Studies towards the total synthesis of solanoeclepin A: synthesis of the 7-oxabicyclo[2.2.1]heptane moiety and attempted seven-membered ring formation

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This paper details studies towards the total synthesis of solanoeclepin A (**1**), the most active natural hatching agent of potato cyst nematodes. The first goal was the preparation of the tetracyclic left-handed substructure **2** in enantiopure form. The 7-oxabicyclo[2.2.1]heptane moiety was obtained *via* a diastereoselective intramolecular Diels–Alder strategy by using (*R*)-phenylglycinol as a chiral auxiliary as pioneered by Mukaiyama. A chromium-mediated nickel-catalysed coupling of aldehyde **5** with vinyl triflate **6** gave α,β-unsaturated lactone **18** as a single stereoisomer. The seven-membered ring was expected to arise from a McMurry coupling of dialdehyde **4**. Surprisingly, oxidation of diol **24** did not lead to the desired dialdehyde **4**, but to the eight-membered ring lactone **25**.

Introduction

Potato cyst nematodes (PCN) are responsible for major losses in potato crops. The quest for an environmentally benign method to control PCN has resulted in the isolation[1] and structure elucidation[2] of the most active hatching agent, solanoeclepin A (**1**, Fig. 1). Its complex heptacyclic structure

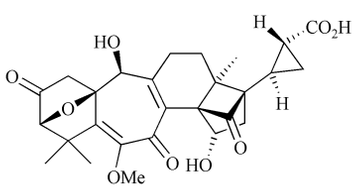

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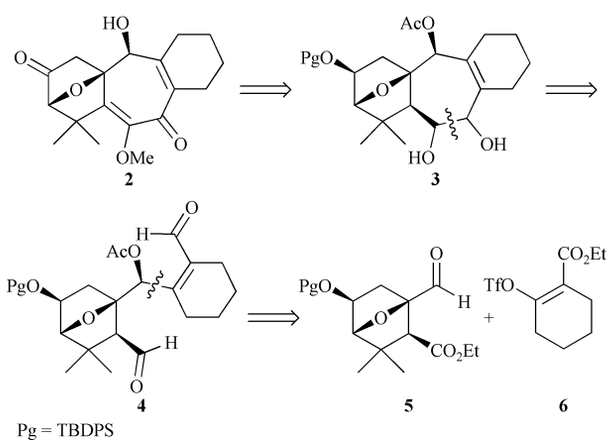
Fig. 1

features nine stereogenic centres and all ring sizes ranging from three to seven. The extreme scarcity of the natural material, its fascinating structure, and its potential role in the search for a benign way to control PCN make **1** a challenging target for total synthesis.[3]

Both this paper and the following paper in this issue detail studies directed at the synthesis of the left-handed substructure **2** (Scheme 1). An obvious approach to arrive at tetracycle **2** would be the closure of the seven-membered ring *via* an acyloin condensation. However, both the drastic conditions required and unfavourable literature reports regarding the use of α,β-unsaturated esters in this reaction[4] led us to take a different approach. The McMurry type pinacol coupling[5] of dialdehyde **4** to diol **3** was deemed a more promising approach in view of its proven utility in total synthesis.[5] It was further assumed that diol **3** could be readily converted into **2**. Dialdehyde **4** should be available *via* a chromium-mediated coupling reaction of aldehyde **5** with vinyl triflate† **6**, followed by partial reduction of the two ester groups.

This strategy made aldehyde **5**, containing the 7-oxabicyclo-[2.2.1]heptane skeleton, the first goal in the synthetic route to



Scheme 1

solanoeclepin A. An obvious way to prepare such a bicyclic structure is *via* a Diels–Alder reaction of a furan. In order to obtain both a favourable rate and regioselectivity this cycloaddition should be carried out in an intramolecular fashion.[6–9] However, it is well-known[10] that such a process usually fails when an ester function is in the tether between the diene and the dienophile. On the other hand, a tertiary amide can be an excellent linking functional group.[8,10] In 1981 an elegant example was published by Mukaiyama and Iwasawa in the synthesis of (+)-farnesiferol C.[11]‡ The intramolecular Diels–Alder reaction of the enantiopure tertiary amide **8** provided the tricyclic lactam **7** in high yield and excellent diastereoselectivity (Scheme 2). (*R*)-Phenylglycinol served as the source of chirality in this synthesis.

The structural resemblance between lactam **7** and aldehyde **5** is obvious. The desired aldehyde **5** should be available, successively, *via* hydroboration of the double bond of **7**, removal of the *N*-substituent and opening of the γ-lactam to an aldehyde ester.

† The IUPAC name for triflate is trifluoromethanesulfonate.

‡ The IUPAC name for farnesiferol C is 7-{[3-methyl-5-(1,3,3-trimethyl-7-oxabicyclo[2.2.1]hept-2-yl)penten-2-yl]oxy}coumarin.

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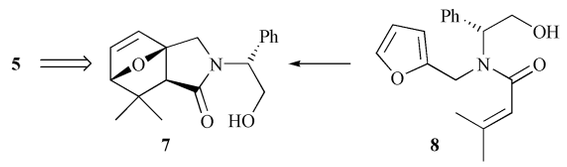
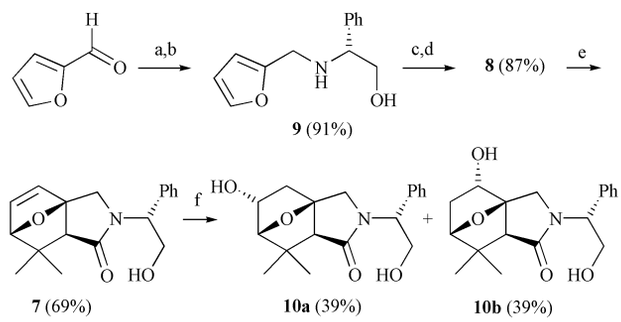


Scheme 2

Results and discussion

Synthesis of aldehyde 5

Although a literature procedure for the synthesis of the Diels–Alder precursor **8** was available,[11,12] the need for multigram amounts required an improved route (Scheme 3). The synthesis



Scheme 3 *Reagents and conditions*: a, (*R*)-phenylglycinol, toluene, reflux; b, $NaBH_4$, isopropanol; c, TMSCl, pyridine, THF; d, 3,3-dimethylacryloyl chloride then 5% HCl, H_2O; e, *n*-BuMgCl, Et_2O, −60 °C then toluene reflux, 16 h; f, $Hg(OAc)_2$, THF–H_2O then NaOH, $NaBH_4$.

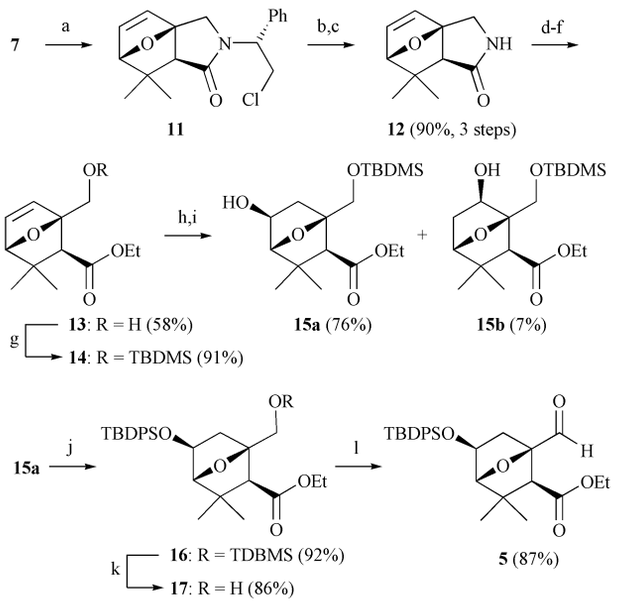
started with the condensation of freshly distilled furfural with (*R*)-phenylglycinol.[13] Reduction of the resulting imine with sodium borohydride in isopropanol gave the amine **9**. All attempts to perform selective *N*-acylation of **9** without competing *O*-acylation resulted in mixtures of mono- and di-acylated products. To circumvent this problem the hydroxy group was first silylated leaving the amine unprotected. The latter was then acylated with 3,3-dimethylacryloyl chloride. Acidic removal of the silyl ether and column chromatographic purification afforded the Diels–Alder precursor **8** in excellent overall yield (79%, 3 steps). The intramolecular Diels–Alder reaction employing the Mukaiyama protocol[11,12] furnished lactam **7** in both satisfactory yield and diastereoselectivity (90 : 10) on a 50 g scale. The pure diastereomer **7** was obtained in 69% yield after recrystallisation of the reaction product and subsequent column chromatography of the mother liquor.

