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Towards the Total Synthesis of Vibsanin E, 15-*O*-Methylcyclovibsanin B, 3-Hydroxyvibsanin E, Furanovibsanin A, and 3-*O*-Methylfuranovibsanin A

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Studies detailing synthetic approaches to a variety of biosynthetically related vibsanin-type diterpenes (i.e. vibsanin E, 15-*O*-methylcyclovibsanin B, 3-hydroxy-vibsanin E, furanovibsanin A, and 3-*O*-methylfuranovibsanin A) are discussed. Biogenetically modelled approaches are coupled with an investigation of classical and modern six- to seven-membered ring-expansion protocols, which gain access to the central core of these natural products.

Introduction

Vibsane-type diterpenes can be regarded as quite rare natural products as they occur exclusively in *Viburnum* species such as *V. awabuki*,[1] *V. odoratissimum*[2] and *V. suspensum*.[3] This family maintain a wide variety of structure types which consist of nine structure subtypes, vibsanin B **1**,[1] vibsanin C **2**,[1] vibsanin E **3**,[1] vibsanin O **4**,[4] cyclovibsanin A **5**,[5] furanovibsanin D **6**,[6] spirovibsanin A **7**,[7] aldolvibsanin B **8**,[8] and neovibsanin A **9**[9] (Figure 1).

Our group has an attraction to caged bicyclic moieties within a natural product carbon skeleton[10] and as such we were attracted to the vibsanin family of molecules, especially those of type **3**, **5**, **6** and **7**[11] (Figure 1). More specifically, however, we targeted direct routes to advanced intermediates of vibsanin E **3**, 15-*O*-methylcyclovibsanin B **10**, 3-hydroxyvibsanin E **11**, furanovibsanin A **12**, and 3-*O*-methylfuranovibsanin A **13** (Figure 2), results of which are reported herein.

In the process of elucidating vibsane biochemical pathways Y. Fukuyama investigated the conversion of vibsanin C (**2**) to vibsanin E (**3**)[12] and found that conversion proceeded smoothly using borontrifluoride–diethyl ether, albeit in moderate yield (50%) (Scheme 1).

In addition to Fukuyama's biosynthetic insight above (Scheme 1), which is further summarized as path A (Scheme 2), he also postulated a relationship to the cyclovibsanins (e.g. **5**, **14**–**16**) originating from the same intermediate according to path B (Scheme 2).[5]

Fukuyama's very plausible biosynthetic relationships formed the basis of our retrosynthetic frame[13] (Scheme 3),

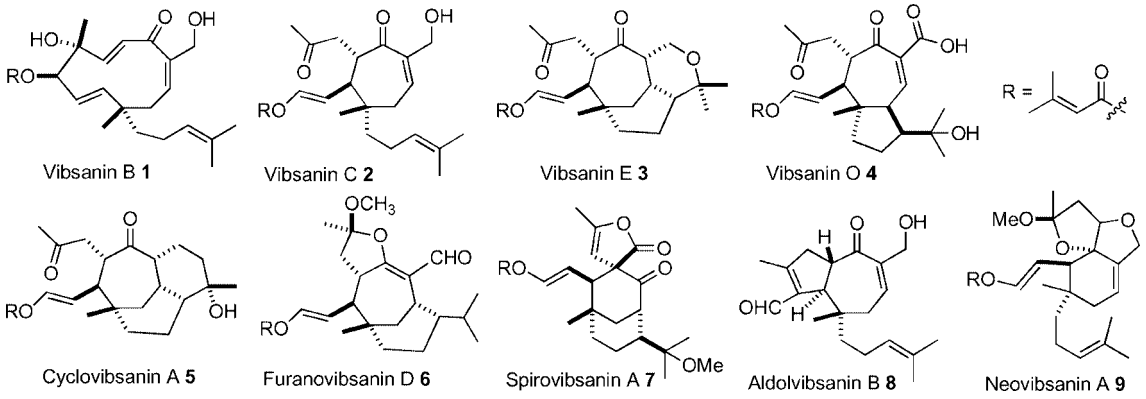

Figure 1. A collection of the structural diversity seen in the vibsanin type diterpene family.

in that the aim was to utilise functionality seen in vibsanin C (**2**) in the form of a six-membered ring **17** rather than a seven-membered ring. Different modes of cyclisation would then gain access to intermediates **18** and **20**, which would

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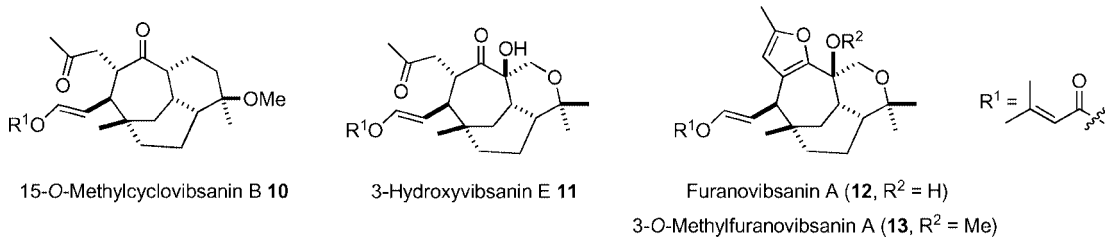
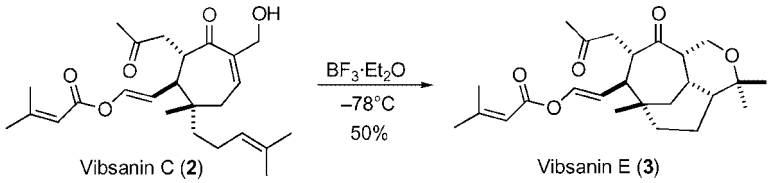
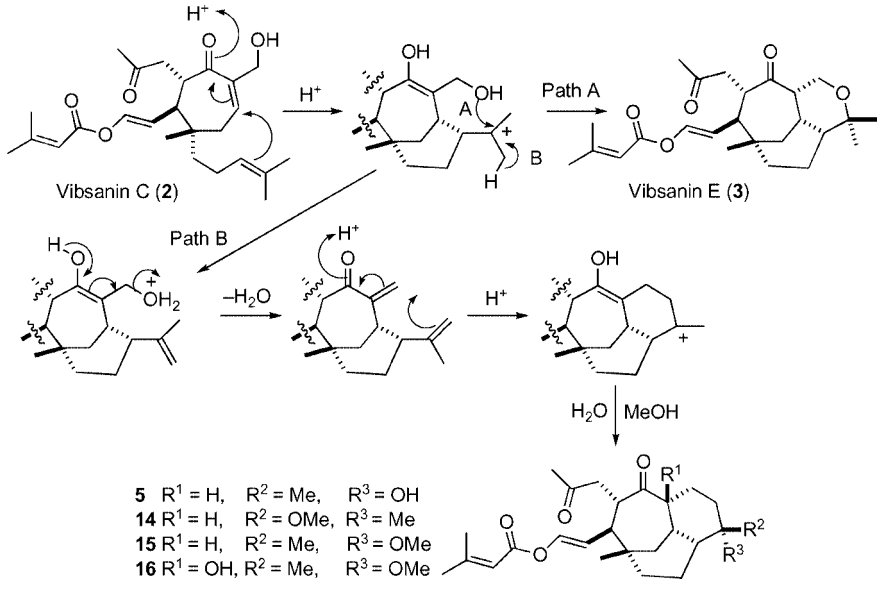


Figure 2. Vibsanin type diterpene synthetic targets.



Scheme 1.

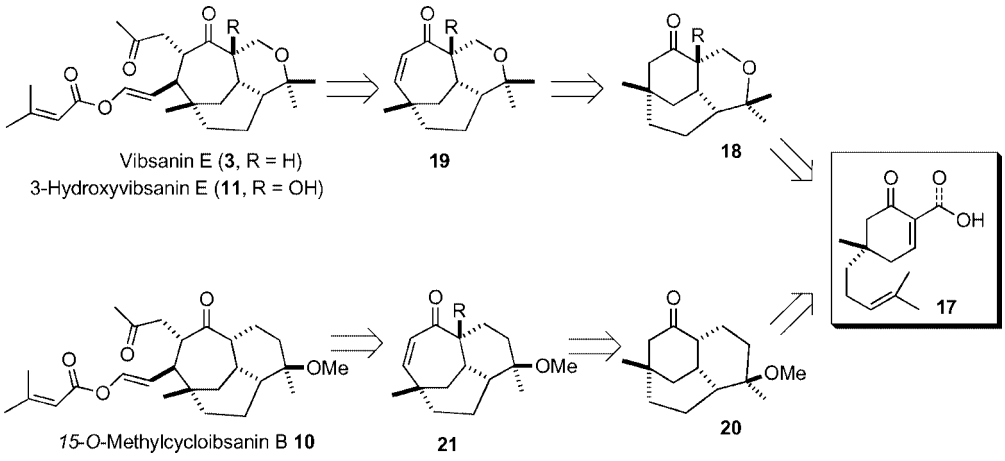


Scheme 2.

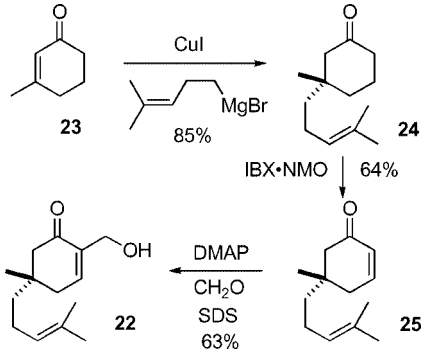
be subjected to ring expansion affording **19** and **21**. If this protocol found success, the approach could essentially be applied to total syntheses of multiple vibsanin targets (e.g. vibsanin E **3**, 3-hydroxyvibsanin E **11** and furanovibsanin A **12**).

