Studies Towards the Synthesis of Aplykurodins − Synthesis of 17,18-Dihydro-3,9-di-*epi*-aplykurodinone B

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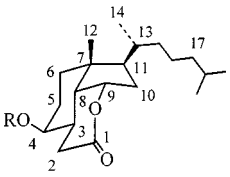
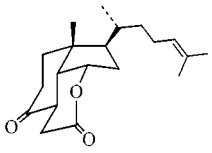
An approach to the synthesis of aplykurodins, ichthyotoxic marine lactones, is presented. The carbon framework was derived from vitamin D3 by conversion of the readily accessible allyl alcohol **13** to the protected Grundmann's hydroxy ketone **22** and subsequent introduction of the C2 side chain through a Pd^0-promoted coupling. Highly stereoselective hetero Diels−Alder reaction with $O2^1$ produced the key intermediate peroxide **25**. Functional group transformations, coupled with a series of chemo- and stereoselective reactions, finally resulted in the synthesis of the unnatural analogue 17,18-dihydro-3,9-di-*epi*-aplykurodinone B (**6**).

Introduction

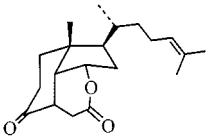
The aplykurodins[1] (**1**−**5**), isolated from marine mollusks of the genus *Aplysia*, are a restricted group of ichthyotoxic lactones which belong to the rare class of highly degraded marine steroids.[2] Their carbon skeleton is probably derived from a dramatic oxidative degradation of the tetracyclic steroid nucleus, with loss of all six carbon atoms of the A ring and of the 19-methyl group (steroidal numbering).



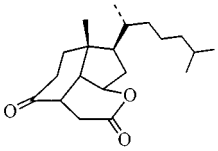
1 R = H, Aplykurodin A
2 R = H, Δ^{17}, Aplykurodin B
3 R = Ac, Δ^{17}, 4-Acetyl-aplykurodin B



4 Aplykurodinone B



5 3-*epi*-Aplykurodinone B



6 17,18-dihydro-3,9-*diepi*-Aplykurodinone B

The structures of the first aplykurodins isolated (**1** and **2**) were determined by spectroscopic methods and by X-ray crystallography.[1a] The last addition to the series, 3-*epi*-aplykurodinone B (**5**), was isolated in 1992 by the Salvà group[1c] and differs from **4**[1b] by the epimeric relationship at C-3. The presence of a strained six-membered lactone, which links two *cis*-fused rings, confers potential acylating activity to these molecules. It is a known fact that when a hydroxy group is present at C-4 (aplykurodin numbering), translactonization to the more stable five-membered ring lactone is easily achieved.[1a,1b]

To date, very little has been published on highly degraded marine steroids,[2] even though the structural complexity and their biological activities have stimulated the synthesis of (17*R*)-17-methylincisterol,[3] a member of a class of lactones related to aplykurodins. Moreover, the presence in the aplykurodins of a a *cis*-hydrindane skeleton is very interesting if we consider that the steroids possessing a *cis*-C/D junction act as powerful inhibitors of histamine release (sub-μM range).[4]

We thus embarked on the synthesis of the aplykurodin skeleton with particular attention to two subjects: the control of the stereochemistry of the three consecutive stereogenic centers (C-3, C-8, and C-9) and the efficient closure of the strained six-membered lactone, which would have been the crucial step of the synthesis.

In this paper we wish to report our approach which resulted in the synthesis of the unnatural 17,18-dihydro-3,9-di-*epi*-aplykurodinone B (**6**) and in some observations about the regio- and stereochemical response of the hydrindane system that have emerged in the course of this undertaking.

Results and Discussion

Our initial target molecule was aplykurodin A (**1**) which in our retrosynthetic plan was considered to be synthesised starting from the Grundmann ketone **11** (Figure 1). We considered the opened bicyclic precursor **7** as a suitable intermediate for the construction of the lactone-bridged tricyclic framework. This was linked back to the 1,2-dioxane *trans*-hydrindane **8**, which emerged from diene **9** through a [4 + 2] photooxidative reaction. Diene **9** could be secured,

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via the corresponding triflate, using a palladium-mediated vinylation of protected hydroxy ketone **10**. The latter can be synthesised from the known Grundmann ketone[5] (**11**), through modest functional group manipulation.