At this point the introduction of a hydroxy group *via* hydroboration of the double bond was investigated. To attain good regioselectivity in this reaction the use of bulky boranes was deemed necessary. Unfortunately, alkene hydroboration[14] of the Diels–Alder product **7** by several different reagents, including diborane and dicyclohexylborane, did not proceed in the desired fashion. In all cases competing reduction of the lactam carbonyl was observed. Oxymercuration with mercuric acetate,[15] however, did enable the desired chemical transformation, but a 1 : 1 mixture of products **10a** and **10b** was obtained. Because of this low regioselectivity it was decided to functionalise the double bond at a later stage of the synthesis.

Removal of the *N*-substituent in **7** was then attempted. Because of the presence of the allylic oxygen bridge, reductive methods[16] were expected to fail, therefore a new non-reductive one-pot procedure had to be developed.[17] The first step was transformation of the hydroxy group into a good leaving group by treatment with toluene-*p*-sulfonyl chloride (Scheme 4). Under these conditions chloride **11** was obtained. The formation of this chloride can be explained by invoking an aziridinium intermediate, which was formed after tosylation followed

Table 1 Hydroboration of oxabicyclic alkene **14**

Hydroborating agent	Selectivity **15a** : **15b**	Yield **15a** (%)
Diborane	50 : 50	36%
Thexylborane	50 : 50	35%
9-BBN	91 : 9	56%
Dicyclohexylborane	95 : 5	63%
Disiamylborane	92 : 8	76%



Scheme 4 *Reagents and conditions*: a, *p*-TsCl, pyridine, CH_2Cl_2; b, DBU, MeCN; c, 5 M HCl; d, $NaNO_2$, AcOH, Ac_2O; e, KOH (1 equiv.), EtOH; f, $NaHCO_3$ (aq); g, TBDMSCl, imidazole, DMF; h, disiamylborane, THF, 0 °C; i, NaOH, H_2O_2; j, TDBPSCl, imidazole, CH_2Cl_2; k, HCl (cat.), EtOH; l, TPAP, NMO, acetone.

by intramolecular nucleophilic attack of nitrogen.[18] DBU-mediated dehydrohalogenation gave the enamide, which upon acidic hydrolysis yielded lactam **12** as a crystalline solid [mp 154 °C; $[\alpha]_D^{22} = +52.4 \times 10^{-1}$ deg cm^2 g^{-1} ($c = 0.82$, $CHCl_3$)].

Hydroboration of the alkene of **12** at this point still failed due to the vulnerability of the lactam carbonyl towards reduction. Therefore, lactam **12** was first converted into the protected hydroxy ester **14**. It is known that an *N*-nitrosolactam can be converted into a γ-hydroxyester with loss of nitrogen gas.[17] Thus, lactam **12** was nitrosated with sodium nitrite in acetic acid in the presence of acetic anhydride. Then, an ethanolic solution of the *N*-nitroso compound was made alkaline with ethanolic potassium hydroxide. Neutralisation using workup by aqueous sodium bicarbonate produced the hydroxy ester **13**, which was then protected as a silyl ether.

Gratifyingly, chemoselective hydroboration[15] of the double bond of **14** appeared to be successful (Table 1). Hydroboration with diborane resulted in a clean reaction, but the regioselectivity was poor. Increasing the steric bulk by using thexylborane§ did not lead to better selectivity. Fortunately, 9-borabicyclo-[3.3.1]nonane, dicyclohexyl- and disiamylborane§ gave good regioselectivity. The desired isomer **15a** was obtained in good yield after separation from its regioisomer **15b** by column chromatography. The highest yield of **15a** was obtained by using disiamylborane, because in this case the alcohol byproduct resulting from the borane substituent could be best separated by column chromatography.

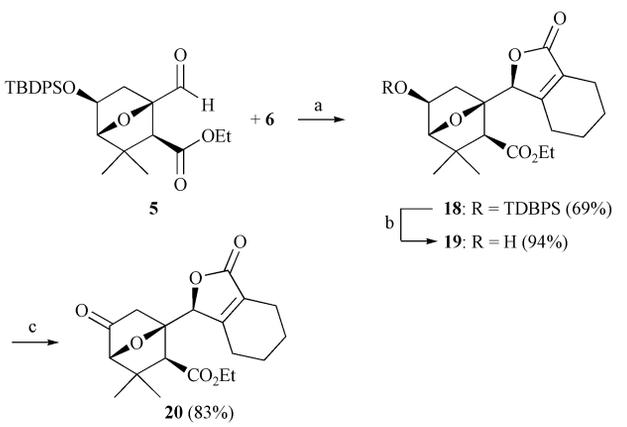
To complete the synthesis of aldehyde **5** the secondary hydroxy group was protected with the large and robust *tert*-butyldiphenylsilyl protecting group. Selective deprotection

§ The IUPAC name for thexyl is 1,1,2-trimethylpropyl. The IUPAC name for disiamyl is 1,2-dimethylprop-1-yl.

of the primary hydroxy group with a catalytic amount of hydrochloric acid in ethanol and subsequent TPAP–NMO oxidation[19] furnished the enantiopure aldehyde **5**, which was synthesised in 11 steps with an overall yield of 13% from furfural.

Attempted seven-membered ring formation

A chromium-mediated nickel-catalysed coupling[20] of aldehyde **5** with vinyl triflate **6**[21] using the conditions of Knochel and Rao[22] afforded a γ-hydroxy ester, which lactonised under the reaction conditions to give the α,β-unsaturated lactone **18** (Scheme 5). This lactone was isolated as a stable crystalline



Scheme 5 *Reagents and conditions*: a, $CrCl_2$ (4 equiv.), $NiCl_2$ (cat.), DMF, 50 °C, 18 h; b, HF·pyridine, THF; c, TPAP, NMO, acetone.

solid (mp 101 °C; $[a]_D^{22} = +8.57 \times 10^{-1}$ deg cm^2 g^{-1} (c = 1.21, $CHCl_3$)). Surprisingly, only a single isomer was found where a mixture of diastereomers was expected. Possibly some type of chromium chelation is responsible for the stereoselective result of this reaction.

It was not possible to determine the relative configuration of the new stereogenic centre by ^{1}H NMR experiments. Therefore, an X-ray crystal structure of lactone **18** was desired. However, the crystals of lactone **18** appeared to be unsuitable for X-ray measurements. Removal of the silyl protecting group and subsequent TPAP, NMO oxidation of alcohol **19** afforded the highly crystalline ketone **20** (mp 168.5–169.5 °C; $[a]_D^{19} = +98.0 \times 10^{-1}$ deg cm^2 g^{-1} (c = 1.25, $CHCl_3$)). The X-ray analysis of this latter compound revealed an (*S*)-configuration for the newly formed centre in the lactone ring, based on the known absolute configuration of the remaining three stereocentres originally derived from the starting material, (*R*)-phenylglycinol[11] (see Fig. 2).

Knowing that lactone **18** possesses the correct stereochemistry the synthesis of dialdehyde **4** was investigated. The two ester groups of **18** were cleanly reduced (Scheme 6) by rapid addition of lithium aluminium hydride to the lactone in diethyl ether at room temperature. The solvent and temperature appeared crucial to achieve a good yield of triol **21**. Before the primary hydroxy groups in **21** could be oxidised, the secondary hydroxy group had to be protected. The following three-step procedure was used for this purpose. First, both primary hydroxy groups of **21** were protected as TBDMS ethers. Then the secondary alcohol in **22** was acetylated and finally acidic cleavage of the two primary silyl ethers of **23** with camphorsulfonic acid (CSA) in methanol yielded diol **24** in good overall yield.