Pivotal to the success of this endeavour was to gain access to cyclohexenones of type **17**. A number of direct approaches based on the carboxylic acid function were investigated, which consisted of attempts reliant on electrocyclic cyclisations or intramolecular Knoevenagel condensations but these failed. Utilising the El Gaïed[14] Baylis–Hillman protocol, however, furnished a cyclohexenone **22** containing the more desirable methylene hydroxy function. 3-Methylcyclohexenone (**23**) was treated with the homoprenylcuprate giving the 1,4-addition product **24** in 85% yield and subsequent dehydrogenation with IBX·NMO[15] afforded the α,β-unsaturated ketone **25** (64%). For the Baylis–Hillman reaction it was found that reaction of **25** using DMAP afforded the allylic alcohol **22** in 32% yield (43% based on recovered starting material). A number of other reported procedures either failed to react[16] or were lower yielding.[17] In the view that yields in the order of 32% are unsatisfactory for early stages of total syntheses we set about improving this result. Considering the substrate **25** is very lipophilic and the transition state for the Baylis–Hillman reaction is very polar surfactants [i.e. sodium dodecyl sulfate (SDS)] were employed so that the substrate could be dissolved in polar media (water). This change in conditions afforded **22** in over double the yield (63%), although on larger scale a lower yield of 53% was obtained which was still a major improvement (Scheme 4).[18]

Cyclisation studies involving cyclohexenone **22** utilising borontrifluoride–diethyl ether, as demonstrated by Fukuyama in the conversion of vibsanin C (**2**) to vibsanin E (**3**), gave cyclized material **26**, albeit only on small scale. Scaling up the reaction always gave unidentified material until it

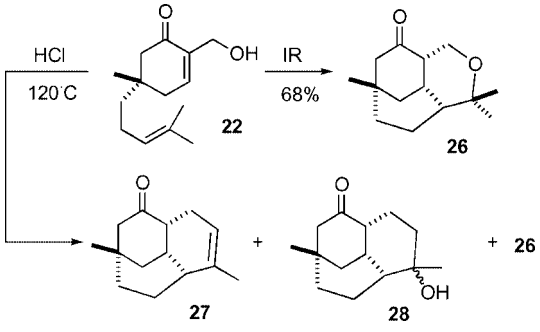


Scheme 3.



Scheme 4.

was realised that $BF_3{\cdot}Et_2O$ was most likely not the active agent, but rather hydrofluoric acid. Treating **22** with anhydrous ethereal hydrochloric acid conversely gave **26** in 58% yield, whereas simply stirring **22** in dichloromethane with Amberlyst® ion exchange resin afforded **26** in 68% (Scheme 5). In fact subsequent investigations showed that all synthetic operations starting from **23** could be performed without purification up to **26** making the whole sequence much more practical (22% overall yield).

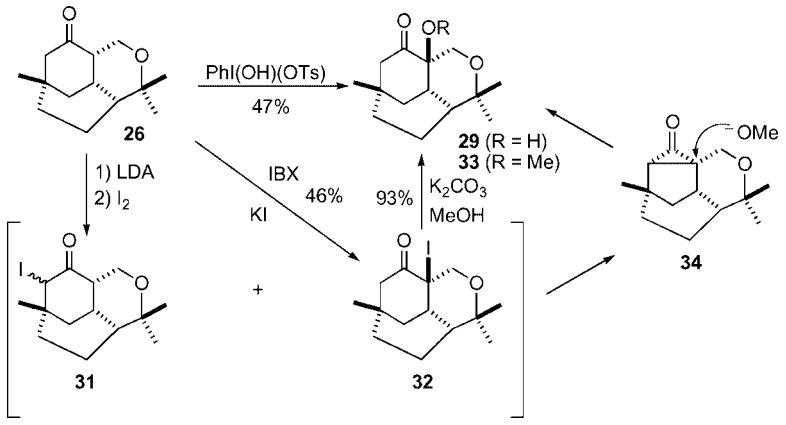


Scheme 5.

Initial attempts at utilising **22** to probe Fukuyama's vibsanin C (**2**) to cyclovibsanin biosynthetic postulate[19] were unsuccessful. It was first envisaged that treating **22** with a suitable protecting group (i.e. trifluoroacetyl) that would also act as leaving group might induce elimination, prevent cyclisation to **26** and afford the desired material, however, this failed. After much thought, in that protonated OH (i.e. ROH_2^+) also acts as a leaving group, **22** was heated in dioxane in the presence of 2 M hydrochloric acid, however, only the oxygenated tricycle **26** was obtained (68%). Increasing the temperature resulted in substantial decomposition. Although, when dioxane was removed and **22** (0.6 mmol) was heated in 3 M hydrochloric acid at 120 °C carbotricycle **27** was obtained in 67% along with **26** (10%). If the scale of the reaction was increased to 2.5 mmol **27** was obtained in 50%, and **26** in 15%, but this time the hydroxylated carbotricycle **28** was also formed in 14% (mixture of diastereoisomers, ca. 1:1; Scheme 5).

With precursor tricycles **26**–**28** in hand further elaboration of these ring systems **26**–**28** was required before ring expansion studies could be performed. For example, to gain access to the cores of 3-hydroxyvibsanin E **11**, furanovibsanin A **12**, and 3-*O*-methylfuranovibsanin A **13**, **26** must undergo regioselective alpha hydroxylation (or methoxylation). Tricycle **27** must also undergo regioselective hydroxylation (or methoxylation) for access to cyclovibsanins **5**, **14**–**16**. Even though **28** contains oxygen functionality at the required position it was not utilized further due to the low yield and lack of stereoselection.

In the case of **26** a number of alpha hydroxylation protocols were investigated. Koser's reagent[20] [PhI(OH)(OTs)] was found to be superior to that of Davis' reagent ($PhCHONSO_2Ph$)[21] (no reaction) and dimethyldioxirane[22] (mixture of regioisomers) in that only the desired regioisomer (i.e. **29**) was obtained, albeit in moderate yield (47%) (Scheme 6). It is worthy of note that to the best of our knowledge this is the first instance that Koser's reagent has given α-hydroxylation directly instead of the normal α-tosylation (which is applicable to 3-hydroxyvibsanin E **11**, furanovibsanin A **12**). Although access to the methoxy derivative (i.e. **33**) is conceivable via alcohol **29** a different route via iodides **31** and **32** was investigated to avoid the moderate yield of **29** (Scheme 6). Treating tricycle **26** with lithium diisopropylamide (LDA) at –78 °C followed by addition of iodine gave a mixture of iodides **31** and **32** in 80% and 14% yield respectively. The method of Pan et al.[23] was



Scheme 6.

also found to give iodide **32**, however, in much lower yield (46%). Initially we had assumed iodide **32**, when reacted with potassium carbonate in methanol, a slight modification to that of Fraser-Reid,[24] was responsible for the formation of **33** (X-ray crystal structure Figure 3) in 93% yield. This result was somewhat confusing as **33** maintained retention of stereochemistry. As both iodides are readily separable both were treated with potassium carbonate in methanol, which gave rise to the same product **33**. This result is easily explained in that a Favorskii type cyclopropanone **34** must have formed which was attacked by methanol (or KOMe) giving **33**. Surprisingly, the reaction did not work in the absence of potassium carbonate and treatment with sodium methoxide in methanol gives lower yields of **33** accompanied by an unidentified product, which is assumed to be associated with Favorskii ring contraction (Scheme 6).

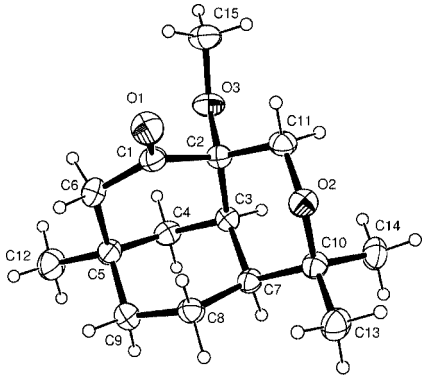
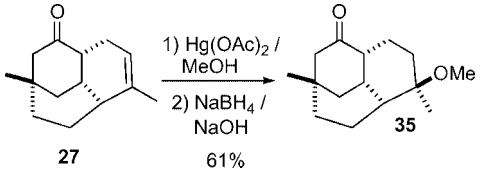


Figure 3. ORTEP3 drawing of compound **33** (30% probability ellipsoids).

Methoxy functionality was easily introduced into **27** both regioselectively and stereoselectively by treating **27** with mercuric acetate in methanol, followed by sodium hydroxide (3 M) and sodium borohydride,[25] which afforded **35** in 61% yield (Scheme 7).



Scheme 7.

