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Towards the Total Synthesis of Spirovibsanin A: Total Synthesis of (±)-5,14-Bis-*epi*-spirovibsanin A

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Studies towards the total synthesis of the complex diterpene spirovibsanin A are herein presented, which culminate in an 18-step total synthesis. Considering the perceived stereochemical uncertainty surrounding the assignment of spirovibsanin A these studies have allowed a direct spectroscopic comparison of the (±)-5,14-bis-*epi* derivative to that of natural spirovibsanin A demonstrating that the carbon framework and stereochemistry assigned to natural spirovibsanin A is most likely correct.

Introduction

Spirovibsanin A (**1**), isolated from *Viburnum awabuki* by Fukuyama,[1] is the only vibsanin-type diterpene not belonging to the three traditional sub-classes, represented by vibsanin B (**2**), vibsanin C (**3**), and neovibsanin A (**4**) (Figure 1).[2] There are, however, structural aspects of spirovibsanin A (**1**) present in 15-*O*-methylneovibsanin F (**5**),[3] and 14-*epi*-15-*O*-methylneovibsanin F (**6**),[3] for example, bicyclo[3.3.1]nonane and isopropyl methyl ether moieties. The intriguing facet of **5** and **6** is that they only differ in configuration at position 14 (Figure 1). Considering that neovibsanin F (**7**)[3] and 14-*epi*-neovibsanin F (**8**),[3] as well as, neovibsanin G (**9**)[3] and 14-*epi*-neovibsanin G (**10**)[3] are also epimeric at position 14 led us to question the relative stereochemical assignment of the isopropyl methyl ether function at position 14 of spirovibsanin A (**1**) (Figure 1). Efforts to investigate the stereochemical incertitude of spirovibsanin A (**1**) were therefore warranted, especially considering no synthetic studies had been reported[4] and our group had prior experience with a variety of vibsanin family members.[5]

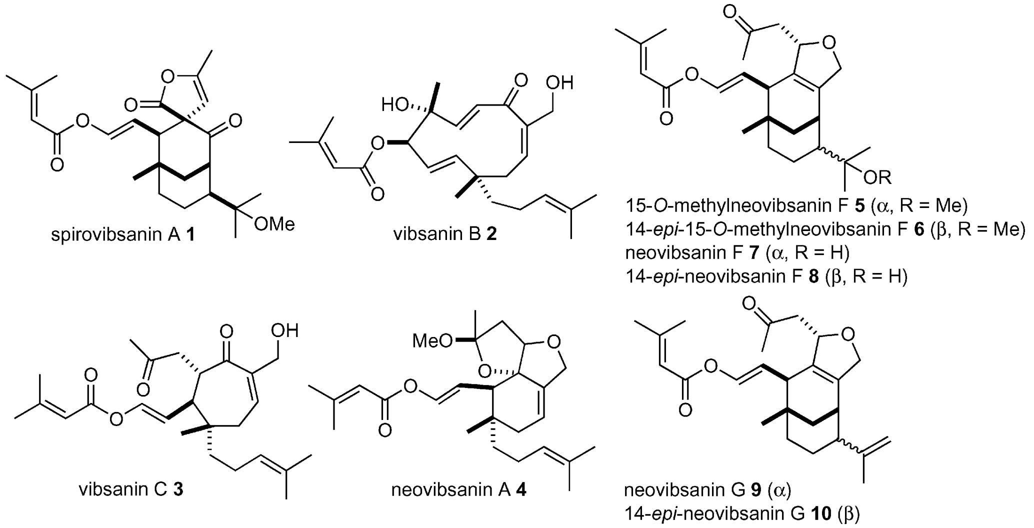

Figure 1. Spirovibsanin A (**1**) and various sub-classes of vibsane-type diterpenes.

Results and Discussion

Retrosynthetic analysis of the target was based on previous work,[6] which described the formation of the bicyclo[3.3.1]nonane **11** from the treatment of the ketone **12**

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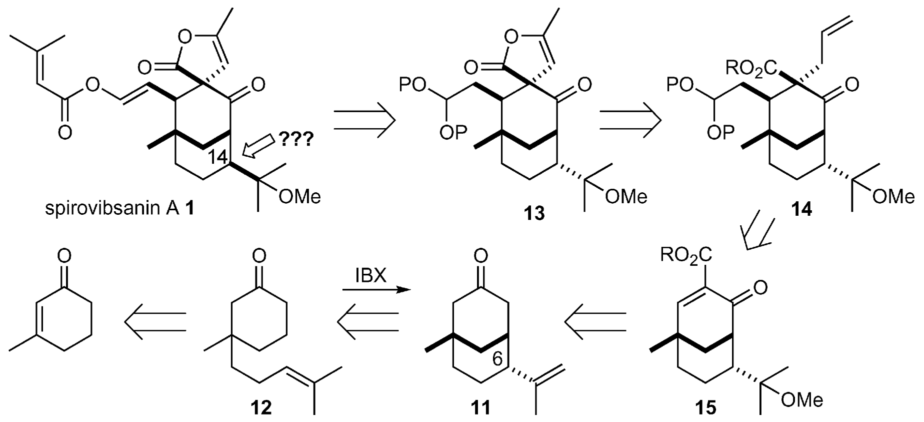
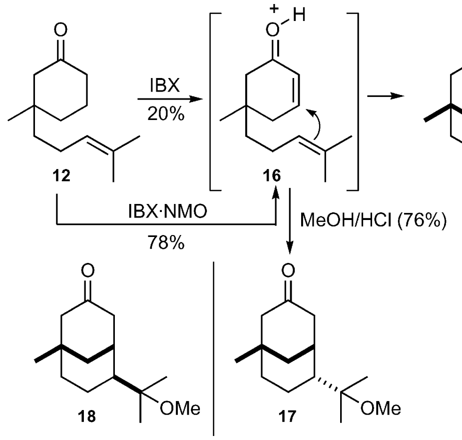


Scheme 1.

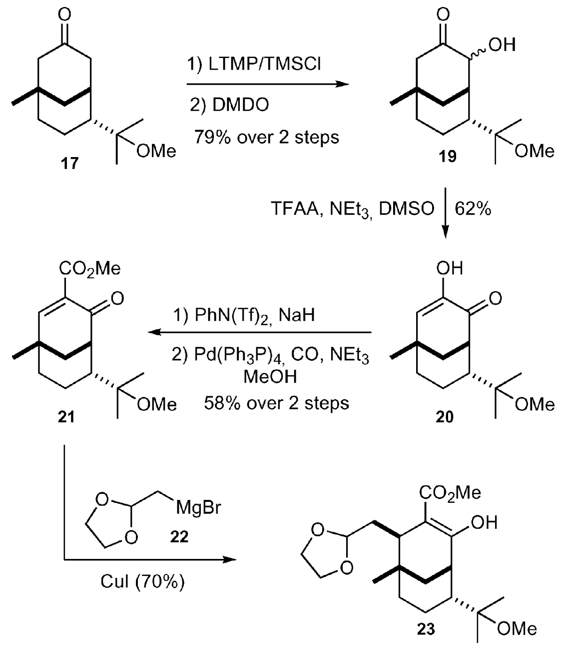
with *o*-iodoxybenzoic acid (IBX) (Scheme 1). Eventhough the functionality at position 6 of **11** was epimeric to that of spirovibsanin A (**1**) at position 14 this was deemed acceptable due to the stereochemical uncertainty posed above. The side chain would be installed last, using the method of Davies,[7] which requires masked aldehyde functionality (i.e. **13**). The spirolactone moiety was perceived best constructed from a palladium-catalysed carboxylic acid alkene oxidative insertion reaction ultimately accessed from allyl and ester functional groups (i.e. **14**). Access to **14** would most likely be achieved with a 1,4-conjugate addition alkylation protocol involving enone **15**, which is derived by functional group manipulation of the bicycle **11** (Scheme 1).

Central to this study was accessing bicycle **11**, which at best was obtained in 20% yield from the ketone **12**[5a–5c] via intermediate **16** (Scheme 2).[6] All attempts to improve this result by screening a barrage of reagents and conditions, failed. When investigations focused on enone **16**, which is better accessed using IBX *N*-methylmorpholine complex (IBX·NMO) in 78% yield, it was discovered that by simply dissolving **16** in methanol and adding trace amounts of concentrated hydrochloric acid, **17** was obtained in 76% yield (Scheme 2). This very fortuitous outcome, confirmed by X-ray crystal structure analysis, gave cyclisation with concomitant methyl ether formation as the sole diastereomer on mass (i.e 60% over 2 steps on a 20-gram scale). All efforts to obtain the β-isomer (i.e. **18**) with such conceivable methods as oxymercuration/radical cyclisation,[8] failed.