Surprisingly, perruthenate oxidation of diol **24** did not give the expected dialdehyde. Instead, the eight membered ring lactone **25** was rapidly formed in a surprisingly good yield.[23] The allylic alcohol was probably oxidised first to give the corresponding allylic aldehyde. Intramolecular attack of the

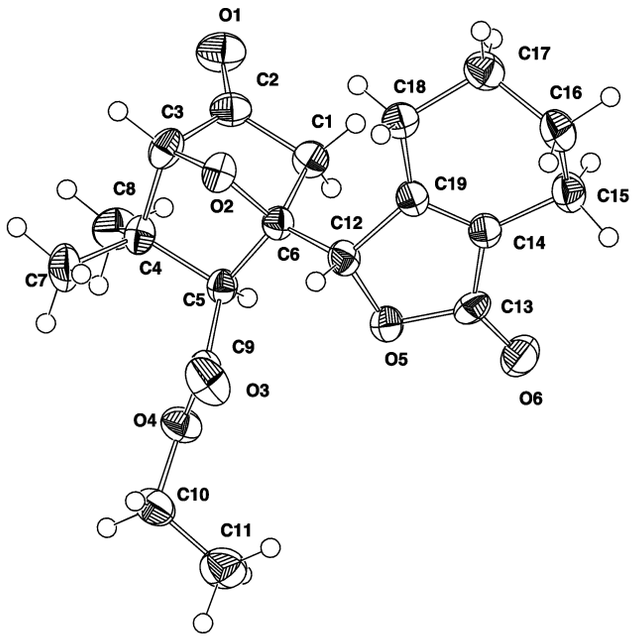
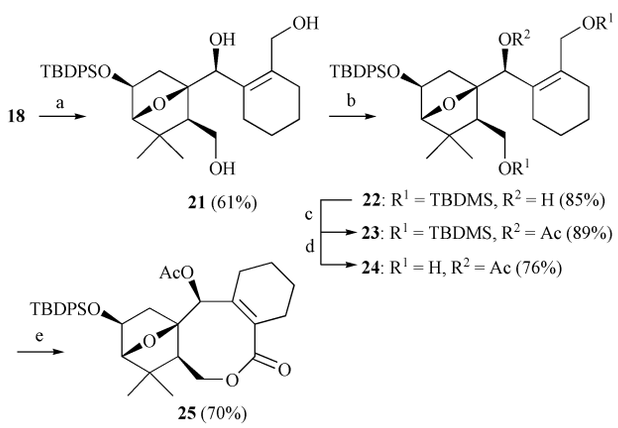


Fig. 2 ORTEP plot of the crystal structure of **20**.



Scheme 6 *Reagents and conditions*: a, $LiAlH_4$, Et_2O, rt, 15 min; b, TBDMSCl, pyridine, DMF; c, Ac_2O, pyridine; d, CSA, MeOH, rt; e, TPAP, NMO, acetone.

remaining hydroxy groups then resulted in the eight-membered ring lactol and this process is apparently faster than oxidation of the second primary hydroxy group. The oxidising agent then converted the lactol into lactone **25**. Alternative oxidative methods such as pyridinium chlorochromate and activated manganese dioxide could not circumvent this problem as these oxidizing agents gave the same lactone as the sole product. An attempted Swern oxidation led to a complex mixture of products.

Having established that the synthesis of dialdehyde **4** could not be readily realised, our plan to construct the desired seven-membered ring *via* **4** was abandoned. A different and successful approach to close the seven-membered ring was then investigated, which will be reported in the next article in this issue.[24]

Conclusion

In this paper, the synthesis of aldehyde **5** in enantiopure form has been reported. A chromium-mediated nickel-catalysed coupling reaction of **5** with vinyl triflate **6** produced lactone **18** with perfect stereocontrol. Unfortunately, further transformation of **18** to prepare the seven-membered ring failed, because it was not possible to prepare the dialdehyde **4** required for a McMurry coupling. A new approach has been developed which will be discussed in the following paper.[24]

Experimental

General

All reactions involving oxygen or moisture sensitive compounds were carried out under a dry nitrogen atmosphere. THF and Et_2O were distilled from sodium and CH_2Cl_2 was distilled from CaH_2. DMF and toluene were distilled from CaH_2 and stored over 4 Å molecular sieves. Triethylamine was stored over KOH pellets and DMSO was dried and stored over 4 Å molecular sieves. Column chromatography was performed using Acros silica gel (0.030–0.075 mm). Petroleum ether (60–80) used for chromatography was distilled prior to use. TLC analyses were performed on Merck F-254 silica gel plates. IR spectra were measured as thin films on NaCl plates unless otherwise noted using a Bruker IFS 28 FT-spectrophotometer and wavelengths (ν) are reported in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz), a Bruker ARX 400 (400 MHz) and a Varian Inova (500 MHz). The latter machines were also used for ^{13}C NMR spectra (50, 100 and 125 MHz respectively). Unless otherwise indicated, $CDCl_3$ was used as the solvent. Chemical shifts are given in ppm (δ) relative to an internal standard of chloroform (7.26 ppm for ^1H-NMR and 77.0 for ^{13}C-NMR). Mass spectra and accurate mass determinations were performed on a JEOL JMS SX/SX102A, coupled to a JEOL MS-MP7000 data system. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm cell in the indicated solvent, and are given in units of 10^{-1} deg cm^2 g^{-1}.

(−)-(2*R*)-2-[(Furan-2-ylmethyl)amino]-2-phenylethanol (9)

To a solution of (*R*)-2-phenylglycinol[13] (84 g, 0.61 mol) in toluene (575 mL) was added furfural (60.9 mL, 0.74 mol, 1.2 equiv.) in toluene (150 mL) and the reaction mixture was refluxed under Dean–Stark conditions for 2 h. After evaporation of the toluene the crude imine was dissolved in isopropanol (900 mL) and cooled to 0 °C. Then $NaBH_4$ (51.2 g, 1.35 mol, 2.2 equiv.) was added in portions (4–5 g) over 15 min and the reaction mixture was allowed to warm to rt. The mixture was stirred for 16 h followed by acidification with HCl (290 mL of a 5 M aqueous solution, 1.45 mol) and most of the organic solvents were evaporated. After neutralisation of the aqueous layer with NaOH (5% solution in water) the aqueous layer was extracted with Et_2O (3 × 400 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4. Removal of the solvent afforded crude aminoalcohol **9** (121 g, 0.56 mol, 91%) as a solid, which was used in the next step without purification. R_f = 0.80 (petroleum ether–Et_2O (1 : 5)); mp 52.0–52.5 °C; $[\alpha]_D^{22}$ −99.8 (*c* = 0.88, $CHCl_3$); (lit.[12] mp 50.5–51.5 °C; $[\alpha]_D^{22}$ −100 (*c* = 0.97, $CHCl_3$)); IR 3340 (br), 2925, 2869, 1451, 1028; ^1H NMR (400 MHz) δ 7.40–7.25 (6H, m), 6.29 (1H, d, *J* = 2.0 Hz), 6.12 (1H, d, *J* = 2.9 Hz), 3.80 (1H, dd, *J* = 8.4, 4.3 Hz), 3.78 (1H, dd, *J* = 10.7, 4.4 Hz), 3.71–3.67 (1H, m), 3.62 (1H, dd, *J* = 11.8, 3.0 Hz), 3.59 (1H, dd, *J* = 10.8, 8.1 Hz), 2.50–2.20 (2H, br s); ^{13}C NMR (100 MHz) δ 153.4, 141.8, 140.0, 128.6, 127.6, 127.3, 110.0, 107.0, 66.7, 63.4, 43.6; HRMS (FAB) [M + H^+] calcd for $C_{13}H_{16}NO_2$: 218.1181, found: 218.1177.