Ring expansion studies were performed on **26** in the first instance and required considerable effort in determining the appropriate protocol. Attempts with stabilized carbenoids (e.g. EtO_2CCHN_2), known to insert regioselectively at the least-substituted carbon alpha to ketones, using $BF_3{\cdot}Et_2O$[26] or Meerwein's salt[27] failed, as did non-stabilized carbenoids,[28] ethyl diazolithioacetate[29] and silyloxycyclopropane homologation.[30] Considering Beckwith–Dowd[31] and variant[32] ring expansion protocols are widely reported, **26** was converted, using Mander's reagent[33] and subsequent retro Dieckmann/Dieckmann reaction, to **36** (X-ray crystal structure of α-CO_2Et, see Figure 4) in 69% overall yield. All attempts to convert **36** to the methylene iodide **37** or bromide **38** failed when **36** was reacted directly with diiodo- or dibromomethane. Reaction of **36** with formalin[34] gave the methylene hydroxy derivative **39** (84%), which using triphenylphosphane iodine and imidazole gave iodide **37** (75%). Unfortunately, treating iodide **37** with sa-

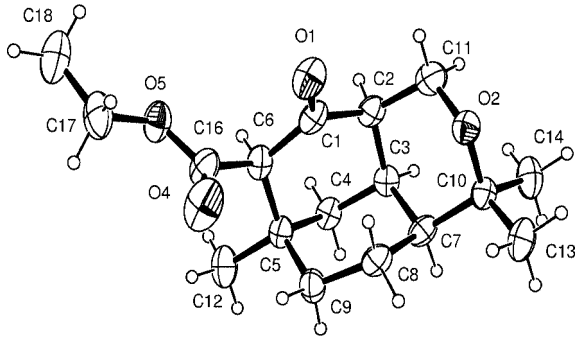
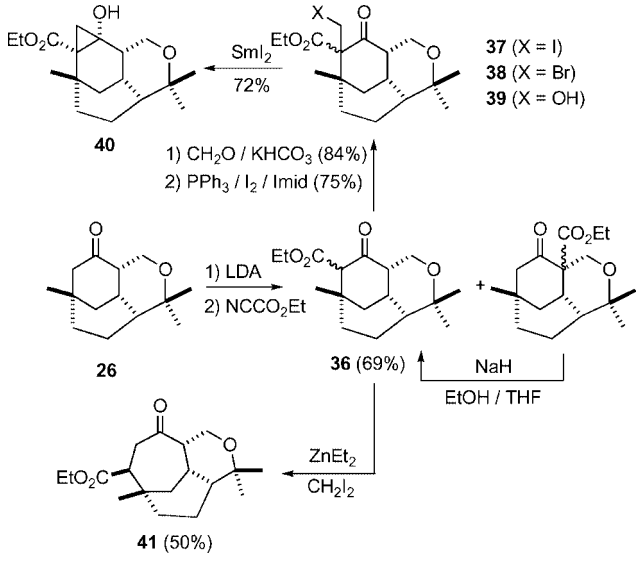


Figure 4. ORTEP3 drawing of compound **36** (30% probability ellipsoids).

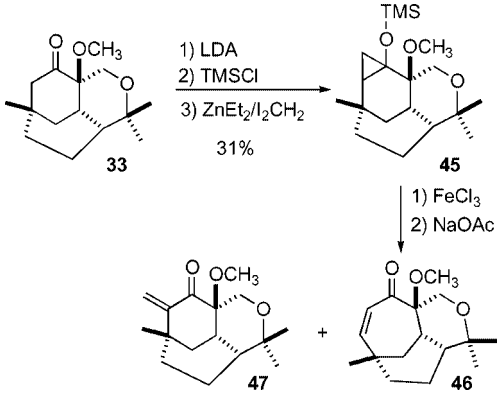
marium diiodide[35] only afforded cyclopropanol **40** (72%) and unidentified products, whereas zinc metal[36] only returned starting material (Scheme 8). Attempts (e.g. DBU, NaOEt) to ring-open **40**, the only donor-acceptor-substituted cyclopropane known to-date,[37] surprisingly failed. Applying the Zercher reaction ($ZnEt_2/CH_2I_2$)[38] however, afforded the desired ring-expanded material **41** in 50% yield (*dr* >95:5). The yield was not increased using Xue's modified Zercher conditions.[39] Molecular mechanics calculations suggest the lowest energy arrangement is where C2 has the ester function in the β position.[40]



Scheme 8.

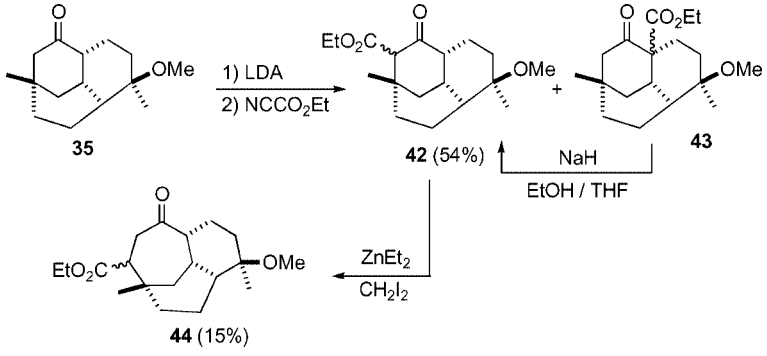
Applying this ring expansion protocol to the cyclovibsanin case (i.e. **35**) performed less admirably, for example, tricycle **35** was converted into **42** in only 54% overall yield. In this instance ethoxide only converted the 1:1 (**42**:**43**) mixture, obtained from the reaction with Mander's reagent, into a mixture of 8:2 (**42**/**43**). Subjecting **42** to the Zercher ring expansion protocol afforded the core **44** in only 15% yield with the choice of conditions being critical. After much experimentation it was found that when the number of equivalents of both diethylzinc and diiodomethane was increased to 16 in toluene[41] the reaction proceeded (*dr* ≈ 1:1; see Scheme 9).

Ring expansion of **33** was also investigated. When given the choice tricycle **26** will undergo regioselective deprotonation at the tertiary position alpha to the carbonyl, which was a limiting factor (regioselection) in choosing 6- to seven-membered ring expansion methods above. However, now that the tertiary position had been blocked by the methoxy function it was possible to investigate the Saegusa ring expansion[42] protocol. The Saegusa protocol has the added advantage in that it achieves two goals in the one transformation, that is, ring expansion and formation of enone functionality, which at the time was seen as important for developing the required side chains seen in the natural products. Davies' recently demonstrated that a photochemical [4+2] cycloaddition will achieve this goal, albeit with the incorrect stereochemistry.[43] Tricycle **33** was deprotonated with LDA in the presence of trimethylsilyl chloride affording the silyl enol ether, which was cyclopropanated ($ZnEt_2/CH_2I_2$) without purification affording **45**. Reaction of **45** with anhydrous iron(III) chloride in *N*,*N*-dimethylformamide followed by treatment with sodium acetate led to a separable mixture of desired endocyclic ring-expanded enone **46** (13%) as the minor product and undesired exocyclic enone **47** (41%) as the major product (Scheme 10). The overall yield (i.e. **33**–**46**) was a very disappointing 4%.

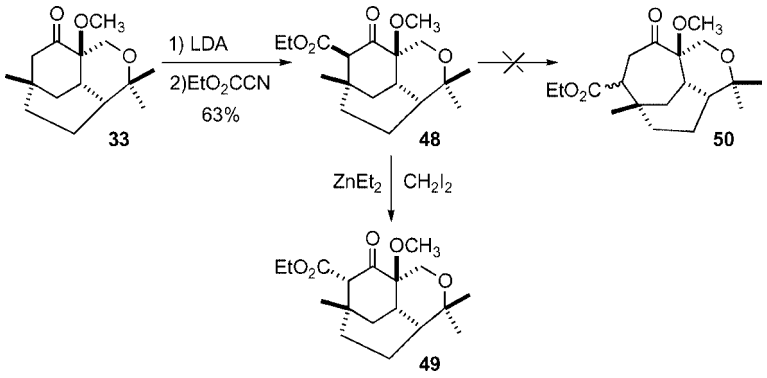


Scheme 10.

For comparative purposes the Zercher reaction was employed, but firstly tricycle **33** was converted via Mander reagent (EtO_2CCN) into ester **48** in 63% yield. Subsequent reaction with Zercher's reagent under a variety of condi-



Scheme 9.



Scheme 11.

tions led to epimeristion of the stereocentre attached to the ester function (i.e. **49**, see Figure 5) without formation of the ring-expanded product **50** (Scheme 11).

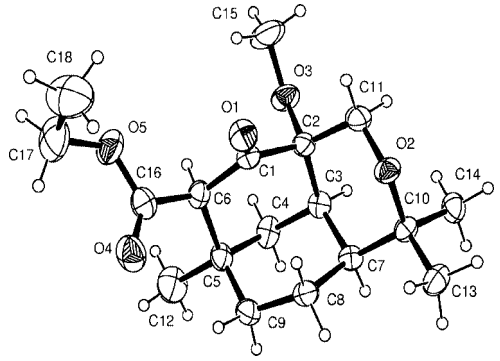


Figure 5. ORTEP3 drawing of compound **49** (30% probability ellipsoids).