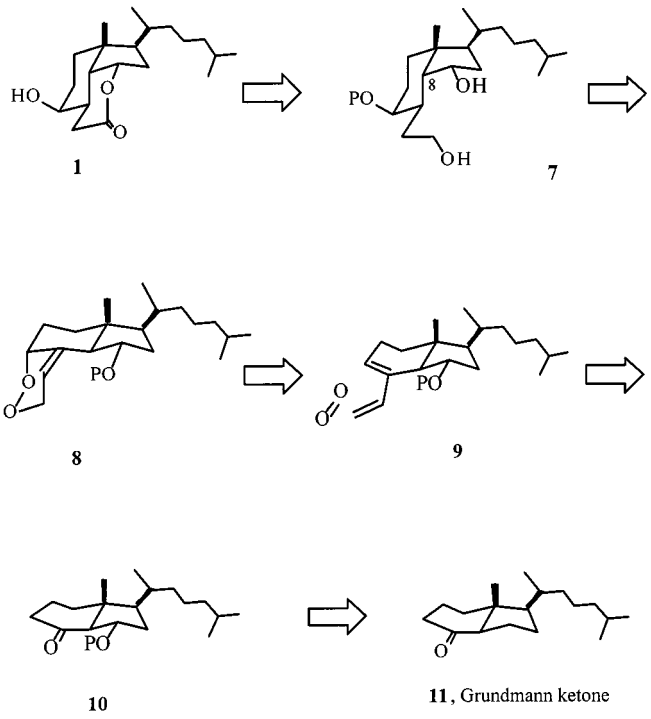
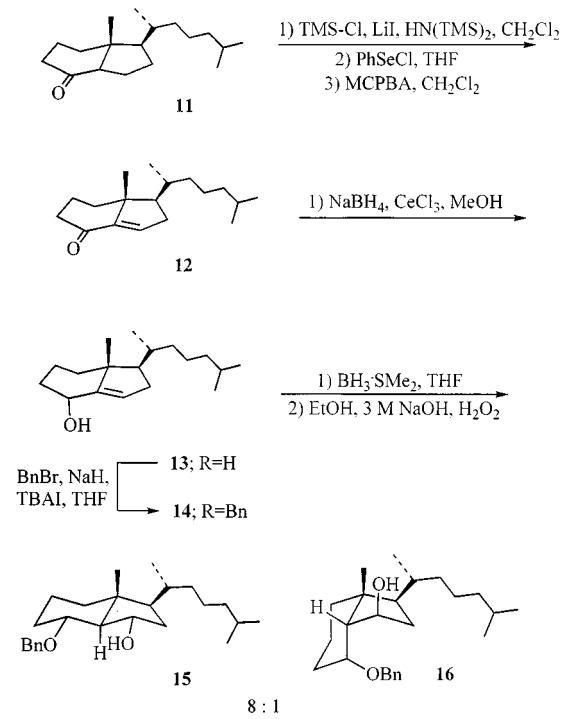


Figure 1. Retrosynthetic analysis for aplykurodin A

The synthesis thus started from the Grundmann ketone (**11**, Scheme 1), readily available from vitamin D_3,[5] which was transformed into the known allylic alcohol **13** in 56% yield, through a previously reported[6] selenium-mediated α,β-dehydrogenation, followed by a stereocontrolled ketone reduction. The resulting 3α-alcohol was protected as the benzyl ether **14** (90% yield), and then subjected to the hydroboration−oxidation reaction to furnish a mixture of two diasteromeric alcohols **15** and **16** in good overall yield (70%) and with a predominance of the *trans*-fused 9α-alcohol **15** (8:1 ratio). The two diastereomers were separated by silica gel flash chromatography and the geometry of the hydrindane ring junction was unambiguously assigned by comparison of ^{13}C-NMR resonances (**15**: δ_C = 13.5; ref.[7] for a *trans*-fused hydrindan: δ_C = 13.4; **16**: δ_C = 20.1; ref.[7] for a *cis*-fused hydrindan: δ_C = 19.0).