(−)-(2*R*)-*N*-Furan-2-ylmethyl-*N*-(2-hydroxy-1-phenylethyl)-3-methylbut-2-enamide (8)

To a solution of crude aminol **9** (116 g, 534 mmol) in THF (800 mL) was added chlorotrimethylsilane (74.9 mL, 867 mmol, 1.6 equiv.) and pyridine (47.5 mL, 587 mmol, 1.1 equiv.). The reaction mixture was stirred for 1 h. To the reaction mixture was added pyridine (95.0 mL, 1.17 mol, 2 equiv.) followed by 3,3-dimethylacryloyl chloride (74.4 mL, 668 mmol, 1.3 equiv.) and stirring was continued for 16 h. The mixture was cooled to 0 °C, acidified to pH = 2 with HCl (1 M aqueous solution) and extracted with Et_2O (3 × 400 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 400 mL) followed by brine. Evaporation of the solvent and column chromatography (petroleum ether–Et_2O (1 : 5)) afforded amide **9** (139 g, 464 mmol, 87%, 2 steps) as a yellow oil. R_f = 0.21 (petroleum ether–Et_2O (1 : 5)); $[\alpha]_D^{22}$ −89.1 (*c* = 1.03, $CHCl_3$); (lit.[12] $[\alpha]_D^{22}$ −88.5 (*c* = 0.853, $CHCl_3$)); IR 3383 (br), 3030, 2935, 1608, 1452; ^1H NMR (400 MHz, 360 K, toluene-d_6) δ 7.14–6.95 (6H, m), 5.97 (2H, m), 5.89 (1H, s), 5.35 (1H, m), 4.36 (1H, d, *J* = 16.7 Hz), 4.07 (1H, d, *J* = 16.6 Hz), 3.99–3.87 (2H, m), 1.93 (3H, s), 1.57 (3H, s); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found: 299.1526.

(−)-(1*R*,5*S*,7*S*)-3-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,6-dimethyl-10-oxa-3-azatricyclo[5.2.1.$0^{1,5}$]dec-8-en-4-one (7)

A solution of alcohol **8** (45.5 g, 152 mmol) in Et_2O (850 mL) was cooled to −60 °C. To the reaction mixture was added freshly prepared *n*-butylmagnesium chloride (176 mL of a 0.95 M solution in Et_2O, 167 mol, 1.1 equiv.). After 45 min the cooling bath was removed and the yellow suspension was allowed to warm to rt. Then the solvent Et_2O was replaced by toluene by distilling off the Et_2O while toluene was continuously added (650 mL). After all the Et_2O had been removed (approximately 2 h) the clear solution was refluxed for 16 h. After cooling to rt HCl (650 mL of a 5% aqueous solution, 0.86 mol) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ followed by brine and subsequently dried over Na_2SO_4. The solvent was removed *in vacuo*. Recrystallisation (CH_2Cl_2–petroleum ether) afforded the Diels–Alder product **7** (19.8 g, 66.2 mmol, 44%) as a yellow crystalline solid. To collect an extra portion of the Diels–Alder product, the mother liquor was concentrated and purified by column chromatography (EtOAc) (11.6 g, 38.8 mmol, 25%) (and its diastereoisomer (3.6 g, 12,1 mmol, 8%)). (Combined yield of **7**: 31.4 g, 104 mmol, 69%.) R_f = 0.13 (EtOAc); mp 154.1 °C; $[\alpha]_D^{22}$ −83.6 (*c* = 1.30, MeOH)); (lit.[11] mp 155.5–156.5 °C; $[\alpha]_D^{25}$ −85.1 (*c* = 6.61, MeOH); IR (KBr) 3469 (br), 2960, 1676, 1355, 1060; ^1H NMR (400 MHz) δ 7.36–7.28 (2H, m), 7.27–7.23 (3H, m), 6.45–6.41 (2H, m), 5.19 (1H, dd, *J* = 8.8, 4.2 Hz), 4.40 (1H, d, *J* = 1.2 Hz), 4.17 (1H, dd, *J* = 11.9, 4.3 Hz), 4.06 (1H, dd, *J* = 11.9, 8.8 Hz), 3.88 (1H, d, *J* = 11.7 Hz), 3.48 (1H, d, *J* = 11.7 Hz), 2.77 (1H, br s), 2.17 (1H, s), 1.42 (3H, s), 1.04 (3H, s); ^{13}C NMR (50 MHz) δ 174.3, 136.7, 136.2, 134.0, 128.8, 127.6, 126.8, 90.2, 88.1, 62.6, 57.6, 57.3, 46.7, 41.9, 25.4, 25.3; HRMS (FAB) [M + H^+] calcd for $C_{18}H_{22}NO_3$: 300.1600, found: 300.1608.

(1*R*,5*S*,7*R*,8*R*)-8-Hydroxy-3-[(1*R*)-2-hydroxy-1-phenylethyl]-6,6-dimethyl-10-oxa-3-azatricyclo[5.2.1.$0^{1,5}$]decan-4-one (10a) and (1*R*,5*S*,7*S*,9*S*)-9-hydroxy-3-[(1*R*)-2-hydroxy-1-phenylethyl]-6,6-dimethyl-10-oxa-3-azatricyclo-[5.2.1.$0^{1,5}$]-decan-4-one (10b)

The Diels–Alder product **7** (202 mg, 0.68 mmol) and mercuric acetate (216 mg, 0.68 mmol, 1 equiv.) were dissolved in THF (1 mL) and water (1 mL). The colourless reaction mixture was stirred for 16 h at rt. To the yellow mixture was added NaOH (1.0 mL of a 3 M aqueous solution) followed by $NaBH_4$ (51 mg, 1.3 mmol, 2 equiv.). The gray solution was saturated with NaCl, extracted with THF (3 × 5 mL) and dried over Na_2SO_4. Evaporation afforded diol **10a** and its regioisomer **10b** as a 50 : 50 mixture (168 mg, 0.53 mmol, 78%), which was separated by chromatography. **10a**: ^1H NMR (400 MHz) δ 7.37–7.20 (5H, m), 5.15 (1H, m), 4.15–3.87 (4H, m), 3.67 (1H, d, *J* = 10.2 Hz), 3.34 (1H, d, *J* = 10.2 Hz), 2.43 (1H, dd, *J* = 13.2, 6.5 Hz), 2.35–2.15 (1H, br s), 2.14 (1H, s), 1.56 (1H, m), 1.23 (3H, s), 1.12 (3H, s). **10b**: ^1H NMR (400 MHz) δ 7.35–7.19 (5H, m), 5.13 (1H, m), 4.15–3.99 (4H, m), 3.95–3.92 (2H), 2.45–2.41 (1H, m), 2.13 (1H, s), 1.54 (1H, m), 1.26 (3H, s), 1.13 (3H, s).

(1*R*,5*S*,7*S*)-3-[(1*R*)-2-Chloro-1-phenylethyl]-6,6-dimethyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-4-one (11)

To a solution of Diels–Alder product **7** (61.4 g, 0.21 mol) in CH_2Cl_2 (400 mL) was added toluene-*p*-sulfonyl chloride (77.8 g, 0.41 mol, 2 equiv.) followed by pyridine (42 mL, 0.52 mol, 2.5 equiv.). The brown solution was stirred at rt for 16 h. To achieve complete conversion the reaction mixture was heated at 50 °C for another 3 h. Then water was added (500 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were washed with brine and subsequently dried on Na_2SO_4. Evaporation of the solvent gave chloride **11** as a brown oil, which was used crude in the next reaction. R_f = 0.55 (EtOAc); ^{1}H NMR (400 MHz) δ 7.41–7.37 (2H, m), 7.35–7.27 (3H, m), 6.46 (2H, m), 5.56 (1H, dd, *J* = 10.0, 4.8 Hz), 4.41 (1H, d, *J* = 1.2 Hz), 4.10 (1H, dd, *J* = 11.8, 4.9 Hz), 3.95 (1H, dd, *J* = 11.7, 10.0 Hz), 3.90 (1H, d, *J* = 11.3 Hz), 3.51 (1H, d, *J* = 11.3 Hz), 2.18 (1H, s), 1.42 (3H, s), 1.05 (3H, s).

