and 3.50 (2H, 2d, J = 10.5 Hz, 6-CH_2), 3.31 (3H, s, OCH_3), 2.77 (1H, t, J = 6.6 Hz, OH), 2.04 (1H, ddd, J = 3.7, 5.7, 14.7 Hz, 4-CH_2), 1.86 (1H, ddd, J = 4.4, 8.3, 14.7 Hz, 4-CH_2), 1.57 and 1.35 (6H, 2s, 2-$(CH_3)_2$), 1.27 (3H, s, 6-CH_3), 0.91 (9H, s, $SiC(CH_3)_3$), 0.08 and 0.07 (6H, 2s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 115.0 (C-2), 105.4 (C-4), 85.2 and 82.3 (C-3a and C-6a), 84.8 (C-6), 69.3 (6-CH_2), 58.7 (CH_2OH), 48.4 (OCH_3), 35.4 (4-CH_2), 25.94, 25.87 and 25.6 ($SiC(CH_3)_3$ and 2-$(CH_3)_2$), 18.5 (6-CH_3), 18.4 ($SiC(CH_3)_3$), −5.4 and −5.6 ($Si(CH_3)_2$); ESIMS (m/z, %): 399 ([M + Na]$^+$, 80).

(3a*R**,4*S**,6*R**,6a*S**)-[6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methoxy-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]acetaldehyde (22)

A solution of DMSO (283 μL, 3.99 mmol) in DCM (5.91 mL) was cooled to −78 °C before addition of oxalyl chloride (232 μL, 2.66 mmol) dropwise. After stirring the reaction mixture for 10 minutes, a solution of **21** (500 mg, 1.33 mmol) in DCM (2.96 mL) was added dropwise. The reaction mixture was stirred for 30 minutes, then triethylamine (742 μL, 5.32 mmol) was added dropwise and the mixture was stirred for 10 minutes. It was allowed to warm to room temperature and stirred for a further 30 minutes. Water was added, followed by DCM and the two layers formed were separated. The aqueous layer was extracted with DCM and the combined organic extracts were washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ solution and brine successively. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 1 petroleum ether : ethyl acetate) to give the product **22** as a white solid (404 mg, 81%). Mp: 52–54 °C; IR (ν_{max}/cm^{-1}): 2933, 2858, 1726, 1379, 1253, 1105, 839, 779; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.73 (1H, dd, J = 2.5, 3.4 Hz, CHO), 4.63 (2H, 2d, J = 6.7 Hz, H-3a and H-6a), 3.51 (2H, 2d, J = 10.4 Hz, 6-CH_2), 3.35 (3H, s, OCH_3), 2.83 (1H, dd, J = 3.5, 15.4 Hz, 4-CH_2), 2.71 (1H, dd, J = 2.4, 15.4 Hz, 4-CH_2), 1.58 and 1.35 (6H, 2s, 2-$(CH_3)_2$), 1.27 (3H, s, 6-CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.07 and 0.05 (6H, 2s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.4 (CHO), 114.9 (C-2), 103.5 (C-4), 85.9 and 82.5 (C-3a and C-6a), 85.4 (C-6), 69.4 (6-CH_2), 49.0 (OCH_3), 48.5 (4-CH_2), 25.9 ($SiC(CH_3)_3$), 25.64 and 25.60 (2-$(CH_3)_2$), 18.5 (6-CH_3), 18.3 ($SiC(CH_3)_3$), −5.4 and −5.6 ($Si(CH_3)_2$); ESIMS (m/z, %): 397 ([M + Na]$^+$, 3), 343 (100).

(3a*R**,6*R**,6a*S**)-*cis*- and *trans*-[6-(*tert*-Butyldimethylsilanyloxymethyl)-2,2,6-trimethyldihydrofuro[3,4-*d*][1,3]dioxol-4-ylidene]acetaldehyde (23a,b)