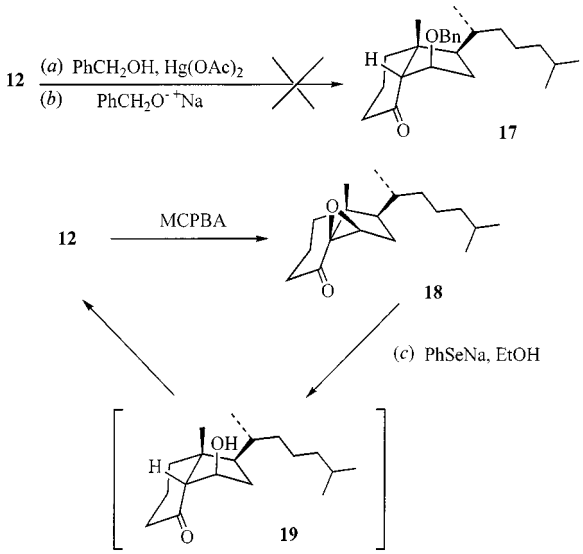
Since the hydroboration reaction furnished **15** with a *trans* ring junction as the major product, we attempted the formation of the *cis*-fused β-hydroxyhydrindanone at this stage, exploring different protocols (Scheme 2). In a first attempt (*a*) we started from the α,β-unsaturated ketone **12** and followed Seebach's benzyloxymercuration/demercuration[8] procedure. From the reaction mixture, we always recovered the unchanged starting material, even under forcing reaction conditions. Extensive decomposition (*b*) was observed when a Michael-like addition of sodium benzoate[9] to acceptor **12** was attempted. Also unsuccessful was the organoselenium-mediated reduction[10] (*c*) of the readily



Scheme 1. Synthesis at the alcohol **15**

synthesized β-epoxy ketone **18**, whose β configuration was tentatively assigned on the basis of ^{1}H-NMR chemical shift considerations, which gave back the α,β-unsaturated ketone **12**, presumably through elimination of water from the intermediate β-hydroxy ketone **19**.

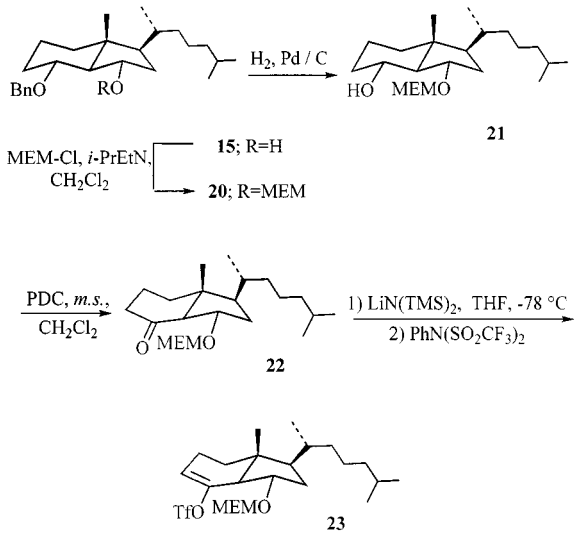
In view of these discouraging results, we decided to introduce the *cis* ring junction at a later stage of the synthetic plan.



Scheme 2. Attempts at the formation of the *cis*-fused hydrindanone

The construction of the C_2 chain at C-3 (Scheme 3) took advantage of the previous strategy set up for the synthesis of (17*R*)-17-methylincisterol.[3] To this end, the monopro-

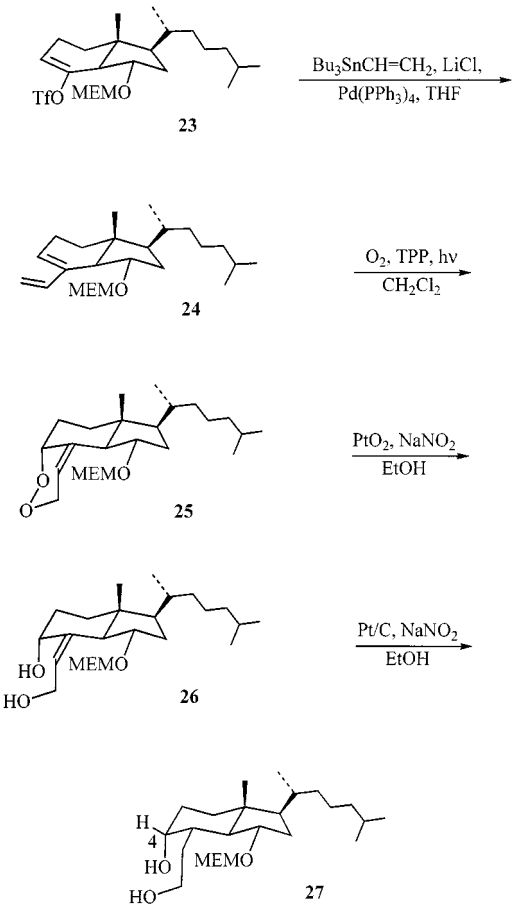
tected diol **15** was transformed into the acetal **20**,[11] which was debenzylated in the conventional way to give **21**. This, in turn, was subjected to pyridinium dichromate[12] (PDC) oxidation, to yield protected β-hydroxy ketone **22** (88%, three steps). Transformation of the base-sensitive **22** into the enol triflate[13] **23** was achieved through a careful choice of reaction conditions.[14]