In conclusion we have demonstrated that the cores (i.e. **41**, **44** and **46**) of vibsanin E (**3**), cyclovibsanins (**5**, **14**–**16**) and 3-*O*-methylfuranovibsanin A **13** can be constructed in overall yields ranging from 0.8–9% and serendipitously without the use of a single protecting group. We are indebted to the El Gaïed Baylis–Hillman variant and the remarkable Zercher reaction which will pave the way for a successful total synthesis and structural confirmation of vibsanin E (**3**). Finally, this work lends strong support to Fukuyama's proposed biosynthesis of these natural products.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV400 (400.13 MHz; 100.62 MHz), AV300 (300.13 MHz; 75.47 MHz) and DRX500 (500.13 MHz; 125.76 MHz) instruments in deuteriochloroform ($CDCl_3$). Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High and low resolution EI mass spectroscopic data were obtained on a KRATOS MS 25 RFA. Microanalyses were performed by the University of Queensland Microanalytical Service. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Anhydrous solvents were prepared according to Perin and Armarego, "Purification of laboratory solvents", 3rd edition. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Fine chemicals were purchased from the Aldrich Chem. Co. Gas Chromatography was performed on a Varian 3300 fitted with an Altech Econo-Cap EC-5 column (30 m × 0.25 mm × 0.25 μM) (flame ionization detection). CCDC-299909 to -299911 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3-Methyl-3-(4-methylpent-3-enyl)cyclohexanone (24): 5-Bromo-2-methyl-2-pentene: Following the method of Biernacki and Gdula.[44] To a solution of methylmagnesium bromide (80.0 mL, 240.0 mmol) (3.0 M in diethyl ether) in anhydrous THF (80 mL) under an argon atmosphere was added dropwise (30 min) a solution of cyclopropyl methyl ketone (16.82 g, 200.0 mmol) in THF (30 mL). The mixture was then heated to reflux for 20 min. On cooling to room temp. the reaction mixture was slowly added to a cooled solution of conc. sulfuric acid in water (1:2, 150 mL) at a rate that the temperature does not raise above 10 °C. After addition stirring was continued for 30 min. The organic layer was then separated, the aqueous solution was extracted with diethyl ether and the combined organic phases were washed with sat. sodium carbonate solution and brine. After drying over sodium sulfate the solvent was removed in vacuo and the residue was distilled (60–65 °C/water aspirator) to afford 5-bromo-2-methyl-2-pentene (25.0 g, 77%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (s, 3 H), 1.70 (s, 3 H), 2.48–2.62 (m, 2 H), 3.32 (t, J = 7.3 Hz, 2 H), 5.04–5.19 (m, 1 H). Magnesium turnings (5.59 g, 230.0 mmol) were stirred under high vacuum and an argon atmosphere introduced. Iodine crystals (20 mg) were added followed by freshly distilled THF (250 mL). 5-Bromo-2-methyl-2-pentene (24.9 g, 152.7 mmol), a portion (2 mL) of which was added directly to the THF suspension to start the reaction (heat was required to initiate), was dissolved in anhydrous THF (20 mL) and the solution added dropwise to the above suspension over 20 min with heating. The mixture was then refluxed for 1.5 h. Copper bromide–dimethyl sulfide complex[45] (1.54 g, 7.5 mmol) was dissolved in anhydrous THF (100 mL) under an argon atmosphere. The solution was then cooled to –20 °C and the Grignard solution added via syringe over 5 min. After 30 min at –20 °C 3-methyl-2-cyclohexenone (**23**)[46] (16.0 g, 145.2 mmol) was added (30 min) and the reaction stirred for 15 min at –20 °C before warming to room temperature out of the bath. The reaction mixture was then treated with sat. NH_4Cl solution and the organic layer separated. The aqueous solution was extracted with diethyl ether and the combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent in vacuo the residue was subjected to vacuum distillation (66 °C/0.8 Torr) yielding the title compound as a colourless oil (23.91 g,

85%). [***Note:*** similar results were obtained when copper(I) iodide (5 mol-%), washed with anhydrous ethanol (×2) then with anhydrous diethyl ether (×4)] was used.] R_f (petroleum ether/ethyl acetate, 20:1) = 0.43. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (s, 3 H), 1.22–1.27 (m, 2 H), 1.48–1.67 (m, 2 H), 1.56 (br. s, 3 H), 1.62 (br. d, J = 1.2 Hz Hz, 3 H), 1.78–1.94 (m, 4 H), 2.06–2.11 (m, 2 H), 2.15–2.19 (m, 2 H), 2.24 (t, J = 6.6 Hz, 2 H), 5.02–5.07 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 21.93, 21.96, 24.7, 25.5, 35.7, 38.4, 40.8, 41.5, 53.5, 124.2, 131.3, 212.0. Mass spectrum: *m*/*z* (EI) 194 ($M^{+\cdot}$, 7%), 151 (8), 111 (100), 97 (5), 83 (6), 69 (23), 55 (18). $C_{13}H_{22}O$ (194.31): calcd. C 80.35, H 11.41; found C 80.25, H 11.64.

5-Methyl-5-(4-methylpent-3-enyl)-2-cyclohexenone (25): A mixture of *o*-iodoxybenzoic acid (IBX)[47] (7.42 g, 26.5 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (3.23 g, 27.6 mmol) was dissolved in 25 mL of DMSO and heated to 70 °C. 3-Methyl-3-(4-methylpent-3-enyl)cyclohexanone (2.145 g, 11.04 mmol) was added at 70 °C and the mixture heated at that temperature for 4.5 h. (The completion of the reaction was determined by GC). On cooling the mixture was diluted with sodium hydrogen carbonate solution (500 mL) (1:1 saturated sodium hydrogen carbonate/water), extracted with diethyl ether (4 × 150 mL) and the combined extracts washed with saturated sodium hydrogen carbonate solution and brine. The diethyl ether layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was subjected to column chromatography (petroleum ether/ethyl acetate, 20:1) yielding the title compound (1.35 g, 64%) as a pale yellow oil. R_f (petroleum ether/ethyl acetate, 20:1) = 0.26. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.00 (s, 3 H), 1.30–1.38 (m, 2 H), 1.56 (br. s, 3 H), 1.64 (br. d, J = 1.1 Hz Hz, 3 H), 1.85–1.98 (m, 2 H), 2.13–2.17 (m, 1 H), 2.21–2.25 (m, 1 H), 2.27–2.33 (m, 2 H), 5.01–5.06 (m, 1 H), 5.99 (dt, J = 2.0, 10.1 Hz Hz, 1 H), 6.81–6.85 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 17.5, 22.3, 24.7, 25.6, 36.5, 38.1, 41.4, 50.1, 124.0, 129.0, 131.7, 148.2, 199.8. Mass spectrum: *m*/*z* (EI) 192 ($M^{+\cdot}$, 12%), 149 (10), 124 (25), 109 (100), 95 (5), 81 (13), 69 (18), 55 (10).

2-Hydroxymethyl-5-methyl-5-(4-methylpent-3-enyl)-2-cyclohexenone (22). Method A: 5-Methyl-5-(4-methylpent-3-enyl)-2-cyclohexenone **25** (2.89 g, 15.0 mmol) was dissolved in THF (15 mL) and 4-(dimethylamino)pyridine (DMAP) (1.83 g, 15.0 mmol) added. The mixture was heated at 50 °C for 30 min before the addition of formalin (15 mL, 37 wt.-%). After 4 h at 50 °C a further portion of formalin (15 mL) and THF (15 mL) was added and the mixture stirred for an additional 5 h. On cooling the reaction was quenched with 1 M hydrochloric acid (250 mL) and extracted with diethyl ether (5 × 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution, brine, and then dried with $MgSO_4$. The solvent was removed in vacuo and the residue subjected to column chromatography (petroleum ether/ethyl acetate, 5:2) yielding starting material (780 mg, 27%) and **22** [1.05 g, 32% (43% based on recovered starting material)] as a pale yellow oil. A minor (<5%) impurity could not be removed from the title compound. [***Note:*** using **25** in crude form (no silica column or plug) for this reaction does not give **22**.]

Method B: To a mixture of water (5 mL) and ketone **25** (1 g, 5.15 mmol) were added SDS (148 mg, 0.52 mmol) and DMAP (630 mg, 5.15 mmol). After stirring for 15 min, formalin (5 mL) was added and the stirring was continued at room temperature. After 3 h additional formalin (5 mL) and DMAP (100 mg) were added and the reaction was stirred for 12 h. The mixture was then quenched with brine (10 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was then purified by column chromatography (ethyl acetate/petroleum ether, 1:2) to give compound **22** (608 mg, 53%) as colourless liquid. [***Note:*** on smaller scale (ca. 100 mg) a yield of 63% was obtained.] R_f (petroleum ether/ethyl acetate, 5:2) = 0.27. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.91 (s, 3 H), 1.22–1.29 (m, 2 H), 1.48 (s, 3 H), 1.56 (s, 3 H), 1.79–1.90 (m, 2 H), 2.10–2.30 (m, 4 H), 2.94 (br. s, OH), 4.14–4.15(m, 2 H), 4.94–4.98 (m, 1 H), 6.70–6.73 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 17.6, 22.4, 24.7, 25.6, 36.7, 38.0, 41.3, 50.3, 60.6, 124.1, 131.7, 137.5, 144.2, 200.4. Mass spectrum: *m*/*z* (EI) 222 ($M^{+\cdot}$, 9%), 204 (14), 189 (10), 164 (8), 161 (15), 139 (22), 121 (86), 109 (53), 97 (22), 83 (18), 69 (49), 55 (39), 41 (100). $C_{14}H_{22}O_2$ (222.32): calcd. C 75.63, H 9.97; found C 75.65, H 10.27.

1,7,7-Trimethyl-6-oxatricyclo[6.2.2.0$^{[4,9]}$]dodecan-3-one (26). Method A: A solution of 2-hydroxymethyl-5-methyl-5-(4-methylpent-3-enyl)-2-cyclohexenone (**22**) (260 mg, 1.17 mmol) in anhydrous CH_2Cl_2 (40 mL) was cooled to –78 °C under an argon atmosphere. Anhydrous ethereal hydrochloric acid (1.25 mL, 2.5 mmol, 2 M) was added and the solution stirred at –78 °C for 1 h and then warmed to 0 °C over 3 h. The reaction was quenched at 0 °C by addition of saturated sodium hydrogen carbonate solution (4 mL). On warming to room temperature a further portion of saturated sodium hydrogen carbonate solution (5 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (5 × 10 mL) and the combined organic phases washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was subjected to column chromatography (petroleum ether/ethyl acetate, 10:1) yielding **22** (150 mg, 58%) as a colourless oil, which crystallised on refrigeration to produce colourless needles, m.p. 61–62 °C. [***Note:*** Column chromatography fractions were analysed by GC as TLC detection of **26** is difficult.]