Functional-group manipulation arriving at the advanced intermediate **21** proceeded via a novel keto transposition/carbonylation sequence (Scheme 3). Regioselective conversion of **17** into hydroxy ketone **19**, via DMDO oxidation of the corresponding silyl enol ether (4:1 ratio of silyl enol ethers in favour of the desired), proceeded in 79% isolated yield over 2 steps. Moffatt–Swern oxidation gave the keto-transposed diosphenol **20** (62%) as confirmed by X-ray crystal structure analysis. Palladium-catalysed carbonylation[9] of the corresponding triflate, formed using either Comins'[10] or McMurry's[11] reagents, then gave rise to the enone **21** in 58% over 2 steps (Scheme 3).



Scheme 2.

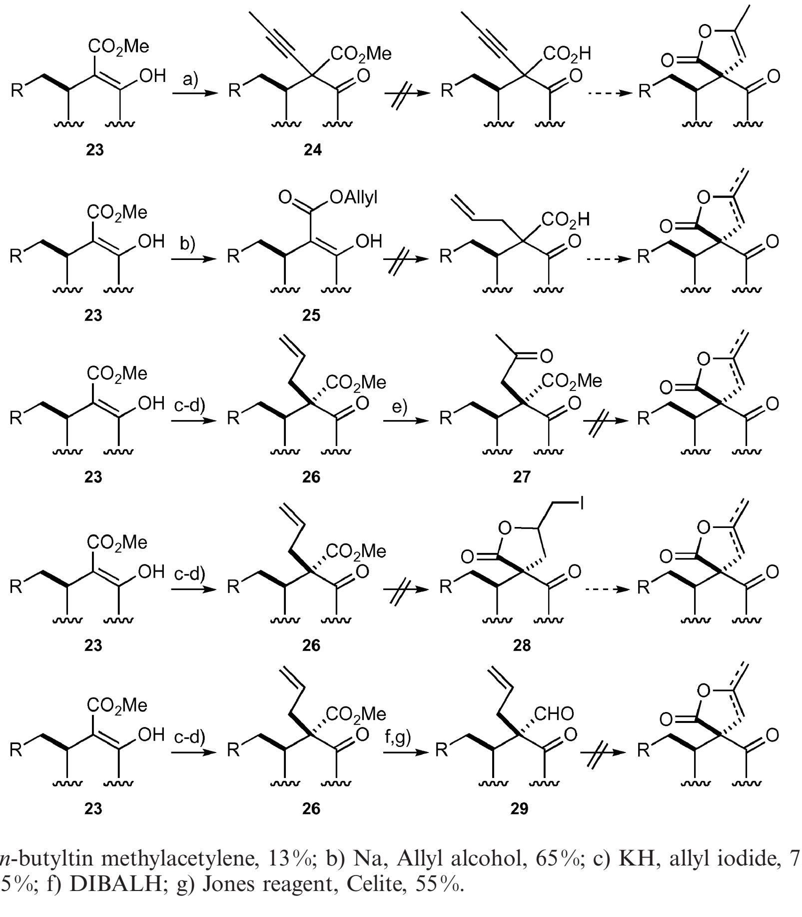


Scheme 3.

The advanced intermediate **21** was now well set for the addition of a 2C-protected aldehyde unit via a 1,4-cuprate addition. (1,3-Dioxolan-2-ylmethyl)magnesium bromide (**22**) was chosen as it satisfied this criteria. Following the literature however, which unfortunately lacks detail,[12] using 2-bromomethyl-1,3-dioxolane to generate the Grignard **22** only gave a maximum yield of ca. 10%. Fortunately, **22** was available commercially and underwent smooth conjugate addition to enone **21**, which occurred stereoselectively affording enol **23** in 70% yield (Scheme 3). Of note was the observation that alkylation of the resulting conjugate addition enolate, with electrophiles such as allyl iodide, completely failed.

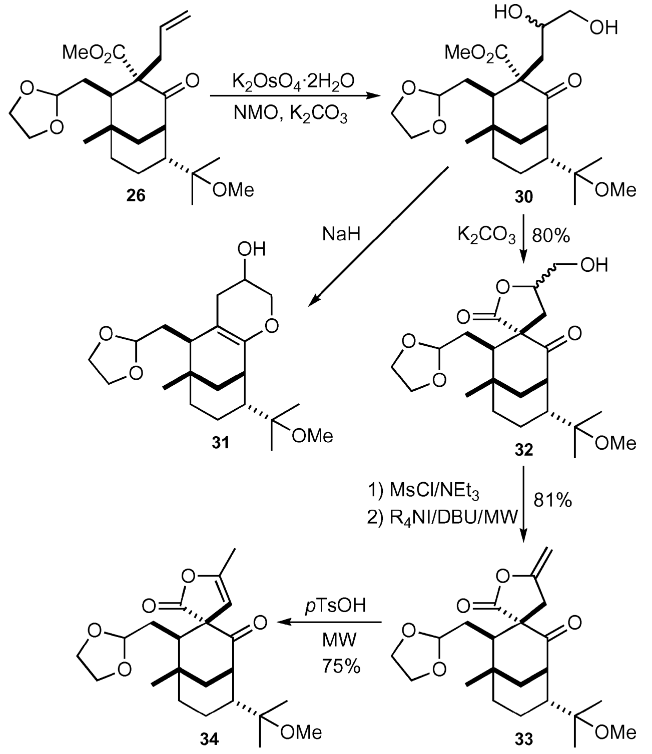
Considering the spirolactone moiety seen in spirovibsanin A (**1**) is rare it is worthy, for educational purposes, to briefly detail the failed attempts made to construct this fragment (Scheme 4). Pinhey coupling,[13] proceeded poorly affording acetylene **24** in only 13%, and subsequent hydroysis could not be forced. Transesterification with allyl alcohol[14] gave **25** in 65%, but palladium-mediated rearrangement to the *C*- or *O*-allylated product failed,[15] only serving to decarboxylate. Direct *C*-allylation failed, but *O*-allylation proceeded with potassium hydride and allyl iodide in 75%, which subsequently underwent Claisen rearrangement in 93% yield (i.e. **26**) when subjected to microwave irradiation (195 °C). The only detracting feature of the rearrangement (most likely occurring via a boat transition state[16]) was that it procured the incorrect stereochemistry at the ester/allyl group juncture to that described for the natural product, which is probably due to the dimethylmethoxy moiety congesting the *endo* face. Wacker oxidation of **26** afforded **27**, but conversion of the 1,4-dicarbonyl to the spirolactone (i.e. Al_2O_3[17]) could not be invoked. One-step iodolactonisation[18] accessed **28**, but the hydrogen iodide formed in situ destroyed the dimethylmethoxy moiety, and addition of base prevented the reaction from proceeding. Global reduction (DIBALH) of **26** followed by global oxidation gave only the aldehyde **29**, which was very resistant to further oxidation.

Fortunately, dihydroxylation of **26** proceeded with catalytic (≈ 5 mol-%) potassium osmate dihydrate, in conjunction with sodium chlorite[19] or *N*-methylmorpholine *N*-oxide (NMO)[20] as co-oxidant, however, the use of NMO as co-oxidant gave superior yields of diol **30**. Intramolecular transesterification of diol **30**, using sodium hydride afforded the undesired six-membered ring **31**, but it was later discovered treating the diol **30** with potassium carbonate afforded the desired five-membered lactone **32** (as confirmed by X-ray crystal structure analysis[4]) in 80% yield over two steps (Scheme 5). Elimination of the pendent alcohol function in **32** was achieved (i.e. **33**), by conversion to the mesylate followed by a one-pot Finkelstein elimination under microwave irradiation, in excellent overall yield. Surprisingly, direct elimination of the mesylate or direct conversion of the alcohol **32** to an iodide failed. Isomerisation of the double bond to the *endo* position (i.e. **34**), via palladium cata-



Scheme 4. a) $Pb(OAc)_4$, tri-*n*-butyltin methylacetylene, 13%; b) Na, Allyl alcohol, 65%; c) KH, allyl iodide, 75%; d) microwave, 195 °C, 93%; e) $PdCl_2$, CuCl, O_2, 65%; f) DIBALH; g) Jones reagent, Celite, 55%.