Scheme 3. Synthesis of the enol triflate **23**

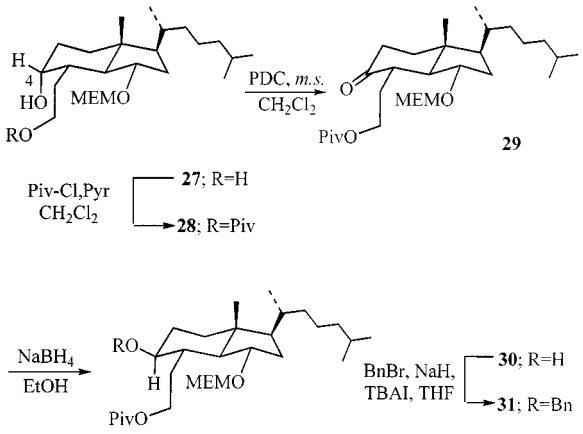
The enol triflate **23** was subjected to vinylation through the Stille palladium(0)-mediated coupling.[15] The reaction proceeded smoothly and delivered the diene **24** in 80% yield (Scheme 4). Hetero Diels−Alder reaction with singlet oxygen[16] afforded the peroxide **25** in good yield (87%) and excellent stereoselectivity (> 95%). The α-face diastereopreference, better than that observed in the case of incisterol synthesis,[3] was attributed to the presence of the OMEM and C-12 angular methyl groups. Acid-free Adam′s reduction[17] afforded the stable allylic diol **26**, whose ^{1}H-NMR spectrum showed a broad singlet at δ = 4.73 for the C-4 methine proton, suggesting a quasi-axial orientation of the hydroxy group. Moreover, the chemical shift values of the C-1−C-4 protons were in good agreement with those of an intermediate prepared during the synthesis of (17*R*)-17-methylincisterol.[3] Hydrogenation of the Δ^2 double bond afforded the saturated diol **27** stereoselectively in excellent yield.

The equatorial nature of the C-4 proton prevented us from inferring the stereochemical outcome of the hydrogenation through ^{1}H-NMR coupling constant values of the C-4/C-5 protons. Thus, the axial C-4 alcohol **27** was converted into its equatorial epimer **30** (Scheme 5). The alcohol inversion was obtained through an easy three-step sequence. Chemoselective acylation,[18] with pivaloyl chloride yielded the ester **28**, which on standard PDC oxidation,[12] followed by a stereoselective $NaBH_4$ reduction gave the required C-4 equatorial alcohol **30**. Benzylation of the free β-alcohol shifted the C-4 methine resonance upfield, and afforded the spectroscopically useful derivative **31**. ^{1}H-NMR analysis of the 4-H coupling constants (J = 10.4, 10.4, 5.6 Hz) allowed



Scheme 4. Synthesis of **27**

for the determination of an equatorial orientation for the C_2 side chain.