(+)-(1*R*,5*S*,7*S*)-6,6-Dimethyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]-dec-8-en-4-one (12)

To a solution of chloride **11** (65.9 g, 0.21 mol) in acetonitrile (225 mL) was added DBU (64 mL, 0.42 mol, 2 equiv.) and the dark reaction mixture was stirred at rt for 16 h. Then the reaction mixture was poured into water (200 mL) and after separation of the organic layer the water layer was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The dark crude product was dissolved in CH_2Cl_2 (100 mL) and HCl (160 mL of a 5 M aqueous solution) was added to hydrolyse the enamide. After 30 min of vigorous stirring the layers were separated and the aqueous layer was extracted with chloroform (4 × 200 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (EtOAc–MeOH (19 : 1)) afforded lactam **12** (33.8 g, 0.19 mol, 90%) as a light yellow solid. R_f = 0.31 (EtOAc–MeOH (19 : 1)); mp 154.2 °C; $[\alpha]_D^{22}$ +52.4 (*c* = 0.82, $CHCl_3$); IR 3288 (br), 2959, 1698, 1666, 1356, 1070; ^{1}H NMR (400 MHz) δ 6.47–6.44 (2H, m), 6.43 (1H, br s), 4.39 (1H, d, *J* = 1.2 Hz), 3.82 (1H, d, *J* = 11.6 Hz), 3.62 (1H, d, *J* = 11.5 Hz), 2.16 (1H, s), 1.41 (3H, s), 1.02 (3H, s); ^{13}C NMR (50 MHz) δ 176.3, 136.2, 134.1, 93.1, 88.2, 55.7, 44.6, 41.6, 26.4, 25.1; HRMS (EI) calcd for $C_{10}H_{13}NO_2$: 179.0946, found: 179.0942; anal. calcd for $C_{10}H_{13}NO_2$: C 67.02, H 7.31, N 7.82, found: C 66.85, H 7.27, N 7.76%.

(1*R*,2*S*,4*S*)-1-Hydroxymethyl-3,3-dimethyl-7-oxabicyclo[2.2.1]-hept-5-ene-2-carboxylic acid ethyl ester (13)

To a solution of lactam **12** (10.0 g, 55.8 mmol) in HOAc (78 mL) and acetic anhydride (225 mL) was added sodium nitrite (11.5 g, 167 mmol, 3 equiv.). The reaction mixture turned yellow immediately and a brown gas escaped. After stirring at rt for 30 min the solvents were evaporated and the remaining solid was dissolved in EtOAc (200 mL) followed by washing with saturated aqueous $NaHCO_3$ (4 × 250 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. To remove residual acetic acid from the crude product the reaction mixture was concentrated after the addition of toluene providing sufficiently pure *N*-nitrosolactam.

A solution of this *N*-nitrosolactam (11.5 g, 55.3 mmol) in EtOH (250 mL) was cooled to −20 °C. To this ethanolic solution was added 67 mL of a 5% potassium hydroxide solution in ethanol (59.3 mmol, 1.05 equiv.). The resulting dark brown reaction mixture was stirred for 20 min at −20 °C and then poured into saturated aqueous $NaHCO_3$ (200 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 250 mL) and the organic layers were washed with brine and subsequently dried over Na_2SO_4. Evaporation of the solvent afforded hydroxy ester **13** (7.2 g, 32 mmol, 58%) as a brown oil, which was protected in the next step without purification. IR 3453, 2977, 2873, 1736, 1179, 1160, 1023; ^{1}H NMR (400 MHz) δ 6.49 (1H, dd, *J* = 5.7, 1.8 Hz), 6.38 (1H, d, *J* = 5.7 Hz), 4.39 (1H, d, *J* = 1.7 Hz), 4.35 (1H, d, *J* = 11.5 Hz), 4.21–4.11 (2H, m), 4.03 (1H, d, *J* = 11.5 Hz), 2.30 (1H, br s), 2.22 (1H, s), 1.27 (3H, t, *J* = 7.1 Hz), 1.17 (3H, s), 1.06 (3H, s); ^{13}C NMR (50 MHz, C_6D_6) δ 172.9, 138.4, 136.2, 93.1, 87.7, 61.8, 60.8, 56.5, 45.6, 26.9, 25.8, 15.1; HRMS (FAB) [M + H$^+$] calcd for $C_{12}H_{19}O_4$: 227.1283, found: 227.1288.

(+)-(1*R*,2*S*,4*S*)-1-(*tert*-Butyldimethylsilyloxymethyl)-3,3-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid ethyl ester (14)

Hydroxy ester **13** (468 mg, 2.12 mmol) was dissolved in CH_2Cl_2 (5 mL). To this solution was added TBDMSCl (477 mg, 3.16 mmol, 1.5 equiv.) and imidazole (288 mg, 4.2 mmol, 2.0 equiv.). The reaction mixture was stirred for 16 h and poured into water (15 mL). After separation of the organic layer the water layer was extracted with CH_2Cl_2 (2 × 15 mL). Evaporation of the solvent and purification by column chromatography (petroleum ether–Et_2O (9 : 1)) afforded protected alcohol **14** (646 mg, 1.93 mmol, 91%) as a colourless oil. R_f = 0.46 (petroleum ether–Et_2O (2 : 1)); $[\alpha]_D^{21}$ +19.4 (*c* = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz) δ 6.44–6.41 (2H, m), 4.33 (1H, d, *J* = 1.4 Hz), 4.30 (1H, d, *J* = 9.8 Hz), 4.19–4.07 (2H, m), 3.97 (1H, d, *J* = 9.8 Hz), 2.21 (1H, s), 1.26 (3H, t, *J* = 7.1 Hz), 1.14 (3H, s), 1.04 (3H, s), 0.88 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz) δ 172.0, 137.3, 135.2, 91.1, 86.9, 61.1, 59.8, 54.7, 44.2, 26.4, 25.7, 25.0, 18.0, 14.3, −5.5, −5.7.

(+)-(1*R*,2*S*,4*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxymethyl)-5-hydroxy-3,3-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (15a) and (+)-(1*R*,2*S*,4*S*,6*R*)-1-(*tert*-butyldimethylsilyloxymethyl)-6-hydroxy-3,3-dimethyl-7-oxabicyclo-[2.2.1]heptane-2-carboxylic acid ethyl ester (15b)

A solution of 2-methylbut-2-ene (2.0 mL of a 2.0 M solution in THF, 4 mmol, 2 equiv.) was cooled to 0 °C. To this solution was added dropwise a borane–methyl sulfide complex (2.0 mL, 2.0 mmol). The reaction mixture was allowed to warm to rt and stirring was continued for 4 h resulting in a 1.0 M solution of disiamylborane in THF. A solution of **14** (96 mg, 0.29 mmol) in THF (1.0 mL) was cooled to 0 °C. To this solution was added disiamylborane (0.6 mL of a 1.0 M solution in THF, 0.6 mmol, 2.0 equiv.). The colourless reaction mixture was stirred at 0 °C for 3 h. Then NaOH (1.0 mL of a 2.0 M solution, 2.0 mmol, 6.8 equiv.) was carefully added followed by H_2O_2 (2.0 mL of a 35 wt% solution in water, 20 mmol, excess) and stirring was continued at rt for 2 h. NH_4Cl (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and then dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (petroleum ether–Et_2O (1 : 3)) furnished alcohol **15a** (79 mg, 0.22 mmol, 76%) and its regioisomer **15b** (7.5 mg, 0.02 mmol, 7%) as colourless oils. **15a**: R_f = 0.18 (petroleum ether–EtOAc (6 : 4)); $[\alpha]_D^{20}$ +14.3 (*c* = 1.12, $CHCl_3$); IR 3383 (br), 2926, 2851, 1740, 1110; ^{1}H NMR (400 MHz) δ 4.29 (1H, dd, *J* = 6.7, 1.5 Hz), 4.22 (1H, d, *J* = 9.8 Hz), 4.12–4.07 (2H, m), 3.94 (1H, d, *J* = 9.8 Hz), 3.82 (1H, d, *J* = 1.5 Hz), 2.30 (1H, s), 2.13 (1H, dd, *J* = 13.8, 6.8 Hz), 1.95–1.72 (1H, br s), 1.62 (1H, d, *J* = 13.8 Hz), 1.24 (3H, t, *J* = 7.1 Hz), 1.18 (3H, s), 10.4 (3H, s), 0.86 (9H), 0.05 (3H, s), 0.02 (3H, s). **15b**: R_f = 0.43 (petroleum ether–EtOAc (6 : 4)); $[\alpha]_D^{22}$ +17.3 (*c* = 1.21, $CHCl_3$); ^{1}H NMR (400 MHz) δ 4.40 (1H, dd, *J* = 9.6 Hz), 4.15–3.99 (3H, m), 3.96–3.94 (2H, m), 2.45–2.41 (1H, m), 2.29–2.21 (1H, br s), 2.12 (1H, s), 1.55–1.45 (1H, m), 1.26 (3H, t, *J* = 7.2 Hz), 1.12 (3H, s), 1.01 (3H, s), 0.87 (9H, s), 0.06 (3H, s), 0.03 (3H, s, $SiCH_3$).