Piperidine (23 μL, 0.23 mmol) was added dropwise to a stirred solution of aldehyde **19** (61 mg, 0.23 mmol) and aldehyde **22** (85.3 mg, 0.23 mmol) in benzene (0.76 mL). Acetic acid (13 μL, 0.23 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. It was then poured onto saturated aqueous $NaHCO_3$ solution, diethyl ether was added and the two layers were separated. The aqueous layer was extracted twice with diethyl ether and the combined organic extracts were washed with brine. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 : 3 ⟶ 10 : 4 petroleum ether : ethyl acetate) to give a mixture of isomers **23a** and **23b** as a white solid (8 : 3, 22 mg, 28%) and recovered starting material **19** (37 mg, 61%). IR (ν_{max}/cm^{-1}): 2933, 2858, 1670, 1639, 1337, 1220, 1092, 839; ^{1}H NMR (500 MHz, C_6D_6): **23a**, δ 10.37 (1H, d, J = 8.5 Hz, CHO), 5.84 (1H, dd, J = 1.4, 8.5 Hz, CH=C), 5.56 (1H, dd, J = 1.4, 5.9 Hz, H-3a), 4.28 (1H, d, J = 5.9 Hz, H-6a), 3.23 and 3.08 (2H, 2d, J = 10.8 Hz, 6-CH_2), 1.29 and 1.19 (6H, 2s, 2-$(CH_3)_2$), 1.14 (3H, s, 6-CH_3), 0.78 (9H, s, $SiC(CH_3)_3$), −0.145 and −0.155 (6H, 2s, $Si(CH_3)_2$); **23b**, δ 10.44 (1H, d, J = 8.3 Hz, CHO), 5.56 (1H, dd, J = 0.8, 8.3 Hz, CH=C), 5.17 (1H, dd, J = 0.8, 5.7 Hz, H-3a), 4.19 (1H, d, J = 5.7 Hz, H-6a), 3.27 and 3.09 (2H, 2d, J = 10.9 Hz, 6-CH_2), 1.31 and 1.20 (6H, 2s, 2-$(CH_3)_2$), 1.16 (3H, s, 6-CH_3), 0.77 (9H, s, $SiC(CH_3)_3$), −0.145 and −0.151 (6H, 2s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, C_6D_6): **23a**, δ 189.4 (CHO) 178.8 (C-4), 113.2 (C-2), 104.3 (CH=C), 91.7 (C-6), 81.6 (C-6a), 81.2 (C-3a), 69.1 (6-CH_2), 26.9 and 26.0 (2-$(CH_3)_2$), 25.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 16.2 (6-CH_3), −5.7 and −6.0 ($Si(CH_3)_2$); **23b**, δ 187.7 (CHO), 175.1 (C-4), 113.0 (C-2), 102.7 (CH=C), 92.9 (C-6), 83.1 (C-3a), 80.7 (C-6a), 69.0 (6-CH_2), 27.1 and 26.2 (2-$(CH_3)_2$), 25.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 16.4 (6-CH_3), −5.7 and −6.0 ($Si(CH_3)_2$); ESIMS (m/z, %): 343 ([M + H]$^+$, 100).

(1*R*,5*R*,6*R*)-2-(5-Isopropyl-2-methyl-6-vinylcyclohex-2-enyl)-*N*-methoxy-*N*-methylacetamide (24)

n-Butyllithium (2.5 M solution in hexanes) (1.68 mL, 4.20

mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (1.50 g, 4.20 mmol) in THF (7.6 mL) at 0 °C. The mixture was stirred for 30 minutes and then it was allowed to room temperature and stirred for further 30 minutes. A solution of **19** (1.02 g, 3.82 mmol) in THF (7.6 mL) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. Water and diethyl ether were added and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 2 petroleum ether : ethyl acetate) to give **24** as a colourless oil (0.73 g, 72%). $[a]_D^{24}$ +114.8 (*c*. 0.4, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2959, 1669, 1460, 1417, 1177, 1107, 1384, 1003, 912; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (1H, dt, J = 10.0, 17.1 Hz, C*H*=CH$_2$), 5.38 (1H, br s, H-3), 5.07 (1H, dd, J = 2.1, 17.1 Hz, CH=C*H*$_2$), 5.01 (1H, dd, J = 2.1, 10.2 Hz, CH=C*H*$_2$), 3.67 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 2.75 (1H, m, H-1), 2.58 (1H, m, 1-CH$_2$), 2.39 (2H, m, H-6 and 1-CH$_2$), 1.99 (1H, m, H-4), 1.88 (1H, m, H-4′), 1.76 (1H, m, C*H*(CH$_3$)$_2$), 1.65 (3H, s, 2-CH$_3$), 1.45 (1H, m, H-5), 0.93 (3H, d, J = 6.7 Hz, CH(C*H*$_3$)$_2$), 0.76 (3H, d, J = 6.7 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C=O), 140.4 (*C*H=CH$_2$), 135.7 (C-2), 121.9 (C-3), 116.0 (CH=*C*H$_2$), 61.3 (OCH_3), 45.0 (C-6), 39.6 (C-5), 38.5 (C-1), 32.6 (NCH_3), 32.3 (1-CH$_2$), 27.8 (*C*H(CH$_3$)$_2$), 24.1 (C-4), 22.1 (2-CH$_3$), 21.0 and 16.9 (CH(*C*H$_3$)$_2$); ESIMS (*m*/*z*, %): 266 ([*M* + H]$^+$, 100).