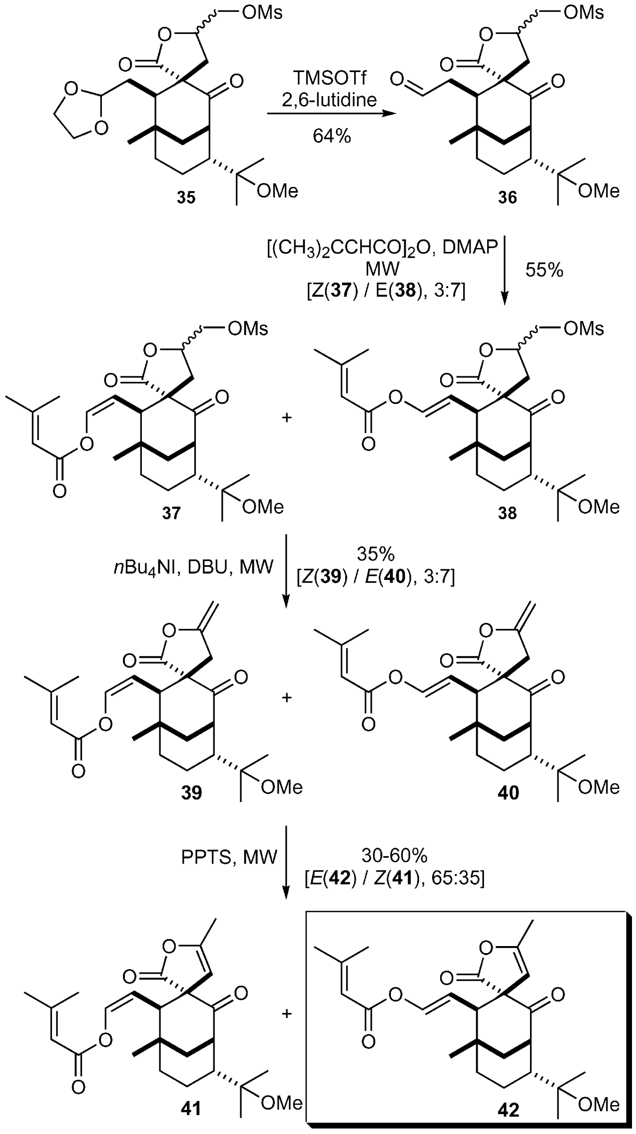
lysts,[21] Wilkinson's catalyst[22] or anhydrous *p*-toluenesulfonic acid,[23,24] were known in the literature. Slight modification (i.e. microwave irradiation) of Jäger's method, which uses anhydrous *p*-toluenesulfonic acid,[23,24] gave the desired spirolactone moiety in 75% yield (Scheme 5).



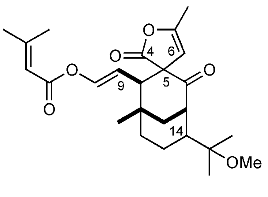
Scheme 5.

Of much disappointment was the slow realisation that deprotection of the dioxolane moiety could not be achieved in the presence of the spirolactone function. Therefore the synthetic strategy was redesigned so that the final stages of the spirolactone construction (i.e. elimination/isomerisation) could be performed toward the end of the sequence. In this view mesylate **35** was deprotected with (trimethylsilyl)methanesulfonate (TMSOTf)[25] to give the aldehyde **36** (64%), which was, using a modified procedure to that of Davies,[7] converted to a mixture of *E*- (**38**) and *Z*-isomers (**37**) of the desired side chain in a ratio of 7:3 (55%) (Scheme 6). The one-pot, microwave-mediated, Finkelstein/elimination reaction developed above gave the *exo*-cyclic enlactones **39** and **40**. The final step required the Jäger *exo*- to *endo*-cyclic double-bond isomerisation, which to our satisfaction, unveiled the desired material as a mixture of isomers [i.e. **41** (*Z*)/**42** (*E*)], using PPTS rather than TsOH (Scheme 6).

Separation of the isomers **41** and **42** by HPLC allowed direct comparison of ^{1}H NMR and ^{13}C NMR spectroscopic data of both **1** and **42**. The most notable differences being; position 14 of spirovibsanin A (**1**) has a proton chemical shift of 2.32 ppm (^{13}C 50.4 ppm) as opposed to 2.73 ppm (^{13}C 52.5 ppm) for **42**. The spirolactone carbon (C-5) is close to identical at δ = 68.1 ppm and 68.2 ppm, whereas both the spirolactone carbonyl carbon (C-4) and lactone double bond carbon (C-6) chemical shifts differ by ca. 3 ppm (Figure 2). Position 9 is also worth noting with a chemical shift difference of 0.55 ppm in the ^{1}H NMR spectra. Overlapping ^{1}H and ^{13}C NMR spectra of both **1** and **42** are presented in the Supporting Information



Scheme 6.



C-4: 172.9 ppm spirovibsanin A (**1**)
176.0 ppm 5-14-bis-*epi*-spirovibsanin A (**42**)

C-5: 68.1 ppm spirovibsanin A (**1**)
68.2 ppm 5-14-bis-*epi*-spirovibsanin A (**42**)

C-6: 107.7 ppm spirovibsanin A (**1**)
104.1 ppm 5-14-bis-*epi*-spirovibsanin A (**42**)

C-14: 50.4 ppm spirovibsanin A (**1**)
52.5 ppm 5-14-bis-*epi*-spirovibsanin A (**42**)

14-H: 2.32 ppm spirovibsanin A (**1**)
2.73 ppm 5-14-bis-*epi*-spirovibsanin A (**42**)

9-H: 5.90 ppm spirovibsanin A (**1**)
5.35 ppm 5-14-bis-*epi*-spirovibsanin A (**42**)

Figure 2. Comparison of relevant ^{1}H and ^{13}C NMR signals, which differentiate spirovibsanin A (**1**) from the synthesized bisepimer (**42**).

Conclusions

In conclusion, considering the stereochemical incertitude over spirovibsanin A **1**, a total synthesis campaign arriving at (±)-5,14-bis-*epi*-spirovibsanin A **42** was warranted. This work gives strong support to Fukuyama's proposed connectivity and relative stereochemistry, but also identifies an efficient route to vibsane type family members containing α stereochemistry at position 14, for example, 15-*O*-methylneovibsanin F (**5**), neovibsanin F (**7**) and neovibsanin G (**9**).

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV300 (300.13 MHz; 75.47 MHz), AV400 (400.13 MHz; 100.62 MHz), DRX500 (500.13 MHz; 125.77 MHz), AV750 (749.41 MHz; 188.46 MHz) and AV900 (900.13 MHz; 226.36 MHz) in deuteriochloroform ($CDCl_3$) or hexadeuteriobenzene (C_6D_6) unless otherwise stated. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. Microwave irradiation was conducted with a CEM Discover microwave in 10 mL or 80 mL pressurized vials. Low-resolution electrospray ionisation mass spectrometry measurements (LRESIMS) were recorded in positive ionization mode with a Bruker Esquire HCT (High Capacity 3D ion trap) instrument with a Bruker ESI source. High-resolution electrospray ionisation (HRESIMS) accurate mass measurements were recorded in positive mode on a Bruker MicrOTOF-Q (quadrupole – Time of Flight) instrument with a Bruker ESI source. Accurate mass measurements were carried out with external calibration using sodium formate as reference calibrant. 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. Analytical high performance liquid chromatography was performed on an Agilent 1100 with Phenomenex Luna 18C 5 µm column. Tetrahydrofuran was freshly distilled from a sodium/benzophenone still. Melting points were determined with a Fischer Johns Melting Point apparatus and are uncorrected.

CCDC-689990 (for **17**) and -689991 (for **20**) 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.