(+)-(1*R*,2*S*,4*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,3-dimethyl-7-oxabicyclo[2.2.1]-heptane-2-carboxylic acid ethyl ester (16)

To a solution of alcohol **15a** (585 mg, 1.63 mmol) in CH_2Cl_2 (25 mL) was added TBDPSCl (636 μL, 2.44 mmol, 1.5 equiv.) and imidazole (222 mg, 3.26 mmol, 2.0 equiv.). The mixture was stirred at rt for 16 h. Then the reaction mixture was poured in water (25 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (petroleum ether–EtOAc (9 : 1)) afforded protected alcohol **16** (831 mg, 1.50 mmol, 92%) as a colourless oil. R_f = 0.73 (petroleum ether–Et_2O (1 : 1)); $[\alpha]_D^{20}$ +11.0 (*c* = 1.31, $CHCl_3$); IR 3018, 2958, 2858, 1740, 1111; ^{1}H NMR (400 MHz) δ 7.68 (2H, d, *J* = 7.9 Hz), 7.64 (2H, d, 7.9 Hz), 7.44–7.35 (6H, m), 4.34 (1H, dd, *J* = 6.9, 2.4 Hz), 4.26 (1H, d, *J* = 9.7 Hz), 4.11–3.99 (2H, m), 3.95 (1H, d, *J* = 9.7 Hz), 3.62 (1H, s), 2.11 (1H, s), 1.98 (1H, dd, *J* = 12.8, 7.0 Hz), 1.77 (1H, dd, *J* = 12.8, 1.9 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 1.06 (9H, s), 0.86 (9H, s), 0.84 (3H, s), 0.72 (3H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz) δ 170.9, 135.8, 135.7, 134.1, 133.9, 129.7, 129.6, 127.6, 91.8, 88.1, 71.9, 63.4, 59.6, 59.0, 47.0, 42.9, 26.9, 25.7, 25.1, 24.6, 19.1, 18.1, 14.3, −5.5, −5.6; HRMS (FAB) [M + H^+] calcd for $C_{34}H_{53}O_5Si_2$: 597.3432, found: 597.3437.

(+)-(1*R*,2*S*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)-1-hydroxymethyl-3,3-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (17)

Compound **16** (831 mg, 1.5 mmol) was dissolved in EtOH (25 mL) and concentrated HCl (250 μL) was added. After 60 min saturated aqueous $NaHCO_3$ (50 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4. Evaporation of the solvents and column chromatography (petroleum ether–Et_2O (1 : 1)) afforded alcohol **17** (622 mg, 1.3 mmol, 86%) as a colourless oil. R_f = 0.22 (petroleum ether–Et_2O (1 : 1)); $[\alpha]_D^{20}$ +14.5 (*c* = 0.91, $CHCl_3$); IR 3469 (br), 3070, 2958, 2857, 1738, 1110, 1068; ^{1}H NMR (400 MHz) δ 7.68 (2H, d, *J* = 8.0 Hz), 7.63 (2H, d, *J* = 8.0 Hz), 7.45–7.36 (6H, m), 4.37 (1H, dd, *J* = 6.6, 2.8 Hz), 4.20 (1H, d, *J* = 11.8 Hz), 4.12–4.02 (2H, m), 3.94 (1H, d, *J* = 11.8 Hz), 3.67 (1H, s), 2.23 (1H, br s), 2.12 (1H, s), 1.91 (1H, dd, *J* = 12.8, 2.7 Hz), 1.85 (1H, dd, *J* = 12.7, 6.6 Hz), 1.21 (3H, t, *J* = 7.1 Hz), 1.06 (9H, s), 0.88 (3H, s), 0.75 (3H, s); ^{13}C NMR (100 MHz) δ 171.6, 135.8, 135.7, 134.0, 133.8, 129.8, 129.7, 127.7, 91.7, 88.0, 72.1, 62.5, 60.2, 59.6, 46.0, 43.8, 26.8, 24.8, 24.3, 19.0, 14.3; HRMS (FAB) [M + Na^+] calcd for $C_{28}H_{38}NaO_5$ Si: 505.2386, found: 505.2372.

(+)-(1*R*,2*S*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)-1-formyl-3,3-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (5)

To a solution of alcohol **17** (1.25 g, 2.59 mmol) in acetone (4 mL) was added NMO (465 mg, 3.97 mmol, 1.5 equiv.) and TPAP (36 mg, 0.10 mmol, 4 mol%). The dark mixture was stirred for 90 min and the reaction mixture was filtered over a thin pad of silica followed by exhaustive rinsing with EtOAc. After evaporation of the solvent, crude aldehyde **5** (1.08 g, 2.25 mmol, 87%) was obtained as a colourless oil and was used without further purification in the next reaction. R_f = 0.35 (petroleum ether–EtOAc (8 : 2)); $[\alpha]_D^{20}$ +25.6 (*c* = 2.10, $CHCl_3$); IR 3071, 2931, 2856, 1732, 1107; ^{1}H NMR (400 MHz) δ 10.13 (1H, s), 7.69 (2H, d, *J* = 7.8 Hz), 7.62 (2H, d, *J* = 7.8 Hz), 7.47–7.36 (6H, m), 4.38 (1H, dd, *J* = 6.7, 2.4 Hz), 4.09–4.03 (2H, m), 3.77 (1H, s), 2.45 (1H, s), 2.03 (1H, dd, *J* = 12.9, 6.7 Hz), 1.78 (1H, dd, *J* = 12.9, 1.9 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 1.07 (9H, s), 0.92 (3H, s), 0.76 (3H, s); ^{13}C NMR (100 MHz) δ 200.1, 170.7, 135.8, 135.6, 134.8, 133.8, 133.4, 129.9, 129.8, 129.6, 127.8, 127.7, 91.8, 90.6, 70.9, 62.2, 60.8, 44.2, 43.4, 26.8, 24.5, 24.1, 19.0, 14.2; HRMS (FAB) [M + H^+] calcd for $C_{28}H_{37}O_5Si$: 481.2410, found: 481.2372.

(+)-(1*R*,2*S*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3,3-dimethyl-1-[(1*S*)-3-oxo-1,3,4,5,6,7-hexahydroisobenzofuran-1-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (18)

To a solution of aldehyde **5** (1.03 g, 2.14 mmol) in DMF (8 mL) was added vinyl triflate **6**[21] (1.60 g, 5.30 mmol, 2.5 equiv.) followed by $CrCl_2$ (1.33 g, 10.8 mmol, 5 equiv.) and $NiCl_2$ (7.4 mg, 57 μmol, *ca.* 2 mol%). The resulting green suspension was stirred at 50 °C for 16 h. After cooling the mixture to 0 °C, the reaction was quenched by adding saturated aqueous NH_4Cl (5 mL) followed by water (15 mL). The aqueous mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (petroleum ether–Et_2O (4 : 1)) afforded lactone **18** (873 mg, 1.48 mmol, 69%) as a white solid. R_f = 0.23 (petroleum ether–Et_2O (1 : 1)); mp 101.5 °C; $[\alpha]_D^{22}$ + 8.57 (*c* = 1.2, $CHCl_3$); IR 3070, 2935, 2858, 1760, 1737, 1111, 1066, 1024; ^{1}H NMR (400 MHz) δ 7.64 (2H, d, *J* = 6.7 Hz), 7.55 (2H, d, *J* = 6.7 Hz), 7.56–7.36 (6H, m), 5.91 (1H, s), 4.30 (1H, d, *J* = 6.0 Hz), 4.12–4.07 (2H, m), 3.6 (1H, s), 2.83–2.77 (1H, m), 2.44–2.39 (1H, m), 2.27–2.24 (3H, m), 1.77–1.72 (6H, m), 1.22 (3H, t, *J* = 7.1 Hz), 1.03 (9H, s), 0.86 (3H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz) δ 173.2, 170.4, 164.0, 135.6, 135.4, 133.6, 133.1, 129.8, 127.8, 127.7, 127.6, 127.6, 91.6, 86.6, 80.3, 71.2, 60.1, 60.0, 43.0, 41.5, 26.6, 24.9, 24.5, 24.2, 21.5, 21.6, 20.0, 18.8, 14.1; HRMS (FAB) [M + H^+] calcd for $C_{35}H_{45}O_6Si$: 589.2985, found: 589.2983; anal. calcd for $C_{35}H_{44}O_6Si$: C 71.39, H 7.53, found: C 71.30, H 7.42.