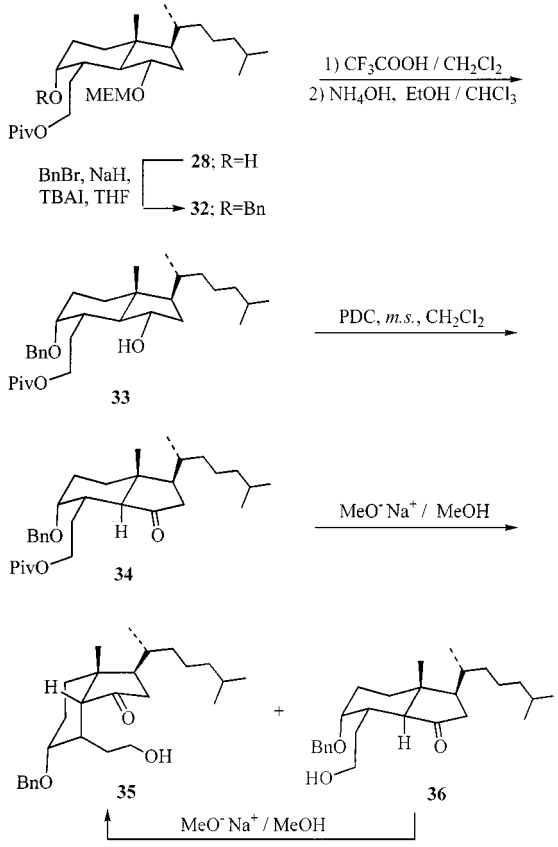


Scheme 5. Assignment of the C-4 configuration in **27**

Since the target molecule aplykurodin A (**1**) had a β-axial orientation of the C_2 side chain, we attemped several different reduction conditions, [catalysts: (1,5-cyclooctadiene)bis-(triphenylphosphane)rhodium(I) hexafluorophosphate dichloromethane complex (1:1), (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphane)iridium(I) hexafluorophosphate, (bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphos-

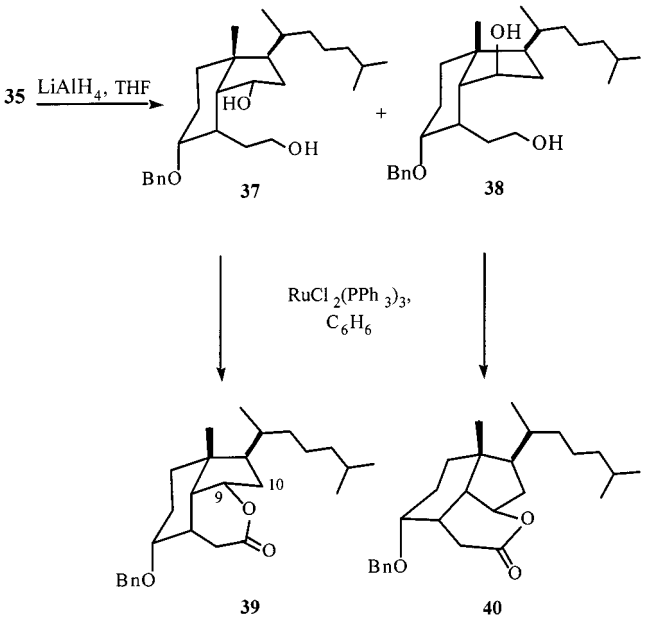
phanyl)butane]rhodium(I) tetrafluoroborate; conditions: dichloromethane at 1 atm or 40 atm] which always resulted in **27** as the unique reaction product or in the recovery of the unchanged starting material. On the other hand, attempted base-catalyzed epimerization of **29** (Na_2CO_3, MeOH) also resulted in the recovery of starting material. At this stage we changed the target, and we planned a synthesis of the dihydro analog of 3-*epi*-aplykurodinone B (**5**), which has an equatorial orientation of the C_2 side chain.

To this end, we planned to isomerize the hydrindanone skeleton to obtain the required *cis* junction (Scheme 6). Thus, benzylation of the pivaloate **28** gave the ether **32**, which was deprotected at C-9 using an efficient CF_3COOH/NH_4OH two-step protocol. Standard PDC oxidation,[12] and base-catalyzed[19] isomerization (MeONa/MeOH) allowed for the formation of the thermodynamically less stable C-1 deprotected ketone **35** in a 1:2 mixture with its epimeric *trans*-hydrindanone **36**.[20] Proton- and carbon-NMR spectra indicated that **36** was the methanolysis product of **34**, while in **35** epimerization at C-8 occurred in addition to methanolysis, as shown by the chemical shift values of the C-12 methyl group in the ^{13}C-NMR spectrum (δ = 19.2 in **35** vs. δ = 12.4 in **36**; cf. **15** and **16**). Compound **35** was easily separated from its prevailing C-8 epimer by silica gel column chromatography. Three successive base-catalyzed isomerizations, repeated on recovered **36**, gave **35** in 67% overall yield.