(1*R*,5*R*,6*R*)-(5-Isopropyl-2-methyl-6-vinylcyclohex-2-enyl)-acetalaldehyde (25)

DIBAL-H (1.0 M solution in hexanes) (5.36 mL, 5.36 mmol) was added dropwise to a stirred solution of **24** (710 mg, 2.68 mmol) in DCM (13.4 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and then it was allowed to warm to 0 °C and stirred for 1 h. A large excess of methanol was added at 0 °C and the aluminium salts that precipitated were filtered through a pad of Celite. The solid was washed several times with diethyl ether and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (30 : 1 petroleum ether : diethyl ether) to give the product **25** as a colourless oil (303 mg, 55%). $[a]_D^{24}$ +206.5 (*c*. 0.2, $CHCl_3$); IR (ν_{max}/cm^{-1}): 2959, 2892, 1725, 1465, 1386, 1009, 916; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.73 (1H, dd, J = 1.9, 2.9 Hz, CHO), 5.69 (1H, dt, J = 10.0, 17.1 Hz, C*H*=CH$_2$), 5.44 (1H, br s, H-3), 5.10 (1H, ddd, J = 0.7, 2.0, 17.1 Hz, CH=C*H*$_2$), 5.06 (1H, dd, J = 2.0, 10.2 Hz, CH=C*H*$_2$), 2.64 (1H, m, H-1), 2.55 (1H, ddd, J = 2.9, 8.0, 16.7 Hz, 1-CH$_2$), 2.37 (2H, m, H-6 and 1-CH$_2$), 1.97 (1H, m, H-4), 1.86 (1H, m, H-4′), 1.79 (1H, m, C*H*(CH$_3$)$_2$), 1.66 (3H, s, 2-CH$_3$), 1.47 (1H, m, H-5), 0.91 (3H, d, J = 7.0 Hz, CH(C*H*$_3$)$_2$), 0.73 (3H, d, J = 6.7 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.1 (CHO), 140.4 (*C*H=CH$_2$), 134.4 (C-2), 122.8 (C-3), 116.8 (CH=*C*H$_2$), 45.5 (C-6), 44.6 (1-CH$_2$), 39.5 (C-1), 38.3 (C-5), 27.6 (*C*H(CH$_3$)$_2$), 23.9 (C-4), 21.9 (2-CH$_3$), 21.0 and 15.7 (CH(*C*H$_3$)$_2$); EIMS (*m*/*z*, %): 206 (M$^+$, 22), 189 (31), 162 (77), 145(89), 119 (97), 91 (82), 81 (98), 43 (100); HRMS (EI): calcd for $C_{14}H_{22}O$ 206.1671, found 206.1672.

(1*R*,5*R*,6*R*)-(5-Isopropyl-2-methyl-6-vinylcyclohex-2-enyl)acetic acid (26)