5-Methyl-5-(4-methylpent-3-enyl)-2-cyclohexenone (16):[5a–5c] A mixture of 2-iodoxybenzoic acid (IBX) (7.42 g, 26.5 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (3.23 g, 27.6 mmol) was dissolved in dimethyl sulfoxide (25 mL) and heated to 45 °C. 3-Methyl-3-(4-methylpent-3-enyl)cyclohexanone (**12**) (2.14 g, 11.04 mmol) was added in one portion at 45 °C and the mixture heated at that temperature for 17 h. On cooling the mixture was extracted directly with petroleum ether (4 × 150 mL) and the combined extracts washed with saturated sodium hydrogen carbonate solution and brine. The organic layer was dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to column chromatography (petroleum ether/ethyl acetate, 20:1) yielding the title compound (1.65 g, 78%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.85–6.81 (m, 1 H), 5.99 (dt, *J* = 10.1, 2.0 Hz, 1 H), 5.06–5.01 (m, 1 H), 2.33–2.27 (m, 2 H), 2.25–2.21 (m, 1 H), 2.17–2.13 (m, 1 H), 1.98–1.85 (m, 2 H), 1.64 (br. d, *J* = 1.1 Hz, 3 H), 1.56 (br. s, 3 H), 1.38–1.30 (m, 2 H), 1.00 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 199.8, 148.2, 131.7, 129.0, 124.0, 50.1, 41.4, 38.1, 36.5, 25.6, 24.7, 22.3, 17.5 ppm. Mass spectrum: GCMS (EI): *m/z* (%) = 192 (12.0) [$M^{+\cdot}$], 149 (10), 124 (25), 109 (100), 95 (5), 81 (13), 69 (18), 55 (10). $C_{13}H_{20}O$: calcd. $M^{+\cdot}$ 192.1514; found $M^{+\cdot}$ 192.1507

6-Isopropenyl-1-methylbicyclo[3.3.1]nonan-3-one (11): A mixture of 2-iodoxybenzoic acid (IBX) (1.46 g, 5.1 mmol) in dimethyl sulfoxide (17 mL) was heated to 70 °C. After complete solvation of IBX, 3-methyl-(4-methylpent-3-enyl)cyclohexanone (**12**) (582 mg, 3 mmol) was added in one portion to the stirring solution. The reaction was monitored by GC and ceased after 70 h. The mixture was added to water, extracted with diethyl ether (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography of the residue (petroleum ether/ethyl acetate, 17:1) provided the title compound (125 mg, 22%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.82 (s, 1 H), 4.58 (s, 1 H), 2.41 (m, 1 H), 2.35–2.32 (m, 1 H), 2.23–2.20 (m, 1 H), 2.08 (m, 1 H), 2.04 (m, 2 H), 1.82–1.79 (m, 1 H), 1.67 (s, 3 H), 1.62–1.53 (m, 3 H), 1.35–1.31 (m, 2 H), 0.97 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 212.7, 146.5, 110.6, 53.8, 46.9, 41.2, 40.8, 39.2, 33.9, 32.6, 31.0, 23.4, 22.5 ppm. Mass spectrum: GCMS (EI): *m/z* (%) = 192 (14.0) [$M^{+\cdot}$], 134 (10), 121 (26), 111 (49), 110 (11), 109 (100), 108 (13), 107 (17), 95 (13), 93 (29), 91 (13), 81 (17), 79 (16), 77 (13). $C_{13}H_{20}O$: calcd. $M^{+\cdot}$ 192.1514; found: $M^{+\cdot}$ 192.1509.

6-(2-Methoxypropan-2-yl)-1-methylbicyclo[3.3.1]nonan-3-one (17): 5-Methyl-5-(4-methylpent-3-enyl)-2-cyclohexenone (**16**) (15.0 g, 78.0 mmol) was added dropwise to a flask containing methanol (400 mL) and concentrated (32%) hydrochloric acid (0.5 mL). The solution was stirred at room temperature and after 30 min, saturated sodium hydrogen carbonate solution (20 mL) was added. The methanol was removed in vacuo and the solution diluted with water (300 mL) and extracted with diethyl ether (4 × 250 mL). The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 9:1) provided the title compound (13.3 g, 76%) as a white solid. Colourless crystals (m.p. 53 °C) were obtained by recrystallisation from petroleum ether. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.12 (s, 3 H), 2.82 (ddd, *J* = 16.2, 4.3, 2.1 Hz, 1 H), 2.57–2.50 (m, 1 H), 2.20–2.01 (m, 3 H), 1.75–1.70 (bdt, *J* = 13.0, 3.0 Hz, 1 H), 1.57–1.45 (m, 4 H), 1.32–1.26 (m, 2 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.9, 76.1, 53.8, 50.3, 48.8, 42.9, 42.6, 40.0, 34.1, 32.1, 31.0, 23.6, 23.1, 20.6 ppm. Mass spectrum: GCMS (EI): *m/z (%)* = 224 (0.4) [$M^{+\cdot}$], 135 (5), 109 (11), 93 (5), 81 (5), 79 (5), 74 (17), 73 (100). $C_{14}H_{24}O_2$ (224.18): calcd. C 74.95, H 10.78; found C 74.96, H 11.05.

4-Hydroxy-6-(2-methoxypropan-2-yl)-1-methylbicyclo[3.3.1]nonan-3-one (19): Following a procedure similar to Myers and Liu,[26] 6-(2-methoxypropan-2-yl)-1-methylbicyclo[3.3.1]nonan-3-one (**17**) (300 mg, 1.34 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL) under argon. The solution was cooled to –78 °C (dry ice/acetone bath) and freshly distilled (CaH_2) chlorotrimethylsilane (187 µL, 1.47 mmol) added. Separately, at 0 °C, anhydrous 2,2,6,6-tetramethylpiperidine (285 µL, 1.68 mmol) was added to a flask containing anhydrous tetrahydrofuran (2 mL) under argon. To this *n*-butyllithium (1.4 M, 1.05 mL, 1.47 mmol) was added dropwise via syringe, and the solution stirred for 15 min. The lithium 2,2,6,6-tetramethylpiperidide solution was then added dropwise via cannula to the above solution at –78 °C and the mixture stirred at this temperature for 1 h. The solution was then warmed to room temperature over 2 h before addition to ice/water and extraction with diethyl ether (4 × 30 mL). The organic phase was washed with saturated ammonium chloride (50 mL), saturated sodium hydrogen carbonate (30 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 50:1) of the residue provided [8-(2-methoxypropan-2-yl)-5-methylbicyclo[3.3.1]non-2-en-3-yloxy]trimethylsilane (377 mg, 95%) as a colourless oil in a ratio of 8:2 in favour of the desired regioisomer (^{1}H NMR). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 4.84 (d, J = 6.8 Hz, 1 H), 3.14 (s, 3 H), 2.54 (bm, 1 H), 1.90,1.72 (AB quartet, J = 17.8 Hz, 2 H), 1.53–1.42 (m, 5 H), 1.25 (bd, 1 H), 1.22 (m, 1 H) 1.08 (s, 3 H), 1.06 (s, 3 H), 0.89 (s, 3 H), 0.17 (s, 9 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 151.6, 105.7, 76.7, 49.3, 48.7, 43.8, 42.1, 41.9, 31.8, 31.2, 31.0, 23.9, 23.3, 20.8, –0.5 (SiMe$_3$) ppm. Mass spectrum: GCMS (EI): m/z (%) = 296 (3.8) [M$^{+\cdot}$], 223 (6), 182 (12), 181 (69), 180 (6), 179 (6), 165 (26), 105 (5), 93 (6), 91 (10), 81 (5), 79 (6), 77 (5), 75 (13), 74 (7), 73 (100), 59 (7), 55 (10). Following a procedure analogous to Adam and Prechtl,[27] 6-(2-methoxypropan-2-yl)-1-methylbicyclo[3.3.1]non-3-en-3-trimethylsilyl ether (1.27 g, 4.3 mmol) was dissolved in distilled acetone (50 mL) and cooled to –78 °C. Dimethyldioxirane[28] (≈ 0.08 M, 4.5 mmol, 57 mL) was added dropwise over 10 min. The reaction was monitored by TLC (petroleum ether/ethyl acetate, 10:1), which showed complete consumption of starting material after 20 min. After pouring the solution (–78 °C) into water (100 mL) at room temperature and removal of acetone in vacuo the aqueous phase was extracted with diethyl ether (4 × 60 mL). The organic phase was washed with brine (50 mL), dried (MgSO$_4$) and concentrated in vacuo which provided **19** (850 mg, 83%) as a colourless oil that was used without further purification. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 4.39–4.37 (m, 1 H), 3.13 (s, 3 H), 2.87–2.80 (m, 1 H), 2.46–2.42 (m, 1 H), 2.43, 2.12 (AB quartet, J = 17.2 Hz, 2 H), 2.00–1.92 (bdt, 1 H), 1.69–1.62 (m, 1 H), 1.59–1.54 (m, 1 H), 1.43–1.32 (m, 3 H), 1.20 (s, 3 H), 1.18 (m, 1 H) 1.14 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 213.2, 76.0, 72.5, 49.9, 49.1, 49.0, 39.9, 39.7, 37.5, 34.6, 31.3, 23.6, 23.5, 20.9 ppm. Mass spectrum: GCMS (EI): m/z (%) = 240 (0.4) [M$^{+\cdot}$], 196 (5), 136 (5), 135 (8), 95 (5), 93 (6), 81 (5), 79 (5), 73 (100). C$_{14}$H$_{24}$O$_3$Na$^+$: calcd. [M + Na]$^+$ 263.1618; found: [M + Na]$^+$ 263.1611.