Method B: To a vigorously stirring solution of **22** (614 mg, 2.77 mmol) in dichloromethane (20 mL) at 0 °C was added Amberlyst-15 (600 mg) in one portion followed by warming to room temperature over 2 h. After additional stirring at room temperature for 2 h the mixture was filtered and concentrated in vacuo. The residue was then purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) on silica affording **26** (420 mg, 68%) as a white solid. R_f (petroleum ether/ethyl acetate, 10:1) = 0.2. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.94 (s, 3 H), 1.04 (s, 3 H), 1.20–1.32 (m, 3 H), 1.24 (s, 3 H), 1.49–1.59 (m, 3 H), 1.76–1.80 (m, 1 H), 1.93–1.95 (m, 1 H), 2.07 (d, J = 16.5 Hz Hz, 1 H), 2.29 (dd, J = 16.5 Hz, 3 Hz, 1 H), 2.66–2.70 (m, 1 H), 3.52 (dd, J = 3.6, 11.9 Hz Hz, 1 H), 4.46 (d, J = 11.9 Hz Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 20.8, 22.8, 27.8, 28.7, 31.0, 31.9, 33.9, 38.9, 41.46, 42.3, 46.4, 53.3, 58.6, 73.7, 210.3. Mass spectrum: *m*/*z* (EI) 222 ($M^{+\cdot}$, 14%), 207 (18), 164 (10), 146 (3), 136 (4), 129 (6), 121 (6), 109 (8), 106 (10), 94 (100), 79 (14). $C_{14}H_{22}O_2$: calcd. $M^{+\cdot}$ 222.1614; found $M^{+\cdot}$ 222.1619.

1,7-Dimethyltricyclo[6.2.2.0^{4,9}]dodec-6-en-3-one (27): *Small-scale synthesis:* 2-Hydroxymethyl-5-methyl-5-(4-methylpent-3-enyl)-2-cyclohexenone (**22**) (130 mg, 0.58 mmol) was placed in a sealed tube with aqueous 3 M hydrochloric acid (8 mL). The mixture was heated at 120 °C for 2 h. On cooling, diethyl ether (30 mL) was added, and the aqueous layer extracted with diethyl ether (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The residue was subjected to column chromatography (petroleum ether/ethyl acetate, 95:5) on silica, which afforded two fractions. Fraction one was the product **27** (79 mg, 67%) as a colourless oil and fraction 2 was 1,7,7-trimethyl-6-oxatricyclo[6.2.2.0^{4,9}]dodecan-3-one (**26**) (13 mg, 10%) as colourless needles.

Large-scale synthesis: Compound **22** (550 mg, 2.47 mmol) placed in a sealed tube with aqueous 3 M hydrochloric acid (35 mL). The

reaction mixture was stirred at 120 °C for 2.5 h. On cooling the mixture was extracted with diethyl ether (3×30 mL), and the organic phase, dried (Na_2SO_4) and concentrated. The oily residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 95:5) affording compound **27** (248 mg, 50%), the alcohol **28** (76 mg, 14%) and tricycle **26** (83 mg, 15%).

1,7-Dimethyltricyclo[6.2.2.0^{4,9}]dodec-6-en-3-one (27): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.95 (s, 3 H), 1.25–1.38 (m, 1 H), 1.44–1.54 (m, 1 H), 1.58 (dd, J = 3.7, 1.8 Hz, 3 H), 1.63 (dt, J = 13.3, 2.6 Hz, 2 H), 1.72–1.86 (m, 3 H), 1.88–2.02 (m, 1 H), 2.09 (br. dt, J = 15.8, 1.2 Hz, 1 H), 2.25 (dd, J = 16.0, 2.8 Hz, 1 H), 2.31–2.38 (m, 2 H), 2.86 (ddd, J = 17.8, 4.3, 1.7 Hz, 1 H), 5.14–5.19 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.1, 23.3, 26.5, 31.0, 35.3, 35.7, 39.2, 39.5, 41.5, 45.9, 53.3, 117.9, 137.9, 212.3. Mass spectrum: *m*/*z* (EI) 204 ($M^{+\cdot}$, 100%), 189 (20), 181 (15), 175 (20), 167 (20), 159 (31), 149 (30), 135 (92), 130 (15), 119 (34), 111 (15), 105 (20), 95 (15), 91 (35). HRMS (EI): $[M]^+$ calcd. for $C_{14}H_{20}O$ M^+ 204.1514, found $M^{+\cdot}$ 204.1519.

1,7-Dimethyl-7-hydroxytricyclo[6.2.2.0^{4,9}]dodecan-3-one (28): ^{1}H NMR ($CDCl_3$, 300 MHz) [mixture of diastereoisomers, ca. 2:1] δ = 0.94 (s, 3 H), 0.96 (s, 3 H), 1.08 (s, 3 H), 1.20–1.34 (m), 1.26 (s, 3 H), 1.45–1.61 (m), 1.78 (br. dt), 2.05–2.41 (m), 2.66–2.71 (m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.7, 20.3, 21.8, 22.5, 26.9, 29.1, 29.7, 30.6, 30.7, 33.4, 34.3, 34.5, 36.2, 38.7, 38.9, 41.3, 41.4, 46.3, 46.4, 46.5, 46.7, 53.2, 53.3, 72.5, 72.8, 195.5, 193.8. Mass spectrum: *m*/*z* (EI) 222 ($M^{+\cdot}$, 25%), 204 (10), 189 (2), 179 (10), 165 (9), 152 (20), 129 (10), 121 (14), 109 (13), 94 (100). HRMS (EI): $[M]^+$ calcd. for $C_{14}H_{22}O_2$ M^+ 222.1614, found $M^{+\cdot}$ 222.1616.

4-Methoxy-1,7,7-trimethyl-6-oxatricyclo[6.2.2.0^{4,9}]dodecan-3-one (33): To a solution of lithium diisopropylamide [prepared from diisopropylamine (103 μL, 0.74 mmol) in THF (5 mL) and *n*-butyllithium 1.32 M (511 μL, 0.67 mmol, solution in hexanes) at 0 °C] at –78 °C was added a solution of **26** (136 mg, 0.61 mmol) in THF (3.0 mL) via cannula dropwise. After stirring for 30 min a solution of iodine (171 mg, 0.67 mmol) in THF (3.0 mL) was added dropwise via syringe. After stirring for 10 min at –78 °C the reaction was quenched by pouring onto ice cold aqueous $Na_2S_2O_4$ (5%) and extracted into diethyl ether (3×30 mL). The organic phases were combined and washed with brine then dried (Na_2SO_4), concentrated in vacuo and the resulting oil (**31/32**) was used in the following reaction without purification. To a vigorously stirring solution of potassium carbonate (170 mg, 1.23 mmol) in methanol (10 mL) at 50 °C was added a solution of iodides **31** and **32** in methanol (2.0 mL). After 2 h the mixture was cooled to room temparature, diluted with diethyl ether (50 mL) and filtered through a short plug of silica and concentrated in vacuo. The resulting residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) on silica affording **33** (114 mg, 74%, 2 steps) as a white solid (m.p. 41–42 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.96 (s, 3 H), 1.07 (s, 3 H), 1.15 (dt, J = 13.1, 2.8 Hz 1 H), 1.20–1.44 (m, 3 H), 1.30 (s, 3 H), 1.54–1.65 (m, 2 H), 2.16–2.36 (m, 3 H), 2.49–2.54 (m, 1 H), 3.05 (s, 3 H), 3.29 (d, J = 11.0 Hz 1 H), 4.42 (d, J = 11.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.6, 22.7, 26.9, 30.7, 34.4, 35.8, 38.2, 38.4, 42.6, 50.9, 51.0, 60.8, 73.7, 74.3, 207.5. HRMS (ESI): $[M]^+$ calcd. for $C_{15}H_{24}NaO_3$ M^+ 275.1623, found $M^{+\cdot}$ 275.1616.