2-Methylbut-2-ene (85%) (2.94 mL, 23.59 mmol) was added to a stirred solution of **25** (103 mg, 0.50 mmol) in 2-methylpropan-2-ol (10.0 mL). An aqueous solution (4 mL) of sodium chlorite (509 mg, 4.5 mmol) and sodium dihydrogenphosphate (408 mg, 3.4 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 2.5 h. The solvent was evaporated under reduced pressure and the residue was dissolved in water. Hexane was added and the two layers separated. The aqueous layer was extracted with hexane and the combined organic extracts were washed with brine. It was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure to give the acid **26** as a colourless oil (94 mg, 85%), which was used directly without further purification. $[a]_D^{24}$ +22.3 (*c*. 0.4, $CHCl_3$); IR (ν_{max}/cm^{-1}): 3500–2400, 2960, 1708, 1414, 1297, 1231, 1006, 915; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (1H, dt, J = 10.0, 17.1 Hz, C*H*=CH$_2$), 5.41 (1H, br s, H-3), 5.11 (1H, dd, J = 2.0, 17.1 Hz, CH=C*H*$_2$), 5.05 (1H, dd, J = 2.0, 10.2 Hz, CH=C*H*$_2$), 2.60 (1H, m, H-1), 2.39 (3H, m, H-6 and 1-CH$_2$), 1.98 (1H, m, H-4), 1.85 (1H, m, H-4′), 1.75 (1H, m, C*H*(CH$_3$)$_2$), 1.68 (3H, s, 2-CH$_3$), 1.45 (1H, m, H-5), 0.91 (3H, d, J = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.75 (3H, d, J = 6.7 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.4 (CO_2H), 139.6 (*C*H=CH$_2$), 134.7 (C-2), 122.6 (C-3), 116.6 (CH=*C*H$_2$), 45.2 (C-6), 39.9 (C-1), 39.0 (C-5), 35.0 (1-CH$_2$), 27.7 (*C*H(CH$_3$)$_2$), 24.0 (C-4), 21.9 (2-CH$_3$), 20.9 and 16.4 (CH(*C*H$_3$)$_2$); EIMS (*m*/*z*, %): 222 (M$^+$, 10), 179 (37), 162 (39), 133 (63), 119 (66), 96 (77), 81 (89), 43 (100); HRMS (EI): calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1620.

(3a*S**,4*R**,6*S**,6a*R**)-*tert*-Butyl{6-methoxy-2,2,4-trimethyl-6-[2-(2-nitrophenylselanyl)ethyl]tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ylmethoxy}dimethylsilane (27)

o-Nitrophenylselenocyanate (217 mg, 0.95 mmol) was added to a stirred solution of alcohol **21** (300 mg, 0.80 mmol) in THF (2.65 mL). It was stirred at room temperature until all of the starting material was dissolved. Tri-*n*-butylphosphine (235 μL, 0.95 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. The solvent was then evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10 : 1.5 petroleum ether : ethyl acetate) to give the product **27** as a yellow viscous oil (0.35 g, 78%). IR (ν_{max}/cm^{-1}): 2933, 2858, 1592, 1515, 1333, 1252, 1107, 1038, 839; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (1H, dd, J = 1.4, 8.3 Hz, ArH), 7.59 (1H, dd, J = 1.2, 8.2 Hz, ArH), 7.51 (1H, m, ArH), 7.31 (1H, m, ArH), 4.66 and 4.54 (2H, 2d, J = 6.7 Hz, H-3a and H-6a), 3.50 (2H, s, 4-CH$_2$), 3.32 (3H, s, OCH_3), 2.93 (2H, m, CH_2Se), 2.33 (1H, ddd, J = 5.2, 12.2, 14.3 Hz, 6-CH$_2$), 1.92 (1H, ddd, J = 4.5, 12.0, 14.3 Hz, 6-CH$_2$), 1.61 and 1.37 (6H, 2s, 2-(CH$_3$)$_2$), 1.27 (3H, s, 4-CH$_3$), 0.89 (9H, s, SiC(CH$_3$)$_3$), 0.06 and 0.04 (6H, 2s, Si(CH$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8 (ArC), 133.65 (ArC), 133.57 (ArCH), 129.3 (ArCH), 126.4 (ArCH), 125.3 (ArCH), 114.7 (C-2), 105.6 (C-6), 85.4 and 82.7 (C-3a and C-6a), 84.7 (C-4), 69.4 (4-CH$_2$), 48.8 (OCH_3), 33.8 (6-CH$_2$), 26.0 (SiC(*C*H$_3$)$_3$), 25.8 and 25.7 (2-(CH$_3$)$_2$), 19.7 (CH_2Se), 18.5 (4-CH$_3$), 18.3 (Si*C*(CH$_3$)$_3$), −5.3 and −5.6 (Si(CH$_3$)$_2$); ESIMS (*m*/*z*, %): 584 ([*M* + Na]$^+$, 44), 530 (100).