(+)-(1*R*,2*S*,4*R*,5*S*)-5-Hydroxy-3,3-dimethyl-1-[(1*S*)-3-oxo-1,3,4,5,6,7-hexahydroisobenzofuran-1-yl]-7-oxabicyclo[2.2.1]-heptane-2-carboxylic acid ethyl ester (19)

A solution of lactone **18** (52 mg, 88 μmol) in THF (1 mL) was cooled to 0 °C. To this solution was added HF·pyridine (70% HF, 30% pyridine, 0.2 mL). The mixture was allowed to warm to rt and stirring was continued for 8 h. The reaction was carefully quenched by adding saturated aqueous $NaHCO_3$ (3 mL) and water (5 mL) and was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (petroleum ether–Et_2O (7 : 1⟶3 : 1)) afforded alcohol **19** (29 mg, 83 μmol, 94%) as a white solid. R_f = 0.13 (petroleum ether–Et_2O (1 : 3)); $[\alpha]_D^{20}$ +17.3 (*c* = 1.37, $CHCl_3$); IR 3470 (br), 2941, 1756, 1738, 1670, 1159, 1008; ^{1}H NMR (400 MHz) δ 5.92 (1H, s), 4.37 (1H, d, *J* = 6.2 Hz), 4.19–4.10 (2H, m), 3.89 (1H, s), 2.47–2.43 (3H, m), 2.30–2.18 (2H, m), 1.87 (1H, dd, *J* = 13.7, 6.7 Hz), 1.75–1.61 (5H, m), 1.27 (3H, t, *J* = 7.1 Hz), 1.20 (3H, s), 1.12 (1H, d, *J* = 13.8 Hz), 1.06 (3H, s); ^{13}C NMR (100 MHz) δ 173.0, 170.5, 163.0, 128.1, 92.2, 87.0, 80.3, 70.2, 60.3, 60.2, 43.1, 41.8, 25.1, 25.0, 24.5, 21.5, 21.5, 20.1, 14.3; HRMS (FAB) [M + H^+] calcd for $C_{19}H_{27}O_6$: 351.1808, found: 351.1813.

(+)-(1*R*,2*S*,4*R*)-3,3-Dimethyl-5-oxo-1-[(1*S*)-3-oxo-1,3,4,5,6,7-hexahydroisobenzofuran-1-yl]-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (20)

To a solution of alcohol **19** (29 mg, 83 μmol) in acetone (2 mL) was added NMO (15 mg, 128 μmol, 1.5 equiv.) and TPAP (2.2 mg, 6.3 μmol, 7.5 mol%). The dark mixture was stirred for 2 h and was filtered over a thin pad of silica followed by exhaustive rinsing with EtOAc. Evaporation of the solvent and purification by column chromatography (CH_2Cl_2) afforded ketone **20** (24 mg, 69 μmol, 83%) as a white solid, which was

recrystallised from Et_2O to give colourless crystals. R_f = 0.30 (petroleum ether–Et_2O (1 : 1)); mp 168.5–169.5 °C; $[a]_D^{21}$ +98.0 (c = 1.25, $CHCl_3$); IR 3022, 2942, 2865, 1753, 1212, 1018; ^{1}H NMR (400 MHz) δ 5.94 (1H, s), 4.22–4.17 (2H, m), 3.86 (1H, s), 2.71 (1H, s), 2.45–2.39 (2H, m), 2.30–2.18 (2H, m), 1.97 (1H, d, J = 17.7 Hz), 1.91 (1H, d, J = 17.8 Hz), 1.78–1.67 (4H, m), 1.30 (3H, t, J = 7.2 Hz), 1.22 (3H, s), 1.15 (3H, s); ^{13}C NMR (100 MHz) δ 207.5, 172.2, 169.7, 162.3, 128.9, 89.6, 82.0, 79.9, 60.8, 59.6, 43.3, 43.2, 24.6, 24.5, 24.0, 21.5, 21.5, 20.1, 14.3; anal. calcd for $C_{19}H_{24}O_6$: C 65.50, H 6.94, found: C 65.17, H 6.82%.

Crystallographic data for **20**:¶ $C_{19}H_{24}O_6$, M_r = 348.3903, monoclinic, $P2_1$, a = 8.5854(7), b = 8.3775(7), c = 12.428(1) Å, β = 103.395°, V = 869.56(13) Å^3, Z = 2, D_x = 1.33 g cm^{-3}, λ-(Cu-Kα) = 1.5481 Å, μ(Cu-Kα) = 8.2 cm^{-1}, F(000) = 372, 253 K, final R = 0.060 for 1655 reflections.

(−)-(*S*)-[(1*R*,2*R*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-hydroxymethyl-3,3-dimethyl-7-oxabicyclo[2.2.1]heptan-1-yl]-(2-hydroxymethylcyclohex-1-enyl)methanol (21)

To a solution of lactone **18** (723 mg, 1.23 mmol) in Et_2O (10 mL) was added lithium aluminium hydride (3.8 mL of a 1.0 M solution in Et_2O, 3.8 mmol, 5 equiv.) in one portion at rt. After 10 min the reaction mixture was cooled to 0 °C and quenched by adding aqueous saturated $NaHCO_3$. After separation of the organic layer the water layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4. Evaporation of the solvent afforded triol **21** (415 mg, 0.75 mmol, 61%) as a colourless oil. Triol **21** was used unpurified in the next reaction. R_f = 0.18 (petroleum ether–Et_2O (1 : 3)); $[a]_D^{21}$ −5.21 (c = 1.6, $CHCl_3$); IR 3427 (br), 2929, 2856, 1245, 1110, 1069; ^{1}H NMR (400 MHz) δ 7.63–7.60 (4H, m), 7.44–7.36 (6H, m), 5.20 (1H, s), 4.41 (1H, d, J = 10.7 Hz), 4.31 (1H, d, J = 6.7 Hz), 3.78 (1H, dd, J = 10.9, 10.8 Hz), 3.63 (1H, dd, J = 10.7, 2.7 Hz), 3.57–3.54 (1H, m), 3.48 (1H, s), 3.46–3.38 (1H, m), 2.58–2.54 (1H, m), 2.33–2.28 (1H, m), 2.17–2.12 (1H, m), 2.03–1.99 (1H, m), 1.96 (1H, dd, J = 12.9, 6.8 Hz), 1.78 (1H, d, J = 12.6 Hz), 1.66–1.48 (5H, m), 1.04 (9H, s), 0.77 (3H, s), 0.72 (3H, s).

(−)-(*S*)-[(1*R*,2*R*,4*R*,5*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,3-dimethyl-7-oxabicyclo[2.2.1]-heptan-1-yl][2-(*tert*-butyldimethylsilyloxymethyl)cyclohex-1-enyl]methanol (22)

To a solution of triol **21** (415 mg, 0.75 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.61 mL, 7.6 mmol, 10 equiv.) and TBDMSCl (343 mg, 2.28 mmol, 3 equiv.). The reaction mixture was stirred at rt for 16 h. Then the solution was poured into water (30 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine and subsequently dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (petroleum ether–EtOAc (97 : 3)) afforded protected alcohol **22** (496 mg, 0.64 mol, 85%) as a colourless oil. R_f = 0.41 (petroleum ether–EtOAc (19 : 1)); $[a]_D^{21}$ −7.11 (c = 1.00, $CHCl_3$); IR 3425 (br), 2929, 2856, 1254, 1110, 1068; ^{1}H NMR (400 MHz) δ 7.65 (2H, d, J = 7.9 Hz), 7.61 (2H, d, J = 7.9 Hz), 7.43–7.34 (6H, m), 4.95 (1H, s), 4.50 (1H, d, J = 12.4 Hz), 4.28–4.24 (2H, m), 4.09 (1H, d, J = 12.4 Hz), 3.70 (1H, dd, J = 10.6, 10.5 Hz), 3.51 (1H, dd, J = 10.7, 3.5 Hz), 3.37 (1H, s), 2.36–2.31 (2H, m), 2.17–1.98 (2H, m), 1.91 (1H, dd, J = 12.7, 6.8 Hz), 1.75 (1H, d, J = 12.8 Hz), 1.68–1.58 (4H, m), 1.45 (1H, dd, J = 10.5, 3.4 Hz), 1.03 (9H, s), 0.92 (9H, s), 0.88 (9H, s), 0.74 (3H, s), 0.67 (3H, s), 0.08 (3H, s), 0.08 (3H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (50 MHz) δ 135.7, 135.7, 134.5, 134.3, 134.1, 130.5, 129.6, 129.5, 127.6, 127.5, 91.5, 91.3, 71.4, 69.4, 63.4, 61.4, 56.8, 43.9, 41.0, 31.9, 27.2, 26.8, 26.1, 25.9, 24.8, 22.8, 22.7, 19.0, 18.5, 18.2, 14.0, −5.1, −5.6; HRMS (FAB) [M + H$^+$] calcd for $C_{45}H_{76}O_5Si_3$: 779.4922, found: 779.4922.