3-Hydroxy-8-(2-methoxypropan-2-yl)-5-methylbicyclo[3.3.1]non-3-en-2-one (20): Following a procedure similar to Kawada et al.,[29] to a solution of anhydrous dimethyl sulfoxide (0.34 mL, 4.8 mmol) in anhydrous dichloromethane (15 mL) under argon was added trifluoroacetic anhydride (0.5 mL, 3.57 mmol) at –78 °C. After 10 min of stirring, hydroxyketone **19** (500 mg, 2.08 mmol) in anhydrous dichloromethane (5 mL) was added. The solution was stirred for 30 min at –78 °C before addition of anhydrous triethylamine (1.72 mL, 12.4 mmol). The reaction was warmed to room temperature over 40 min and then poured into water (20 mL). The mixture was extracted with dichloromethane (4 × 15 mL) and the organic phase washed with brine (20 mL), dried (MgSO$_4$) and concentrated in vacuo. The crude was subjected to column chromatography (petroleum ether/ethyl acetate, 15:1) affording the title compound (308 mg, 62%) as a white solid. A sample was then crystallised from (50:50) petroleum ether/diethyl ether giving colourless crystals (m.p. 82 °C). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 5.98 (s, 1 H), 5.67 (d, J = 1.8 Hz, 1 H), 3.10 (s, 3 H), 2.91 (m, 1 H), 2.11 (ddd, J = 12.6, 2.9, 2.9 Hz, 1 H), 1.76–1.52 (m, 5 H), 1.47–1.41 (m, 1 H), 1.17 (s, 3 H), 1.11 (s, 6 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 198.6, 148.3, 123.3, 75.7, 49.0, 48.6, 44.4, 42.5, 35.6, 33.0, 29.5, 22.7, 22.4, 20.0 ppm. Mass spectrum: GCMS (EI): m/z (%) = 238 (1.4) [M$^{+\cdot}$], 79 (4), 77 (4), 74 (5), 73 (100), 67 (5), 55 (9). C$_{14}$H$_{22}$O$_3$ (238.33): calcd. C 70.56, H 9.30; found C 70.40, H 9.47.

Methyl 6-(2-Methoxypropan-2-yl)-1-methyl-4-oxobicyclo[3.3.1]non-2-ene-3-carboxylate (21): Following a procedure similar to Kuroso et al.,[30] compound **20** (420 mg, 1.76 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) under argon and the solution cooled to –78 °C. Sodium hydride (60 wt.-% in paraffin oil, 141 mg, 3.52 mmol), washed with petroleum ether (2 × 3 mL), was added to the flask in portions and the solution stirred for 30 min after which time effervescence ceased. *N*-Phenyl-bis(trifluoromethanesulfonimide) (943 mg, 2.64 mmol) was then added and the solution stirred for 40 min after which time TLC (petroleum ether/ethyl acetate, 10:1) indicated consumption of starting material. Water (10 mL) was added at –78 °C and the solution warmed to room temperature over 1 h. The mixture was extracted with diethyl ether (3 × 20 mL), and the combined organic phase washed with brine (10 mL), dried (MgSO$_4$) and concentrated in vacuo. The triflate was often used in subsequent reactions without further purification; however, purification by column chromatography (petroleum ether/ethyl acetate, 15:1) in this case afforded 6-(2-methoxypropan-2-yl)-1-methyl-4-oxobicyclo[3.3.1]non-2-en-3-yl trifluoromethanesulfonate (518 mg, 80%) as a colourless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 6.40 (m, 1 H), 3.04 (s, 3 H), 2.96 (m, 1 H), 2.14 (ddd, J = 13.0, 2.9, 2.9 Hz, 1 H), 1.83–1.78 (m, 1 H), 1.72–1.49 (m, 5 H), 1.17 (s, 3 H), 1.12 (s, 3 H), 1.10 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 192.7, 145.3, 143.6, 122.8 (q, $_{\mathrm{CF}}J$ = 320 Hz), 75.5, 49.5, 48.6, 44.0, 43.0, 35.0, 35.0, 28.4, 22.7, 22.4, 19.8 ppm. Mass spectrum: GCMS (EI): m/z (%) = 370 (0.2) [M$^{+\cdot}$] 355 (10), 93 (5), 91 (5), 82 (8), 81 (5), 79 (5), 77 (5), 74 (15), 73 (100), 72 (5), 69 (17), 67 (6), 55 (10). C$_{15}$H$_{21}$O$_5$SF$_3$Na$^+$ calcd. [M + Na]$^+$ 393.0954; found: [M + Na]$^+$ 393.0942. Following a procedure analogous to Yamamoto[9] tetrakis(triphenylphosphane)palladium(0) (373 mg, 0.32 mmol) was added in one portion to a flask containing 8-(2-methoxypropan-2-yl)-5-methylbicyclo[3.3.1]non-3-en-2-one-3-yl trifluoromethanesulfonate (2.33 g, 6.30 mmol) dissolved in anhydrous tetrahydrofuran (100 mL) under argon at room temperature. Carbon monoxide was slowly bubbled through the solution (solution became dark red) for 30 min before the addition of anhydrous triethylamine (4.70 mL, 33.8 mmol) and anhydrous methanol (10.3 mL, 0.25 mol). The mixture was heated at reflux for 90 min with a continuous stream of carbon monoxide being passed through the solution. At this point a further addition of palladium catalyst, triethylamine and methanol (two-thirds of the original quantities) was carried out. The reaction was complete (TLC) within 30 min. The reaction mixture was cooled to room temperature, then poured onto water (100 mL) and extracted with diethyl ether (3 × 100 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 15:1) of the residue provided the title compound (1.27 g, 72%) as a colourless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.12 (d, J = 2.5 Hz, 1 H), 3.74 (s, 3 H), 3.01 (s, 3 H), 2.80–2.75 (m, 1 H), 2.09 (ddd, J = 12.9, 3.1, 3.1 Hz, 1 H), 1.76–1.37 (m, 6 H), 1.10 (m, 9 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 198.1, 165.0, 160.4, 133.9, 75.5, 51.9, 48.7, 48.6, 45.4, 42.2, 34.9, 34.2, 27.9, 22.8, 22.5, 19.9 ppm. Mass spectrum: GCMS (EI): m/z (%) = 280 (0.1) [M$^{+\cdot}$], 247 (8), 209 (8), 208 (14), 119 (5), 115 (5), 107 (5), 105 (8), 93 (7), 91 (16), 81 (6), 79 (16), 77 (15), 74 (19), 73 (100). C$_{16}$H$_{24}$O$_4$Na$^+$: calcd. [M + Na]$^+$ 303.1567; found: [M + Na]$^+$ 303.1563.

Methyl 4-[(1,3-Dioxolan-2-yl)methyl]-2-hydroxy-8-(2-methoxypropan-2-yl)-5-methylbicyclo[3.3.1]non-2-ene-3-carboxylate (23): Copper(I) iodide (658 mg, 3.46 mmol) was added to a flask containing anhydrous tetrahydrofuran (130 mL) under argon. The flask was cooled to –78 °C and commercial (1,3-dioxolan-2-ylmethyl)magnesium bromide (**22**) (0.5 M, 13.8 mL, 6.92 mmol) was added dropwise via syringe over 10 min. The solution was stirred for 30 min before addition of **21** (1.29 g, 4.60 mmol) in anhydrous tetrahydrofuran (5 mL) dropwise over 5 min. The mixture was warmed to room temperature (≈ 4 h) and then stirred overnight. The mixture was then gently heated at 45 °C until consumption of **21** was complete

(TLC). The mixture was poured onto a saturated ammonium chloride solution (100 mL) and then extracted with diethyl ether (3 × 80 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 8:1) provided the title compound (1.19 g, 70%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 12.35 (s, 1 H), 4.86 (dd, *J* = 6.0, 3.9 Hz, 1 H), 3.94–3.84 (m, 2 H), 3.81–3.71 (m, 2 H), 3.73 (s, 3 H), 3.11 (s, 3 H), 2.68–2.63 (m, 1 H), 2.39 (dd, *J* = 6.6, 3.3 Hz, 1 H), 1.97 (ddd, *J* = 15.1, 6.7, 3.9 Hz, 1 H), 1.93–1.86 (m, 1 H), 1.72–1.12 (m, 7 H), 1.18 (s, 3 H), 1.02 (m, 3 H), 0.92 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4, 172.3, 104.5, 104.3, 76.6, 64.7, 64.4, 51.2, 50.3, 48.7, 43.4, 39.2, 38.8, 37.5, 36.7, 32.7, 29.2, 22.5, 22.1, 21.1 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 368 (4.0) $[M^{+\cdot}]$, 295 (4), 208 (4), 206 (4), 196 (5), 175 (5), 150 (4), 148 (5), 141 (7), 137 (6), 131 (4), 126 (4), 113 (7), 107 (7), 74 (5), 73 (100), 59 (7), 55 (11). $C_{20}H_{32}O_6Na^+$: calcd. $[M + Na]^+$ 391.2091; found: $[M + Na]^+$ 391.2101.