(3aS*,4R*,6S*,6aR*)-*tert*-Butyl(6-methoxy-2,2,4-trimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ylmethoxy)dimethylsilane (28)

Hydrogen peroxide (30%) (0.34 mL, 3.33 mmol) was added dropwise to a solution of selenide **27** (350 mg, 0.63 mmol) in THF (6.3 mL) at 0 °C, then the reaction mixture was allowed to warm to room temperature and stirred for 5 h. It was quenched by addition of ice water and the mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10 : 1 petroleum ether : diethyl ether) to give **28** as a colourless oil (180 mg, 80%). IR (ν_{max}/cm^{-1}): 2933, 2859, 1462, 1378, 1253, 1103, 993, 840, 778; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (1H, dd, J = 10.7, 17.4 Hz, C*H*=CH$_2$), 5.48 (1H, dd, J = 1.9, 17.4 Hz, CH=C*H*$_2$), 5.25 (1H, dd, J = 1.9, 10.7 Hz, CH=C*H*$_2$), 4.65 and 4.49 (2H, 2d, J = 6.7 Hz, H-3a and H-6a), 3.54 and 3.51 (2H, 2d, J = 10.2 Hz, 4-CH$_2$), 3.25 (3H, s, OCH_3), 1.62 and 1.35 (6H, 2s, 2-(CH$_3$)$_2$), 1.29 (3H, s, 4-CH$_3$), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.06 and 0.05 (6H,

2s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.1 (*C*H=CH_2), 117.5 (CH=*C*H_2), 114.7 (C-2), 104.5 (C-6), 87.0 and 82.6 (C-3a and C-6a), 84.6 (C-4), 69.1 (4-CH_2), 49.4 (OCH_3), 25.8 and 25.7 ($SiC(CH_3)_3$ and 2-$(CH_3)_2$), 18.7 (4-CH_3), 18.2 ($SiC(CH_3)_3$), −5.4 and −5.6 ($Si(CH_3)_2$); ESIMS (*m*/*z*, %): 381 ([*M* + Na]$^+$, 2), 327 (100).

(3a*S,4*R**,6*S**,6a*R**)-(6-Methoxy-2,2,4-trimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]methanol (29)**

Tetra-*n*-butylammonium fluoride (1.0 M solution in THF) (0.75 mL, 0.75 mmol) was added dropwise to a stirred solution of **28** (180 mg, 0.50 mmol) in THF (3.4 mL), then the reaction mixture was stirred at room temperature for 30 minutes. Water was added, followed by ethyl acetate and the two layers formed were separated. The aqueous layer was extracted with ethyl acetate, then the combined organic extracts were washed with brine. They were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2 : 1 petroleum ether : ethyl acetate) to give the product **29** as a white solid (98 mg, 80%). Mp: 47–49 °C; IR (ν_{max}/cm^{-1}): 3483, 2983, 2937, 1458, 1379, 1215, 1100, 1046, 991, 868; ^1H NMR (500 MHz, C_6D_6): δ 5.75 (1H, dd, J = 10.8, 17.4 Hz, C*H*=CH_2), 5.37 (1H, dd, J = 1.8, 17.4 Hz, CH=C*H*$_2$), 4.99 (1H, dd, J = 1.8, 10.8 Hz, CH=C*H*$_2$), 4.58 and 4.46 (2H, 2d, J = 6.7 Hz, H-3a and H-6a), 3.29 (1H, dd, J = 3.8, 11.3 Hz, C*H*$_2$OH), 3.20 (1H, dd, J = 8.5, 11.3 Hz, C*H*$_2$OH), 3.18 (3H, s, OCH_3), 1.72 and 1.27 (6H, 2s, 2-$(CH_3)_2$), 1.38 (1H, m, CH_2OH), 1.33 (3H, s, 4-CH_3); ^{13}C NMR (125 MHz, C_6D_6): δ 137.6 (*C*H=CH_2), 116.8 (CH=*C*H_2), 115.2 (C-2), 105.0 (C-6), 87.4 and 83.1 (C-3a and C-6a), 84.9 (C-4), 69.2 (CH_2OH), 49.3 (OCH_3), 26.3 and 26.2 (2-$(CH_3)_2$), 18.8 (4-CH_3); HRMS (EI): calcd for $C_{12}H_{20}O_5$ 244.1311, found 244.1316.