7-Methoxy-1,7-dimethyltricyclo[6.2.2.0^{4,9}]dodecan-3-one (35): Ketone **27** (165 mg, 0.8 mmol) and mercury acetate (205 mg, 0.8 mmol) were dissolved in anhydrous methanol (20 mL) under an argon atmosphere. The mixture was stirred at room temperature for 5 h before a further portion of mercury acetate (410 mg, 1.6 mmol) was added. At the completion of the reaction [TLC (petroleum ether/ethyl acetate, 90:10)], sodium hydroxide solution 3 M (4 mL) was added. After stirring for 10 min, sodium borohydride (35 mg, 0.8 mmol) in sodium hydroxide 3 M (3 mL) was added and after 30 min the mixture was filtered. The filtrate was extracted with diethyl ether (2×20 mL), the combined organic layers dried ($MgSO_4$), and the solvent removed in vacuo. The residue was subjected to column chromatography (petroleum ether/ethyl acetate, 95:5) on silica yielding the **35** as a colourless oil (115 mg, 61%), which crystallised (hexane) on standing at +5 °C for about 12 h. M.p. 28 °C. ^{1}H NMR (C_6D_6, 300 MHz): δ = 0.69 (s, 3 H), 0.79 (s, 3 H), 0.91–1.22 (m, 4 H), 1.23–1.57 (m, 6 H), 1.72–1.85 (m, 2 H), 2.17 (dd, J = 15.9, 3.0 Hz, 1 H), 2.39–2.48 (m, 1 H), 2.51–2.62 (m, 1 H), 2.94 (s, 3 H). ^{13}C NMR (C_6D_6, 75 MHz): δ = 20.1, 22.0, 22.5, 26.4, 30.9, 33.3, 34.3, 39.4, 41.6, 43.7, 46.5, 47.8, 53.5, 76.2, 210.4. Mass spectrum: *m*/*z* (EI) 236 ($M^{+\cdot}$, 35%), 221 (6), 204 (16), 189 (7), 175 (6), 162 (7),n 143 (10), 142 (14), 121 (5), 109 (6), 94 (24), 85 (100), 79 (7), 72 (56). HRMS (EI): $[M]^+$ $C_{15}H_{24}O_2$ calcd. M^+ 236.1776, found $M^{+\cdot}$ 236.1779.

Ethyl 1,7,7-Trimethyl-3-oxo-6-oxatricyclo[6.2.2.0^{4,9}]dodecane-2-carboxylate (36): To a solution of ketone **26** (552 mg, 2.49 mmol) at –78 °C in anhydrous THF (15 mL) under n argon atmosphere was added dropwise a solution of lithium diisopropylamide [prepared from diisopropylamine (418 μL, 2.99 mmol) in THF (24 mL) and *n*-butyllithium 1.3 M (2.1 mL, 2.74 mmol, solution in hexanes) at 0 °C]. After 30 min ethyl cyanoformate was added followed by hexamethylphosphorous triamide (600 μL) and then the reaction was warmed to room temperature over 12 h. The reaction was quenched by pouring onto ice-cold satd. aqueous ammonium chloride (15 mL) then extracted with diethyl ether (3×25 mL) and the combined organic layers were then washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was dissolved in anhydrous THF (3 mL) and added dropwise to an ice cold solution of sodium ethoxide [prepared from ethanol (620 μL, 9.96 mmol) in anhydrous THF (10 mL) and sodium hydride (200 mg, 4.98 mmol, 60% dispersion on mineral oil) at 0 °C] then warmed to room temperature over 2 h. The reaction was worked up as above then purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to afford the title compound **36** [337 mg, 46% (based on recovered starting material 69%)] as a white solid (m.p. 122–123 °C) and recovered starting material (185 mg, 33%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.99 (s, 3 H), 1.07 (s, 3 H), 1.07–1.24 (m, 2 H), 1.25 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.29–1.47 (m, 1 H), 1.54–1.68 (m, 2 H), 1.85 (dt, J = 13.3, 3.2 Hz, 1 H), 2.03–2.07 (m, 1 H), 2.35–2.45 (m, 1 H), 2.67–2.75 (m, 1 H), 3.06 (s, 1 H), 3.58 (dd, J = 12.0, 3.6 Hz, 1 H), 4.12–4.29 (m, 2 H), 4.44 (d, J = 12.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.2, 20.6, 22.5, 27.5, 29.1, 31.8, 34.6, 37.5, 42.3, 43.2, 46.2, 58.1, 60.6, 66.2, 73.5, 168.8, 204.5. Mass spectrum: *m*/*z* (EI) 294 ($M^{+\cdot}$, 14%), 279 (18), 276 (3), 266 (4), 249 (9), 236 (9), 233 (7), 221 (2), 205 (2), 190 (11), 181 (3), 175 (3), 162 (8), 143 (26), 134 (11), 115 (9), 109 (12), 94 (100), 79 (19). $C_{17}H_{26}O_4$: calcd. $M^{+\cdot}$ 294.1831, found: $M^{+\cdot}$ 294.1831.

Tetracyclic Compound 40: Ester **36** (70 mg, 0.238 mmol) was dissolved in ethanol (3.0 mL). Formalin (1.5 mL) was added followed by potassium hydrogen carbonate (50 mg) and triethylamine (0.5 mL). The mixture was then heated at 65 °C for 1 h. On cooling the reaction mixture was filtered and evaporated in vacuo and the residue subjected to silica gel column chromatography (ethyl acetate/petroleum ether, 1:1), which afforded to product **39** (77 mg, 84%) as a colourless oil. Alcohol **39** (50 mg, 0.154 mmol), triphenylphosphane (0.162 mg, 0.616 mmol) and imidazole (42 mg, 0.616 mmol) were dissolved in anhydrous diethyl ether (2.0 mL) and anhydrous acetonitrile (1.0 mL) under an argon atmosphere. The reaction flask was placed in an ice-bath and iodine (117 mg,

0.462 mmol) added in one portion. After 5 min the flask was removed from the ice-bath and the mixture stirred at room temperature for 3.5 h. Cooling with an ice-bath the reaction was firstly diluted with diethyl ether (5 mL) and quenched with aqueous sodium thiosulfate (20%, 5 mL). The ether layers were combined, dried (Na_2SO_4) and evaporated in vacuo. The residue was subjected to silica gel column chromatography (ethyl acetate/petroleum ether, 8:92), which afforded iodide **37** (50 mg, 75%) as a colourless oil. Iodide **37** (25 mg, 0.0058 mmol) was dissolved in anhydrous tetrahydrofuran (3.0 mL) under an argon atmosphere. To this solution was added hexamethylphosphorous triamide (0.6 mL, 0.345 mmol) followed by cooling to –78 °C. On cooling samarium iodide (3.45 mL, 0.1 M, 0.345 mmol) was added dropwise over 60 s and after 10 min the reaction was quenched [satd. ammonium chloride solution (4 mL)] and warmed to room temperature over 20 min. The reaction mixture was then diluted with water (5 mL) and extracted with a mixture of diethyl ether and petroleum ether (2:1, 20 mL). The combined extracts were evaporated, dried (Na_2SO_4) and the residue subjected to silica gel column chromatography (ethyl acetate/petroleum ether, 3:7), which afforded **40** (13 mg, 72%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.36 (d, J = 5.9 Hz, 1 H), 0.57 (d, J = 5.9 Hz, 1 H), 0.92 (s, 3 H), 0.99–1.09 (m, 3 H) 1.12 (s, 3 H), 1.26–1.33 (m, 1 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.31 (s, 3 H), 1.40 (dt, J = 13.8, 3.4 Hz, 1 H), 1.52–1.58 (m, 1 H), 1.62–1.68 (m, 1 H), 2.03–2.13 (m, 1 H), 2.39 (br. q, 1 H), 2.98 (s, 1 H), 3.66 (d, J = 12.1 Hz, 1 H), 3.85 (d, J = 12.1 Hz, 1 H), 4.13–4.26 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.4, 18.4, 19.9, 22.5, 27.4, 27.6, 29.4, 31.3, 31.4, 37.0, 37.7, 43.0, 57.3, 57.6, 60.6, 62.2, 74.0, 173.1. Mass spectrum: *m*/*z* (EI) 308 ($M^{+\cdot}$, 55%), 290 (9), 262 (18), 247 (10), 233 (7), 219 (12), 204 (16), 194 (11), 177 (12), 161 (21), 148 (28), 136 (43), 121 (32), 111 (40), 94 (70), 73 (80), 55 (100). $C_{18}H_{28}O_4$: calcd. $M^{+\cdot}$ 308.1988, found: $M^{+\cdot}$ 308.1992.

Ethyl 1,8,8-Trimethyl-4-oxo-7-oxatricyclo[6.3.2.0^{5,10}]dodecane-2-carboxylate (41): To a solution of diethylzinc (3.77 mL, 3.77 mmol, 1 M in hexanes) in anhydrous dichloromethane (10 mL) at 0 °C was added diiodomethane (1 g, 3.77 mmol) dropwise under an argon atmosphere. The reaction was stirred for 30 min then a solution of keto ester **36** (270 mg, 0.88 mmol) in anhydrous dichloromethane (5.0 mL) was added dropwise and then stirred at room temperature. After 12 h the mixture was poured onto ice cold aqueous ammonium chloride (15 mL, sat.) and extracted with diethyl ether (3 × 25 mL) and combined. The organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) on silica affording recovered **36** (203 mg) and **41** [34 mg, 12% (yield based on recovered starting material 50%)] as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10–1.21 (m, 1 H), 1.22–1.28 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.27 (s, 3 H), 1.31–1.47 (m, 1 H), 1.52–1.62 (m, 1 H), 1.73 (dd, J = 14.5, 5.4 Hz, 1 H), 1.95 (dt, J = 14.5, 2.5 Hz, 1 H), 2.16–2.25 (m, 2 H), 2.54–2.62 (m, 1 H), 2.63 (s, 1 H), 2.64 (AB, 1 H), 3.05–3.18 (m, 1 H), 3.62 (dd, J = 11.8, 3.6 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 4.31 (dd, J = 10.7, 1.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.2, 21.9, 23.8, 27.4, 31.2, 33.0, 33.7, 34.2, 42.8, 44.3, 46.4, 51.3, 51.6, 60.4, 61.7, 73.6, 174.0, 210.1. Mass spectrum: *m*/*z* (EI) 308 ($M^{+\cdot}$, 4%), 293 (14), 290 (4), 275 (1), 269 (1), 263 (5), 250 (68), 245 (1), 214 (1), 204 (19), 196 (6), 177 (10), 156 (90), 135 (10), 128 (18), 110 (23), 101 (94), 94 (100). $C_{18}H_{28}O_4$: calcd. $M^{+\cdot}$ 308.1988, found: $M^{+\cdot}$ 308.1989.