Methyl 2-[(1,3-Dioxolan-2-yl)methyl]-3-allyl-6-(2-methoxypropan-2-yl)-1-methyl-4-oxobicyclo[3.3.1]nonane-3-carboxylate (26): Compound **23** (1.19 g, 3.23 mmol) was dissolved in freshly distilled, anhydrous *N*,*N′*-dimethylpropylene urea (35 mL). Potassium hydride (30 wt.-% dispersion in mineral oil) (431 mg, 6.46 mmol) was added and the solution stirred for 35 min until effervescence had ceased. Allyl iodide (705 mg, 4.20 mmol) was added and the reaction monitored (TLC) until consumption of **23** (30 min). The reaction mixture was carefully poured onto water (50 mL) and then extracted with diethyl ether (3 × 60 mL). The combined organic fractions were washed with brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 10:1) of the residue provided methyl 4-[(1,3-dioxolan-2-yl)methyl]-2-allyloxy-8-(2-methoxypropan-2-yl)-5-methylbicyclo[3.3.1]non-2-ene-3-carboxylate as a colourless oil (0.99 g, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.97 (dddd, *J* = 17.2, 10.6, 5.6, 5.4 Hz, 1 H), 5.29–5.22 (m, 1 H), 5.15–5.10 (m, 1 H), 4.90 (dd, *J* = 6.1, 3.9 Hz, 1 H), 4.39–4.24 (m, 2 H), 3.94–3.83 (m, 2 H), 3.81–3.70 (m, 2 H), 3.70 (s, 3 H), 3.15 (s, 3 H), 2.77–2.73 (m, 1 H), 2.45–2.42 (m, 1 H), 1.87–1.20 (m, 9 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 0.94 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.5, 157.8, 134.4, 122.7, 116.8, 103.7, 76.8, 71.2, 64.7, 64.5, 51.3, 50.7, 48.6, 43.9, 41.1, 38.6, 37.2, 32.4, 32.2, 28.7, 23.5, 21.4, 21.0 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 408 (0.2) $[M^{+\cdot}]$, 393 (0.4), 377 (1), 345 (1), 316 (1), 288 (1), 281 (3), 267 (2), 254 (1), 228 (1), 213 (4), 207 (5), 196 (6), 181 (9), 164 (12), 149 (4), 137 (4), 135 (6), 109 (6), 107 (6), 95 (5), 93 (14), 91 (8), 81 (6), 79 (8), 73 (95), 67 (5), 59 (5), 45 (25), 44 (100). $C_{23}H_{36}O_6Na^+$: calcd. $[M + Na]^+$ 431.2404; found: $[M + Na]^+$ 431.2412. Methyl 4-[(1,3-dioxolan-2-yl)methyl]-2-(allyloxy)-8-(2-methoxypropan-2-yl)-5-methylbicyclo[3.3.1]non-2-ene-3-carboxylate (300 mg, 0.82 mmol) was dissolved in anhydrous toluene (2.5 mL) under argon and the mixture heated under microwave irradiation for 60 min (maximum temperature 195 °C, 250 W). This provided an approximately 12:1 ratio of *C*-allylated material (**26**) to *O*-allylated material. The solvent was removed in vacuo, and column chromatography (petroleum ether/ethyl acetate, 10:1) of the residue provided the title compound **26** [279 mg, 93%] as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.74–5.62 (m, 1 H), 4.91 (m, 1 H), 4.89–4.86 (m, 1 H), 4.83 (dd, *J* = 6.3, 3.5 Hz, 1 H), 3.91–3.82 (m, 2 H), 3.79–3.73 (m, 2 H), 3.64 (s, 3 H), 3.10 (s, 3 H), 2.99–2.94 (m, 1 H), 2.73 (dd, *J* = 9.2, 4.5 Hz, 1 H), 2.55–2.52 (m, 1 H), 2.15–2.10 (m, 1 H), 2.07 (dd, *J* = 14.3, 9.8 Hz, 1 H), 1.99 (ddd, *J* = 14.6, 9.2, 3.5 Hz, 1 H), 1.75–1.61 (m, 4 H), 1.42 (ddd, *J* = 14.7, 6.3, 3.4 Hz, 1 H), 1.27 (dd, *J* = 14.1, 2.0 Hz, 1 H), 1.24 (s, 3 H), 1.20 (m, 1 H), 1.07 (s, 3 H), 1.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.9, 173.7, 134.9, 116.3, 103.6, 76.6, 65.6, 64.8, 64.6, 52.1, 51.4, 48.5, 44.9, 42.9, 39.7, 37.6, 36.1, 32.8, 31.0, 27.9, 22.5, 21.2, 20.8 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 408 (0.1) $[M^{+\cdot}]$ 213 (4), 196 (8), 181 (6), 164 (5), 136 (4), 121 (3), 109 (3), 107 (3), 93 (5), 91 (5), 81 (4), 79 (6), 73 (100), 67 (5), 55 (6). $C_{23}H_{36}O_6Na^+$: $[M + Na]^+$ 431.2404; found: $[M + Na]^+$ 431.2523.

Dihydroxylation/Lactonisation of 26 Affording 32: Following a procedure similar to Köckritz et al.,[19] compound **26** (442 mg, 1.08 mmol) was dissolved in *tert*-butyl alcohol/water (1:1, 20 mL). To this was added potassium carbonate (168 mg, 1.22 mmol), *N*-methylmorpholine *N*-oxide (140 mg, 1.20 mmol) and potassium osmate(VI) dihydrate (26 mg, 0.08 mmol). The mixture was stirred at room temperature for 16 h. Saturated sodium sulfite solution (2 mL) was added and the solution stirred for 30 min. The solvent was removed in vacuo and the residue dissolved in dichloromethane and passed through a plug of Celite®. The residue was redissolved in *tert*-butyl alcohol/water (1:1, 10 mL), potassium carbonate (750 mg, 5.40 mmol) added and the mixture stirred at room temperature overnight. The solvent was removed in vacuo, the residue dissolved in dichloromethane and passed through a plug of Celite®. After concentration in vacuo, the residue was dissolved in ethyl acetate to facilitate crystallisation of the lactone (**32**). Any unreacted diol (**30**) remaining in solution was re-subjected to the lactonisation protocol. This procedure provided the desired lactone (**32**) as a mixture of diastereomers (60:40), partially separable on recrystallisation, as colourless crystals (386 mg, 87% over two steps). Minor diastereomer only: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.90 (dd, *J* = 6.4, 3.5 Hz, 1 H), 4.57–4.49 (m, 1 H), 3.98–3.75 (m, 5 H), 3.62 (dd, *J* = 12.4, 5.4 Hz, 1 H), 3.10 (s, 3 H), 2.89–2.86 (m, 1 H), 2.79 (bdd, *J* = 8.9, 3.5 Hz, 1 H), 2.35 (dd, *J* = 13.7, 9.3 Hz, 1 H), 2.19–1.94 (m, 3 H), 1.92–1.63 (m, 5 H), 1.45–1.21 (m, 3 H), 1.20 (s, 3 H), 1.09 (s, 3 H), 1.08 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 215.0, 176.7, 103.6, 77.9, 76.2, 64.8, 64.7, 64.2, 61.9, 51.4, 48.6, 44.0, 41.4, 40.9, 36.8, 33.7, 31.7, 30.5, 28.0, 22.4, 22.0, 20.8 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 410 (0.03) $[M^{+\cdot}]$, 379 (0.4), 364 (0.3), 363 (0.5), 348 (0.1), 337 (2), 322 (0.2), 316 (0.2), 309 (0.3), 292 (0.3), 280 (0.2), 273 (0.2), 269 (0.1), 256 (0.1), 249 (0.4), 233 (0.4), 219 (0.2), 215 (4), 207 (1), 196 (4), 191 (0.4), 181 (1), 175 (1), 173 (1), 164 (4), 153 (2), 149 (1), 147 (1), 137 (2), 136 (3), 135 (2), 122 (2), 121 (3), 109 (3), 95 (3), 93 (4), 91 (5), 81 (5), 79 (5), 77 (3), 73 (100), 67 (5), 55 (7). $C_{22}H_{34}O_7Na^+$: calcd. $[M + Na]^+$ 433.2197; found: $[M + Na]^+$ 433.2186.