(1*R*,3′a*S*,4′*R*,5*R*,6*R*,6′*S*,6′a*R*)-(5-Isopropyl-2-methyl-6-vinylcyclohex-2-enyl)acetic acid 6′-methoxy-2′,2′,4′-trimethyl-6′-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ylmethyl ester (30a) and (1*R*,3′a*R*,4′*S*,5*R*,6*R*,6′*R*,6′a*S*)-(5-isopropyl-2-methyl-6-vinylcyclohex-2-enyl)acetic acid 6′-methoxy-2′,2′,4′-trimethyl-6′-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ylmethyl ester (30b)

DCC (137 mg, 0.66 mmol) was added to a stirred solution of acid **26** (74 mg, 0.33 mmol) and alcohol **29** (81 mg, 0.33 mmol) in DCM (3.3 mL). DMAP (20 mg, 0.16 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. The solid formed was filtered and washed with diethyl ether and the filtrate was washed with saturated aqueous NH_4Cl solution. It was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 : 1 petroleum ether : ethyl acetate) to give an inseparable mixture of two diastereomers **30a** and **30b** (1 : 1) as a colourless oil (92 mg, 62%). IR (ν_{max}/cm^{-1}): 2958, 2937, 1740, 1458, 1379, 1252, 1154, 1105, 992, 869; ^1H NMR (500 MHz, $CDCl_3$): δ 5.84 (2H, 2dd, J = 6.2, 10.7 Hz, 6′-C*H*=CH_2), 5.75 (2H, 2dt, J = 10.1, 17.1 Hz, 6-C*H*=CH_2), 5.44 (2H, 2dd, J = 1.7, 7.4 Hz, 6′-CH=C*H*$_2$), 5.40 (2H, br s, H-3), 5.26 (2H, dt, J = 1.9, 10.7 Hz, 6′-CH=C*H*$_2$), 5.08 (2H, dd, J = 2.0, 17.1 Hz, 6-CH=C*H*$_2$), 5.03 (2H, dd, J = 2.0, 10.1 Hz, 6-CH=C*H*$_2$), 4.54 (2H, 2d, J = 6.7 Hz, H-3′a and H-6′a), 4.53 (2H, 2d, J = 6.7 Hz, H-3′a and H-6′a), 4.08 (2H, 2d, J = 11.4 Hz, 4′-CH_2), 3.97 (2H, 2d, J = 11.4 Hz, 4′-CH_2), 3.25 (6H, 2s, OCH_3), 2.57 (2H, m, H-1), 2.42–2.29 (6H, m, H-6 and 1-CH_2), 1.96 (2H, m, H-4), 1.88–1.68 (4H, m, H-4′ and C*H*$(CH_3)_2$), 1.64 (6H, s, 2-CH_3), 1.62 and 1.35 (12H, 2s, 2′-$(CH_3)_2$), 1.44 (2H, m, H-5), 1.38 (6H, s, 4′-CH_3), 0.91 (6H, 2d, J = 6.9 Hz, CH(C*H*$_3)_2$), 0.73 (6H, t, J = 6.9 Hz, CH(C*H*$_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3 (C=O), 140.0 and 139.9 (6-*C*H=CH_2), 136.9 (6′-*C*H=CH_2), 134.7 and 134.6 (C-2), 122.6 and 122.5 (C-3), 117.6 (6′-CH=*C*H_2), 116.3 and 116.2 (6-CH=*C*H_2), 115.3 (C-2′), 104.62 and 104.57 (C-6′), 86.90 and 86.86 (C-3′a or C-6′a), 82.8 (C-3′a or C-6′a), 82.61 and 82.57 (C-4′), 69.5 and 69.3 (4′-CH_2), 49.6 (OCH_3), 45.5 and 45.2 (C-6), 40.6 and 40.0 (C-1), 39.0 and 38.4 (C-5), 35.3 and 35.1 (1-CH_2), 27.7 (*C*H$(CH_3)_2$), 25.9 (2′-$(CH_3)_2$), 25.6 (2′-$(CH_3)_2$), 24.0 and 23.9 (C-4), 21.9 (2-CH_3), 21.0 and 20.9 (CH(*C*H$_3)_2$), 19.0 (4′-CH_3), 16.4 and 16.0 (CH(*C*H$_3)_2$); ESIMS (*m*/*z*, %): 471 ([*M* + Na]$^+$, 55), 417 (100).

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