Ethyl 7-Methoxy-1,7-dimethyl-3-oxotricyclo[6.2.2.0^{4,9}]dodecane-2-carboxylate (42): A solution of **35** (296 mg, 1.25 mmol) in anhydrous tetrahydrofuran (6 mL) and hexamethylphosphorous triamide (260 μL, 1.5 mmol) was stirred at –50 °C under an argon atmosphere for 10 min. Lithium diisopropylamide (1.5 mmol) [prepared from diisopropylamine (1 mL, 7.1 mmol) in tetrahydrofuran (10 mL) and *n*-butyllithium 1.6 M (4.5 mL, 7.1 mmol, solution in hexanes) between –20 and 0 °C] cooled to –50 °C was added dropwise, and the mixture was warmed to 0 °C over 1 h. The mixture was then stirred for 30 min at –80 °C, and ethyl cyanoformate (250 μL, 2.5 mmol) added neat. The mixture was warmed to room temperature overnight. The mixture was quenched with saturated aqueous ammonium chloride (8 mL), and the aqueous phase extracted with diethyl ether (4 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. Column chromatography (petroleum ether/ ethyl acetate, 9:1) of the residue gave a colourless oil (281 mg) as a mixture of isomers (1:1). Sodium hydride (65 mg, 1.61 mmol, 60% dispersion in oil) was suspended in anhydrous tetrahydrofuran (3 mL) at 0 °C under an argon atmosphere. Anhydrous ethanol (190 μL, 3.2 mmol) was then slowly added. After effervescence ceased, the above residue (249 mg) in anhydrous tetrahydrofuran (3 mL) was cooled to 0 °C before slow addition. The reaction mixture was stirred at room temp. overnight. Ethyl acetate (6 mL) followed by saturated aqueous ammonium chloride were added, and the aqueous layer extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), the solvent removed in vacuo, and the residue subjected to column chromatography (petroleum ether/ethyl acetate, 95:5) on silica. Compound **42** was isolated as a colourless oil (169 mg, 44%) along with recovered starting material (33 mg, 13%) and a (1:1) mixture isomers **42** and **43** (69 mg, 20%). Spectral data reported for **42** only. ^{1}H NMR (C_6D_6, 300 MHz): δ = 0.74 (s, 3 H), 0.88 (s, 3 H), 0.90–0.96 (m, 1 H), 1.04 (t, J = 7.0 Hz, 3 H), 1.17 (dd, J = 13.5, 3.6 Hz, 1 H), 1.20–1.28 (m, 2 H), 1.30–1.52 (m, 5 H), 1.77 (br. t, J = 2.8 Hz, 1 H), 2.24–2.36 (m, 1 H), 2.45–2.52 (m, 1 H), 2.68 (dd, J = 6.4, 3.4 Hz, 0.5 H), 2.64 (dd, J = 6.4, 3.4 Hz, 0.5 H), 2.91 (s, 3 H), 2.96 (s, 1 H), 4.02–4.18 (m, 2 H). ^{13}C NMR (C_6D_6, 100 MHz): δ = 14.3, 20.0, 22.0, 22.6, 26.2, 29.3, 33.5, 35.1, 38.3, 43.3, 43.7, 46.4, 47.8, 60.3, 66.0, 76.1, 169.0, 206.2. Mass spectrum: *m*/*z* (EI) 308 ($M^{+\cdot}$, 11%) 276 (19), 263 (6), 247 (6), 243 (3), 202 (6), 94 (13), 85 (100), 72 (48). HRMS (EI): $C_{18}H_{28}O_4$ calcd. M^+ 308.1988, found $M^{+\cdot}$ 308.1988.

Ethyl 8-Methoxy-1,8-dimethyl-4-oxotricyclo[6.3.2.0^{5,10}]dodecane-2-carboxylate (44): To a solution of diethylzinc 1 M (2 mL, 2.0 mmol, 16 equiv.) in anhydrous toluene (4 mL) at 0 °C under an argon atmosphere was added neat freshly distilled diiodomethane (170 μL, 2.0 mmol). The mixture was stirred at 0 °C for 15 min, then tricycle **42** (50 mg, 0.13 mmol) in anhydrous toluene (3 mL) was added. The reaction was stirred for 24 h at room temperature. On completion the reaction was quenched with saturated aqueous ammonium chloride (2 mL) followed by addition of diethyl ether (8 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was subjected to column chromatography (petroleum ether/ethyl acetate, 95:5) on silica affording **44** as a colourless oil (6 mg, 15%). ^{1}H NMR (C_6D_6, 300 MHz; mixture of diastereomers, ca. 1:1): δ = 0.787 (s, 3 H), 0.792 (s, 3 H), 0.84 (s, 3 H), 0.85–1.15 (m, 4 H), 0.96 (t, J = 7.1 Hz, 3 H), 0.99 (s, 3 H), 1.00 (t, J = 7.1 Hz, 3 H), 1.20–1.42 (m, 6 H), 1.46–1.52 (m, 5 H), 1.55 (dt, J 15, 2.5, 1 H), 1.67 (dt, J 15, 2.5, 1 H), 1.86–1.95 (m, 3 H), 2.18 (dt, J 10, 2.7, 1 H), 2.22–2.28 (m, 1 H), 2.30–2.40 (m, 2 H), 2.41–2.50 (m, 3 H), 2.55 (d, J 15, 1 H), 2.84–3.02 (m, 2 H), 2.94 (s, 3 H), 2.95 (s, 3 H), 3.54 (dd, J 15, 0.7, 1 H), 3.74 (d, J = 9.5 Hz, 1 H), 3.87–4.10 (m, 4 H). ^{13}C NMR (C_6D_6, 75 MHz; mixture of diastereomers, ca. 1:1): δ = 14.0, 14.2, 16.8, 21.9, 22.0, 22.6, 22.7, 22.8, 23.1, 26.9, 27.4, 31.1,

31.7, 33.1, 33.7, 34.3, 35.1, 37.7, 39.6, 40.3, 44.1, 45.9, 46.2, 46.4, 47.9, 50.7, 51.1, 51.1, 52.7, 53.5, 60.0, 60.9, 75.9, 76.0, 172.3, 174.0, 209.3, 210.0. Mass spectrum: *m/z* (EI) 322 ($M^{+\cdot}$, 9%), 304 (11), 290 (30), 277 (10), 250 (9), 232 (13), 225 (14), 217 (10), 205 (9), 193 (31), 121 (10), 111 (10), 105 (17), 91 (21), 85 (95), 72 (100). HRMS (EI): $C_{19}H_{30}O_4$ calcd. M^+ 322.2144, found $M^{+\cdot}$ 322.2145.

Saegusa Ring Expansion. Preparation of 46 and 47: To an ice cold solution of lithium diisopropylamide, under an argon atmosphere, [prepared from diisopropylamine (248 μL, 1.78 mmol) in THF (12 mL) and *n*-butyllithium 1.35 M (1.21 mL, 1.63 mmol, solution in hexanes) at 0 °C] was added a solution of ketone **33** (359 mg, 1.42 mmol) and trimethylsilyl chloride (177 mg, 208 μL, 1.63 mmol) in THF (5.0 mL) dropwise via cannula. The reaction was stirred for 35 min then poured onto ice cold aqueous $NaHCO_3$ (20 mL) and extracted with diethyl ether (3 × 20 mL). The organic layers were combined, washed with brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo which afforded an oil that was used in the following procedure without purification. To a solution of diethylzinc (8.52 mL, 8.52 mmol, 1 M solution in hexanes) in anhydrous diethyl ether (15 mL), under an argon atmosphere, was added diiodomethane (2.28 g, 8.52 mmol). The reaction was gently heated to reflux for 15 min then after the reaction cooled to room temperature a solution of the silylenol ether in anhydrous diethyl ether (10 mL) was added via syringe then stirred for 30 min at room temperature. After additional diethylzinc (1.50 mL) and diiodomethane (400 mg, 1.50 mmol) were added the reaction was refluxed for 2.5 h then cooled to room temperature and poured onto aqueous $NaHCO_3$ (20 mL) and extracted with diethyl ether (3 × 20 mL). The organic layers were combined, washed with brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo which gave a residue that was purified by flash chromatography (5% TEA in petroleum ether) to give **45** (147 mg, 31%) as a colourless oil that was somewhat acid-sensitive. To a solution of iron trichloride (155 mg, 0.96 mmol) in anhydrous *N*,*N*-dimethylformamide (5.0 mL) at 0 °C was added **45** in solution of anhydrous *N*,*N*-dimethylformamide (3.5 mL) and anhydrous dichloromethane (3.0 mL) dropwise over 1 h followed by stirring overnight at room temperature. The reaction was poured into ice cold hydrochloric acid (1 M, 20 mL) and extracted with dichloromethane (3 × 15 mL). The organic phases were combined then washed with aqueous sodium hydrogen carbonate (15 mL), brine, dried (Na_2SO_4) and concentrated in vacuo. The crude material was then dissolved in methanol (5 mL, sat. with NH_4OAc) and refluxed overnight. The resulting residue, after concentration in vacuo, was suspended in brine (10 mL) and extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo to give a residue that was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) affording **46** (15 mg, 4%) and **47** (47 mg, 13%) as colourless oils.