(−)-(*S*)-Acetic acid [(1*R*,2*R*,4*R*,5*S*)-2-(*tert*-butyldimethylsilyl-oxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-3,3-dimethyl-7-oxa-bicyclo[2.2.1]heptan-1-yl][2-(*tert*-butyldimethylsilyloxymethyl)-cyclohex-1-enyl]methyl ester (23)

To a solution of alcohol **22** (150 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added acetic anhydride (0.2 mL, 2.1 mmol, 12 equiv.) and pyridine (2 mL). The reaction mixture was stirred at 40 °C for 16 h. The brown solution was concentrated *in vacuo* and the product was purified by column chromatography (petroleum ether–EtOAc (98 : 2)) to afford protected triol **23** (132 mg, 0.16 mmol, 89%) as a colourless oil. R_f = 0.45 (petroleum ether–EtOAc (19 : 1)); $[a]_D^{20}$ −6.51 (c = 0.97, $CHCl_3$); IR 2932, 2858, 1760, 1112, 1068; ^{1}H NMR (400 MHz) δ 7.64 (2H, d, J = 7.9 Hz), 7.61 (2H, d, J = 7.9 Hz), 7.44–7.34 (6H, m), 5.75 (1H, s), 4.41 (1H, d, J = 12.6 Hz), 4.32 (1H, dd, J = 6.6, 1.9 Hz), 4.16 (1H, d, J = 12.6 Hz), 3.68 (1H, dd, J = 10.0, 4.3 Hz), 3.51 (1H, dd, J = 10.6, 10.0 Hz), 3.46 (1H, d, J = 1.8 Hz), 2.36 (1H, s), 2.29–2.24 (1H, m), 2.11–2.06 (2H, m), 2.04 (3H, s), 1.83 (1H, dd, J = 12.6, 6.8 Hz), 1.66 (1H, d, J = 12.6 Hz), 1.58–1.50 (4H, m), 1.37 (1H, dd, J = 10.8, 4.3 Hz), 1.04 (9H, s), 0.96 (3H, s), 0.91 (9H, s), 0.83 (9H, s), 0.67 (3H, s), 0.09 (3H, s), 0.09 (3H, s), −0.02 (3H, s), −0.04 (3H, s); ^{13}C NMR (100 MHz) δ 169.2, 136.7, 135.8, 135.7, 134.3, 134.1, 129.6, 127.5, 127.0, 92.3, 88.2, 72.6, 71.5, 62.9, 60.9, 57.1, 45.9, 41.6, 26.8, 26.7, 26.1, 25.8, 25.5, 23.1, 22.7, 22.4, 20.9, 19.1, 18.5, 18.0, −5.3, −5.4, −5.6, −5.7; HRMS (EI) calcd for $C_{47}H_{76}O_6Si_3$: 820.4950, found: 820.4888.

(−)-(*S*)-Acetic acid [(1*R*,2*R*,4*R*,5*S*)-5-(*tert*-butyldiphenyl-silyloxy)-2-hydroxymethyl-3,3-dimethyl-7-oxabicyclo[2.2.1]-heptan-1-yl](2-hydroxymethylcyclohex-1-enyl)methyl ester (24)

To a solution of diol **23** (42 mg, 51 μmol) in MeOH (1 mL) were added a few crystals of CSA. The reaction mixture turned yellow immediately and decolourised after stirring for 4 h. Then water was added (5 mL) and the aqueous layer was extracted with Et_2O (4 × 5 mL). The combined organic layers were washed with brine and subsequently dried on Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (petroleum ether–Et_2O (1 : 3)) afforded diol **24** (23 mg, 39 μmol, 76%) as a colourless oil. R_f = 0.27 (petroleum ether–Et_2O (1 : 3)); $[a]_D^{20}$ −14.3 (c = 1.53, $CHCl_3$) IR 3385 (br), 2932, 2824, 1757, 1111, 1069; ^{1}H NMR (400 MHz) δ 7.64–7.57 (4H, m), 7.49–7.35 (6H, m), 5.07 (1H, s), 4.34–4.30 (2H, m), 4.28–4.15 (2H, m), 3.58 (1H, d, J = 11.5 Hz), 3.51 (1H, s), 2.59–2.54 (1H, m), 2.33–2.26 (1H, m), 2.16–2.09 (1H, m), 2.03 (3H, s), 2.02–1.98 (1H, m), 1.93 (1H, dd, J = 13.0, 6.7 Hz), 1.79 (1H, d, J = 12.8 Hz), 1.66–1.55 (5H, m), 1.04 (9H, s), 0.87 (3H, s), 0.71 (3H, s); ^{13}C NMR (50 MHz) δ 170.1, 136.4, 135.7, 135.7, 133.9, 133.7, 132.3, 129.7, 127.7, 127.7, 92.2, 89.6, 71.1, 68.8, 62.8, 60.2, 53.4, 43.6, 41.4, 29.7, 29.4, 26.8, 26.2, 25.0, 23.5, 22.8, 21.0, 19.0; HRMS (FAB) [M + Na$^+$] calcd for $C_{35}H_{48}NaO_6Si$: 615.3118, found: 615.3068.

(+)-(2*S*,3*R*,5*R*,10*R*,19*S*)-Lactone 25

To a solution of diol **24** (12 mg, 20 μmol) in acetone (1 mL) were added NMO (7.0 mg, 60 μmol, 3 equiv.) and TPAP (2.1 mg, 6.0 μmol, 0.3 equiv.). The dark mixture was stirred for 90 min followed by filtration over a thin pad of silica and exhaustive rinsing with EtOAc. Evaporation of the solvent and column chromatography (petroleum ether–Et_2O (1 : 1)) afforded lactone **25** (8.3 mg, 14 μmol, 70%) as a colourless oil. R_f = 0.60 (petroleum ether–Et_2O (1 : 3)); $[a]_D^{21}$ +26.7 (c = 1.29, $CHCl_3$); IR 3070, 2935, 2859, 1761, 1744, 1671, 1235, 1112, 1025; ^{1}H NMR (400 MHz, C_6D_6) δ 7.68 (2H, d, J = 7.9 Hz), 7.62 (2H, d, J = 7.9 Hz), 7.20–7.11 (6H, m), 4.60 (1H, s), 4.40

¶ CCDC reference number 180411. See http://www.rsc.org/suppdata/p1/b2/b201987f/ for crystallographic files in .cif or other electronic format.

(1H, dd, J = 11.2, 4.6 Hz), 4.23 (1H, dd, J = 6.6, 1.4 Hz), 4.10 (1H, dd, J = 11.2, 8.4 Hz), 3.52 (1H, s), 2.89–2.78 (1H, m), 2.21–2.14 (1H, m), 2.09–2.00 (2H, m), 1.95 (3H, s), 1.57 (1H, m), 1.49 (1H, dd, J = 13.0, 6.7 Hz), 1.40–1.21 (5H, m), 1.13 (9H, s), 0.76 (3H, s), 0.46 (3H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 172.8, 170.8, 163.1, 136.8, 136.6, 135.0, 135.5, 134.5, 130.9, 130.9, 129.2, 129.1, 93.7, 88.0, 80.7, 72.6, 63.0, 54.3, 42.7, 41.9, 27.7, 24.1, 23.5, 22.7, 22.6, 22.6, 21.3, 21.3, 19.8; HRMS (FAB) [M + H$^+$] calcd for $C_{35}H_{45}O_6Si$: 589.2985, found: 589.2971.

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