{2-[(1,3-Dioxolan-2-yl)methyl]-6-(2-methoxypropan-2-yl)-1-methyl-2′,4-dioxodihydro-2′*H*-spiro[bicyclo[3.3.1]nonane-3,3′-furan]-5′-yl}methyl Methanesulfonate (35): Compound **32** (250 mg, 0.61 mmol) was dissolved in anhydrous dichloromethane (6 mL) under argon. To this was added anhydrous triethylamine (170 µL, 1.22 mmol) followed by mesyl chloride (71 µL, 0.92 mmol). The solution was stirred at room temperature for 30 min and then added to water (5 mL). The aqueous phase was extracted with dichloromethane (3 × 5 mL) and the organic phase then washed with brine, dried ($MgSO_4$) and concentrated in vacuo to provide the title compound (>95%) as a mixture of diastereomers (50:50) which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.87–4.80 (m, 1 H), 4.72–4.62 (m, 1 H), 4.41–4.23 (m, 2 H), 3.96–3.85 (m, 2 H), 3.83–3.72 (m, 2 H), 3.08–3.05 (m, 6 H), 2.92–2.73 (m, 2 H), 2.52–2.19 (m, 1 H), 2.18–1.90 (m, 2 H), 1.94–1.62 (m, 5 H), 1.39–1.23 (m, 3 H), 1.18–1.15 (m, 3 H), 1.09–1.08 (m, 3 H), 1.04–1.03 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 214.5, 176.1, 103.4, 76.1, 74.0, 69.6, 64.9, 64.7, 60.9, 51.4, 48.6, 44.1, 41.4, 40.7, 37.8, 36.8, 33.6, 32.0, 30.5, 27.9, 22.4, 22.1, 20.7 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 488 (0) $[M^{+\cdot}]$, 392 (5), 323 (4), 175 (5), 145 (6), 135 (6), 131 (6), 121 (6), 119 (7), 117 (6), 107 (8), 105 (10), 93 (7), 91 (5), 87 (5), 81 (5), 79 (12), 77 (13), 74 (7), 73 (100), 69 (7), 67 (9), 59 (7), 55 (6). $C_{23}H_{36}O_9SNa^+$: calcd. $[M + Na]^+$ 511.1972; found: $[M + Na]^+$ 511.1963.

{6-(2-Methoxypropan-2-yl)-1-methyl-2′,4-dioxo-2-(2-oxoethyl)dihydro-2′*H*-spiro[bicyclo[3.3.1]nonane-3,3′-furan]-5′-yl}methyl Methanesulfonate (36): Following a procedure similar to Fujioka et al.;[25] mesylate **35** (528 mg, 1.08 mmol) was dissolved in anhydrous dichloromethane (30 mL) under argon. To this was added anhydrous 2,6-lutidine (1.14 mL, 9.80 mmol), followed by trimethylsilyl trifluoromethanesulfonate (1.17 mL, 6.5 mmol). The reaction was followed (TLC) to note disappearance of the starting material and appearance of a polar spot on the baseline of the TLC plate (30 min). At this point water (20 mL) was added and the mixture monitored (TLC) for the formation of a newly running spot. The mixture was then extracted with dichloromethane (3 × 30 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 1:2) of the residue provided the title compound (305 mg, 64%), as a colourless oil (*dr* = 45:55). ^{1}H NMR ($CDCl_3$, 400 MHz) Minor: δ = 9.40 (m, 1 H), 4.43–4.37 (m, 1 H), 4.15 (d, J = 4.1 Hz, 1 H), 4.01 (dd, J = 11.8, 4.6 Hz, 1 H), 3.39 (dd, J = 10.1, 3.1 Hz, 1 H), 2.99 (s, 3 H), 2.73 (m, 1 H), 2.55 (s, 3 H), 2.52–2.45 (m, 1 H), 1.93–1.77 (m, 3 H), 1.71–1.62 (m, 2 H), 1.57–1.33 (m, 3 H), 1.14 (m, 6 H), 0.97–0.88 (m, 2 H), 0.64 (s, 3 H) ppm. Major: δ = 9.36 (m, 1 H), 4.38–4.31 (m, 1 H), 4.19 (dd, J = 11.8, 2.7 Hz, 1 H), 4.14 (d, J = 6.5 Hz, 1 H), 3.26 (dd, J = 10.4, 2.9 Hz, 1 H), 3.00 (s, 3 H), 2.69 (s, 1 H), 2.54 (s, 3 H), 2.38–2.30 (m, 1 H), 1.93–1.77 (m, 3 H), 1.71–1.62 (m, 2 H), 1.57–1.33 (m, 3 H), 1.13 (m, 6 H), 0.97–0.88 (m, 2 H), 0.66 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 213.9, 212.1, 199.8, 199.4, 176.1, 175.4, 75.8, 75.8, 74.4, 73.9, 70.0, 68.7, 61.8, 60.6, 51.9, 51.8, 48.6, 48.6, 44.3, 44.1, 44.1, 43.7, 41.3, 41.1, 40.6, 40.2, 37.1, 37.0, 35.8, 34.6, 32.3, 31.8, 30.3, 30.2, 27.4, 27.3, 22.6, 22.5, 22.2, 22.2, 21.1, 20.9 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 348 (0.4) $[M^{+\cdot}]$, 298 (1), 281 (2), 249 (1), 207 (3), 196 (3), 191 (2), 173 (2), 164 (19), 153 (7), 149 (5), 135 (9), 121 (5), 119 (4), 109 (10), 107 (8), 96 (11), 93 (12), 91 (10), 81 (9), 79 (13), 73 (100), 67 (7), 55 (10). $C_{21}H_{32}O_8SNa^+$: calcd. $[M + Na]^+$ 467.1710; found: $[M + Na]^+$ 467.1724.

(*E*/*Z*)-2-(6-(2-Methoxypropan-2-yl)-1-methyl-5′-methylene-2′,4-dioxodihydro-2′*H*-spiro[bicyclo[3.3.1]nonane-3,3′-furan]-2-yl}vinyl 3-Methylbut-2-enoate (40/39): To aldehyde **36** (179 mg, 0.40 mmol) dissolved in anhydrous toluene (3 mL) was added 4-(dimethylamino)pyridine (82 mg, 0.67 mmol) and 3-methylbut-2-enoic anhydride[31] (102 mg, 0.56 mmol). The mixture was heated under microwave irradiation for 20 min (maximum temperature 85 °C, 250 W). On cooling, diethyl ether (10 mL) was added and the organic layer washed with water (2 × 10 mL), saturated sodium hydrogen carbonate solution (10 mL), brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 2:3, with 1% triethylamine) provided the title compounds (115 mg, 55%) as an inseparable mixture of (*E*)-2-{6-(2-methoxypropan-2-yl)-1-methyl-5′-[(methylsulfonyloxy)methyl]-2′,4-dioxodihydro-2′*H*-spiro[bicyclo[3.3.1]nonane-3,3′-furan]-2-yl}vinyl 3-methylbut-2-enoate (**38**) and (*Z*)-2-{6-(2-methoxypropan-2-yl)-1-methyl-5′-[(methylsulfonyloxy)methyl]-2′,4-dioxodihydro-2′*H*-spiro[bicyclo[3.3.1]nonane-3,3′-furan]-2-yl}vinyl 3-methylbut-2-enoate (**37**) (7:3) isomers (colourless oil).