1,8,8-Trimethyl-7-oxatricyclo[6.3.2.0^{5,10}]dodecan-2-en-4-one (46): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11 (s, 3 H), 1.14 (s, 3 H) 1.10–1.39 (m, 4 H), 1.31 (s, 3 H), 1.49–1.60 (m, 2 H), 1.57 (s, 3 H), 2.45–2.50 (m, 1 H), 2.62 (dt, *J* = 14.0, 2.4 Hz, 1 H), 3.03 (s, 1 H), 3.24 (d, *J* = 10.8 Hz, 1 H), 4.51 (d, *J* = 10.8 Hz, 1 H), 6.02 (AB, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.4, 23.9, 27.2, 32.0, 36.4, 36.5, 37.3, 38.2, 44.1, 51.1, 62.7, 73.5, 130.3, 151.7, 198.5. Mass spectrum (GCMS): *m/z* (EI) 264 ($M^{+\cdot}$, 4%), 249 (58), 232 (85), 217 (24), 204 (10), 189 (26), 175 (20), 161 (23), 147 (40), 137 (50), 119 (51), 105 (53), 93 (60), 81 (59), 67 (50), 41 (100). HRMS: $C_{16}H_{24}NaO_3$ calcd. 287.1623, found 287.1615.

1,7,7-Trimethyl-2-methylene-6-oxatricyclo[6.2.2.0^{4,9}]dodecan-3-one (47): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.10 (s, 3 H), 1.15 (s, 3 H) 1.20 (dd, *J* = 13.0, 3.0 Hz, 1 H), 1.15 (s, 3 H), 1.24–1.59 (m, 4 H), 1.32 (s, 3 H), 1.62–1.70 (m, 1 H), 2.31 (dt, *J* = 13.1, 3.2 Hz, 1 H), 2.48 (br. q, 1 H), 3.00 (s, 1 H), 3.31 (d, *J* = 11.1 Hz, 1 H), 4.46 (d, *J* = 11.1 Hz, 1 H), 5.25 (m, 1 H), 5.92 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.9, 22.7, 26.9, 27.3, 36.2, 36.9, 37.6, 40.4, 42.4, 50.8, 61.5, 73.6, 74.9, 119.6, 153.6, 196.6. Mass spectrum (GCMS): *m/z* (EI) 264 ($M^{+\cdot}$, 9%), 249 (8), 232 (100), 219 (28), 206 (53), 191 (46), 177 (22), 163 (52), 150 (81), 137 (37), 124 (39), 105 (33). HRMS: $C_{16}H_{24}O_3$ calcd. 264.1725, found 264.1721.

Ethyl (2β)-4-Methoxy-1,7,7-trimethyl-3-oxo-6-oxatricyclo[6.2.2.0^{4,9}]-dodecane-2-carboxylate (48): To a solution of ketone **33** (200 mg, 0.79 mmol) at –78 °C in THF (5.0 mL) under an argon atmosphere was added a solution of lithium diisopropylamide dropwise [prepared from diisopropylamine (121 μL, 0.87 mmol) in THF (6 mL) and *n*-butyllithium 1.3 M (640 μL, 0.83 mmol, solution in hexanes) at 0 °C]. After 30 min ethyl cyanoformate (82 mg, 0.83 mmol) was added followed by hexamethylphosphorous triamide (100 μL) and stirring continued for 40 min. The reaction was quenched by pouring onto ice cold aqueous ammonium chloride (sat. 15 mL) followed by extraction with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was then purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) affording **48** (101 mg, 39%) as a colourless oil and recovered starting material (75 mg, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz; one diastereoisomer only): δ = 1.00 (s, 3 H), 1.01 (s, 3 H) 1.18–1.45 (m, 4 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.28 (s, 3 H), 1.55–1.66 (m, 2 H), 2.50 (br. q, 1 H), 2.85 (dt, *J* = 13.6, 3.2 Hz, 1 H), 2.94 (s, 3 H), 3.22 (d, *J* = 2.0 Hz, 1 H), 3.29 (d, *J* = 11.2 Hz, 1 H), 4.02–4.20 (m, 2 H), 4.39 (d, *J* = 11.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 21.0, 22.5, 26.8, 27.0, 31.6, 35.0, 37.2, 41.2, 42.2, 50.6, 60.9, 61.4, 65.1, 73.5, 74.3, 167.2, 200.3. Mass spectrum (GCMS): *m/z* (EI) 324 ($M^{+\cdot}$, 6%), 309 (1), 294 (40), 279 (24), 264 (59), 247 (11), 228 (6), 218 (28), 212 (36), 203 (10), 190 (22), 183 (45), 175 (12), 165 (24), 151 (19), 135 (31), 121 (18), 107 (28), 94 (100). HRMS calcd. for $C_{18}H_{28}NaO_5$: 347.1834; found 347.1826.

Ethyl (2α)-4-Methoxy-1,7,7-trimethyl-3-oxo-6-oxatricyclo[6.2.2.0^{4,9}]-dodecane-2-carboxylate (49): To a solution of diethylzinc (440 μL, 0.44 mmol, 1 M in hexanes) in anhydrous dichloromethane (3.0 mL) at 0 °C under an argon atmosphere was added trifluoroacetic acid (32 μL, 0.44 mmol). After 30 min. diiodomethane (36 μL, 0.44 mmol) was added and the mixture stirred for a further 30 min. followed by dropwise addition keto ester **48** (48 mg, 0.15 mmol) in anhydrous dichloromethane (1.0 mL). After 12 h at room temperature the mixture was poured onto ice-cold satd. aqueous ammonium chloride (15 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by flash chromatography (dichloromethane) on silica affording **49** (29 mg, 58%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (s, 3 H), 1.07–1.17 (m, 1 H), 1.08 (s, 3 H) 1.22 (dd, *J* = 13.2, 3.0 Hz, 1 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.33–1.48 (m, 2 H), 1.59–1.68 (m, 1 H), 2.32 (dt, *J* = 9.9, 3.3 Hz, 1 H), 2.40 (br. dq, 1 H), 2.53 (br. q, 1 H), 3.07 (s, 3 H), 3.30 (d, *J* = 11.2 Hz, 1 H), 3.38 (AB, 1 H), 4.18–4.25 (m, 2 H), 4.40 (d, *J* = 11.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 21.5, 22.5, 26.8, 28.9, 34.1, 37.5, 38.1, 38.3, 42.5, 51.0, 60.5, 63.2, 73.6, 74.8, 168.8, 202.4. Mass spectrum (GCMS): *m/z* (EI) 324 ($M^{+\cdot}$, 1%), 309 (2), 294 (22), 279 (7), 264 (28), 247 (7), 228 (3), 218 (10), 203 (4), 183 (10), 173 (19), 160 (7), 139 (12), 122 (11), 107 (14), 94 (100). HRMS: $C_{18}H_{28}O_5$ calcd. 324.1937, found 324.1934.

X-ray Crystallography: X-ray data were collected on an Enraf–Nonius CAD4 diffractometer with graphite-monochromatized

Mo-K_α radiation, λ = 0.71073 Å operating in the ω-2θ scan mode. Data reduction and corrections for decay and absorption were performed with the WINGX package.[48] Structures were solved by direct methods with SHELXS and refined by full-matrix refinement on F^2 with SHELXL.[49] Drawings were produced with the program ORTEP3.[50]

33: $C_{15}H_{24}O_3$, M = 252.34, monoclinic, space group $P2_1/n$, a = 6.472(2) Å, b 19.291(2) Å, c = 11.852(2) Å, β = 104.62(3)°, V = 1431.8(5) Å^3, Z = 4, D_c = 1.171 g cm^{-3}, T = 293 K, μ = 0.080 mm^{-1}, $F(000)$ = 552, colourless prism (0.47 × 0.47 × 0.37 mm); total reflections 2730, unique reflections 2498 (R_{int} = 0.0784). Final refinement: data/restraints/parameters 2498/0/163, goodness-of-fit on F^2 = 1.011, R_1 = 0.0497 [for 1201 obsd. reflections $I > 2\sigma(I)$], wR_2 = 0.1482 (all data).

36: $C_{17}H_{26}O_4$, M = 294.38, monoclinic, space group $P2_1/c$, a = 10.617(2) Å, b 9.735(2) Å, c = 15.548(5) Å, β = 95.35(2)°, V = 1600.0(7) Å^3, Z = 4, D_c = 1.222 g cm^{-3}, T = 293 K, μ = 0.085 mm^{-1}, $F(000)$ = 640, colourless prism (0.60 × 0.30 × 0.20 mm); total reflections 2964, unique reflections 2804 (R_{int} = 0.0628). Final refinement: data/restraints/parameters 2804/0/190, goodness-of-fit on F^2 = 0.941, R_1 = 0.0721 [for 854 obsd. reflections $I > 2\sigma(I)$], wR_2 = 0.2406 (all data).

49: $C_{18}H_{28}O_5$, M = 324.40, monoclinic, space group $P2_1/a$, a = 10.019(2) Å, b 10.006(1) Å, c = 17.750(3) Å, β = 101.46(2)°, V = 1744.0(5) Å^3, Z = 4, D_c = 1.236 g cm^{-3}, T = 293 K, μ = 0.089 mm^{-1}, $F(000)$ = 704, colourless prism (0.55 × 0.33 × 0.13 mm); total reflections 3189, unique reflections 2998 (R_{int} = 0.0477). Final refinement: data/restraints/parameters 2998/0/213, goodness-of-fit on F^2 = 0.961, R_1 = 0.0591 [for 1032 obsd. reflections $I > 2\sigma(I)$], wR_2 = 0.1767 (all data).

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