To mesylates **37** and **38** (27 mg, 0.05 mmol) dissolved in anhydrous dioxane (1.5 mL) under argon was added tetra-*n*-butylammonium iodide (21 mg, 0.06 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (12 µL, 0.08 mmol). The mixture was heated under microwave irradiation for 30 min (maximum temperature 155 °C, 270 W). The mixture was diluted with diethyl ether (2 mL) on cooling and then washed with sodium metabisulfite solution (1 mL) and water (2 mL). The organic phase was dried ($MgSO_4$) and solvent removed in vacuo providing the title compound as a mixture of unresolved *E*/*Z* (7:3) diastereomers (colourless oil). *E*-Isomer (**40**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.62 (d, J = 12.2 Hz, 1 H), 5.53–5.50 (m, 1 H), 5.33 (dd, J = 12.1, 11.2 Hz, 1 H), 4.62–4.58 (m, 1 H), 3.92–3.87 (m, 1 H), 3.21 (d, J = 11.2 Hz, 1 H), 3.01 (s, 3 H), 2.67–2.62 (m, 1 H), 2.53–2.44 (dm, 1 H), 2.26–2.20 (dm, 1 H), 2.11–2.03 (m, 1 H), 1.97 (d, J = 1.3 Hz, 3 H), 1.85–1.28 (m, 4 H), 1.34 (d, J = 1.3 Hz, 3 H), 1.19–1.14 (m, 6 H), 1.08–0.78 (m, 2 H), 0.68 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.1, 173.7, 162.6, 160.0, 153.0, 139.1, 114.9, 108.2, 88.5, 75.8, 62.0, 52.1, 48.6, 44.3, 41.9, 41.2, 39.6, 34.8, 31.1, 28.2, 27.0, 22.5, 21.9, 20.9, 20.3 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 430 (0.1) $[M^{+\cdot}]$, 399 (0.1), 398 (0.2), 370 (0.2), 355 (0.1), 330 (0.1), 317 (0.2), 316 (0.8), 288 (0.2), 270 (0.4), 235 (0.3), 227 (0.3), 196 (1), 164 (1), 137 (1), 136 (1), 135 (1), 107 (1), 105 (1), 93 (2), 91 (2), 83 (100), 73 (26), 55 (19). $C_{25}H_{34}O_6Na$: calcd. $M^{+\cdot}$ 453.2248; found: $M^{+\cdot}$ 453.2242. *Z*-Isomer (**39**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.39 (d, J = 6.6 Hz, 1 H), 5.75–5.72 (m, 1 H), 4.62–4.58 (m, 1 H), 4.36 (dd, J = 10.7, 6.6 Hz, 1 H), 4.16 (d, J = 10.7 Hz, 1 H), 3.92–3.87 (m, 1 H), 2.99 (s, 3 H), 2.71–2.66 (m, 1 H), 2.53–2.44 (dm, 1 H), 2.20–2.15 (dm, 1 H), 2.11–2.03 (m, 1 H), 2.00 (d, J = 1.3 Hz, 3 H), 1.85–1.28 (m, 4 H), 1.26 (d, J = 1.4 Hz, 3 H), 1.19–1.14 (m, 6 H), 1.08–0.78 (m, 2 H), 0.71 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.4, 173.7, 162.8, 160.3, 153.3, 137.0, 115.1, 107.0, 88.2, 75.9, 60.9, 52.2, 48.6, 44.3, 42.1, 39.8, 37.9, 35.1, 31.2, 28.4, 26.9, 22.6, 21.9, 21.1, 20.4 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 430 (0.2) $[M^{+\cdot}]$, 399 (0.2), 398 (0.3), 370 (0.2), 355 (0.1), 330 (0.1), 317 (0.5), 316 (0.8), 288 (0.5), 270 (0.3), 235 (0.2), 227 (0.3), 196 (1), 164 (1), 137 (1), 136 (1), 135 (1), 107 (1), 105 (1), 93 (3), 91 (3), 83 (100), 73 (32), 55 (22).

(E/Z)-5,14-Bis-*epi*-spirovibsanin A (42/41): Compounds **39** and **40** (8 mg, 0.02 mmol) were dissolved in anhydrous 1,2-dichloroethane (0.5 mL). A catalytic amount (≈ 1 mol-%) of anhydrous pyridinium *p*-toluenesulfonate was added and the mixture heated under microwave irradiation for 30 min (maximum temperature 110 °C, 50 W). The mixture was diluted with dichloromethane (2 mL), and the organic layer was washed with saturated sodium hydrogen carbonate (0.5 mL), water (1 mL), brine (0.5 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (petroleum ether/ethyl acetate, 5:1, with 1% triethylamine) of the residue provided a colourless oil (crude yield 53%) consisting of a 65:35 mixture of (*E*/*Z*)-5,14-bis-*epi*-spirovibsanin A (**42/41**). HPLC (0.2 mL/min, methanol/water gradient elution) purification provided the E (**42**) (0.5 mg, 6%) and Z (**41**) (1.5 mg, 19%) isomers. *E*-Isomer (**42**): ^{1}H NMR (C_6D_6, 900 MHz): δ = 7.58 (d, J = 11.7 Hz, 1 H), 5.51 (br. s, 1 H), 5.35 (dd, J = 11.7, 11.7 Hz, 1 H), 4.58 (br. s, 1 H), 3.13 (dd, J = 11.7 Hz, 1 H), 3.04 (s, 3 H), 2.73–2.71 (m, 1 H), 1.98 (s, 3 H), 1.74–1.70 (m, 1 H), 1.68–1.64 (m, 1 H), 1.58 (ddd, J = 13.5, 3.6, 3.6 Hz, 1 H), 1.50 (ddd, J = 12.6, 3.6, 3.6 Hz, 1 H), 1.43–1.40 (m, 1 H), 1.42 (s, 3 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.21 (s, 3 H), 0.99–0.94 (m, 1 H), 0.93–0.89 (m, 1 H), 0.77 (s, 3 H) ppm. ^{13}C NMR (C_6D_6, 226 MHz): δ = 209.6, 176.0, 162.7, 159.7, 155.2, 137.6, 115.0, 110.3, 104.1, 76.0, 68.1, 52.5, 48.6, 45.0, 43.6, 41.9, 39.5, 31.5, 28.1, 26.9, 22.5, 21.8, 21.2, 20.2, 13.7 ppm. Mass spectrum: GCMS (EI): *m*/*z* (%) = 430 (0.1) $[M^{+\cdot}]$, 316 (1), 295 (0.1), 273 (0.1), 270 (0.1), 236 (0.1), 227 (0.1), 218 (0.1), 196 (1), 173 (0.1), 164 (2), 153 (1), 149 (0.4), 137 (1), 136 (2), 135 (1), 127 (1), 121 (1), 109 (1), 107 (1), 105 (1), 95 (1), 93 (3), 83 (100), 73 (15). $C_{25}H_{34}O_6Na^+$: calcd. $M^{+\cdot}$ 453.2248; found: $M^{+\cdot}$ 453.2249. *Z*-Isomer (**41**): ^{1}H NMR (C_6D_6, 750 MHz): δ = 7.42 (d, J = 6.5 Hz, 1 H), 5.73–5.72 (m, 1 H), 4.56 (br. s, 1 H), 4.49 (dd, J = 10.7, 6.6 Hz, 1 H), 4.09 (d, J = 10.4 Hz, 1 H), 3.01 (s, 3 H), 2.75–2.74 (m, 1 H), 2.10–2.05 (m, 1 H), 2.01 (d, J = 1.1 Hz, 3 H), 1.86–1.84 (m, 2 H), 1.61–1.59 (m, 1 H), 1.57–1.54 (m, 1 H), 1.45 (d, J = 1.1 Hz, 3 H), 1.28 (s, 3 H), 1.22 (s, 3 H), 1.19 (s, 3 H), 1.10–1.07 (td, J = 12.9, 4.4 Hz, 1 H), 1.01 (dd, J = 13.7, 1.9 Hz, 1 H), 0.79 (s, 3 H) ppm. ^{13}C NMR (C_6D_6, 125 MHz): δ = 209.8, 176.0, 163.0, 106.0, 155.3, 135.8, 115.2, 108.8, 140.4, 76.1, 67.3, 52.6, 48.6, 45.0, 42.8, 39.7, 39.5, 31.5, 28.3, 26.9, 22.6, 21.7, 21.4, 20.4, 13.7 ppm. Mass spectrum: GCMS (EI): m/z (%) = 430 (0.1) [M$^{+\cdot}$], 398 (0.1), 370 (0.1), 333 (0.1), 330 (0.3), 316 (1), 301 (0.1), 298 (0.2), 288 (0.1), 273 (0.1), 270 (0.2), 255 (0.1), 246 (0.1), 235 (0.2), 229 (0.1), 227 (0.1), 218 (0.1), 207 (0.1), 200 (0.2), 196 (1), 180 (0.1), 173 (0.1), 164 (2), 159 (0.2), 153 (1), 149 (1), 147 (0.3), 137 (1), 136 (2), 135 (1), 131 (0.4), 127 (1), 121 (1), 109 (1), 107 (1), 105 (1), 93 (3), 83 (100), 73 (17). $C_{25}H_{34}O_6$ Na$^+$: calcd. [M + Na]$^+$ 453.2248; found: [M + Na]$^+$ 453.2238.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all compounds. Comparisons of spirovibsanin A and bis-epi-spirovibsanin A.

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