Scheme 6. Synthesis of **35**

Attention was now directed to the C-9 carbonyl reduction and lactonization reaction (Scheme 7). While $NaBH_4$ reduction of **35** gave two epimers **37** and **38** in a nearly 1:1 ratio, $LiAlH_4$ reduction gave **37** and **38** in a 5.6:1 ratio, the major one having the desired stereochemistry at C-9. The stereochemical identity of the two epimers was convincingly established after lactonization, which was obtained in excellent yield for both diols through exposure to $RuCl_2(PPh_3)_3$,[21] producing the two conformationally rigid lactones **39** and **40**.



Scheme 7. Synthesis of lactones **39** and **40**

The isomeric lactones **39** and **40** were separated by silica gel chromatography and their stereochemical assignment was achieved through the unambiguous rationalization of ^{1}H-NMR spectra using a combination of COSY-45, ROESY,[22] and NOE diff techniques. In particular, for lactone **39** the NOE experiments showed two key enhancements on irradiating the signal at δ = 4.84 (9-H): one at δ = 2.09 (8-Hβ) and the other at δ = 2.01 (10-Hβ). The NOE experiments for lactone **40** showed, when irradiated at the 9-H (δ = 4.68), an unexpected enhancement at δ = 1.42 (5-Hα).

Molecular modeling of the two lactones (Figure 2) using the MM2 force field[23] confirmed the NOE evidences. In fact, the three-dimensional structures of the predicted more stable conformations fit well with the expected dipolar effects. In particular, in lactone **40** it is evident that 9-H and 5α-H face one another (distance = 2.28 Å) confirming the proposed stereochemical assignments.

Having established the stereochemistry of the lactones, we prepared for the final steps of the synthetic plan, namely the removal of the protecting group and the oxidation to keto lactones. Unexpectedly, lactones **39** and **40** gave different results.

The hydrogenolysis of **40** (Pd/C in methanol) led to the expected hydroxy lactone **41**, whose ^{1}H-NMR spectrum

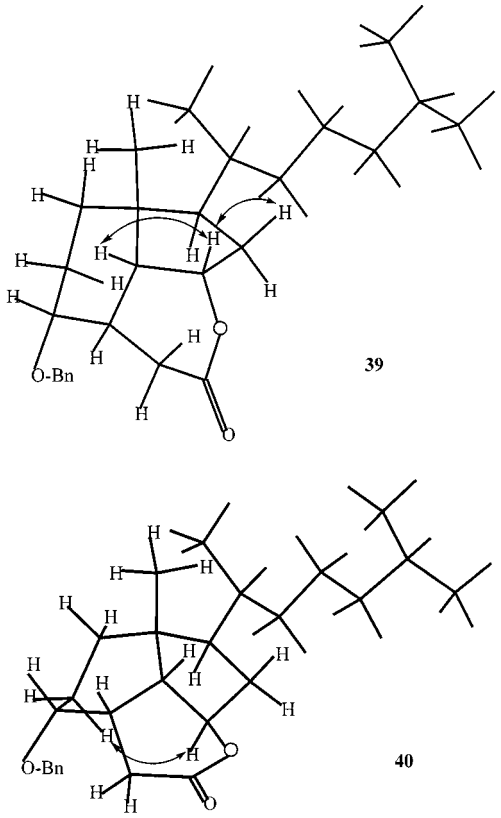
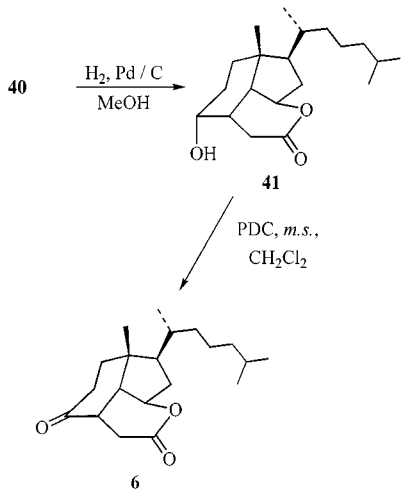


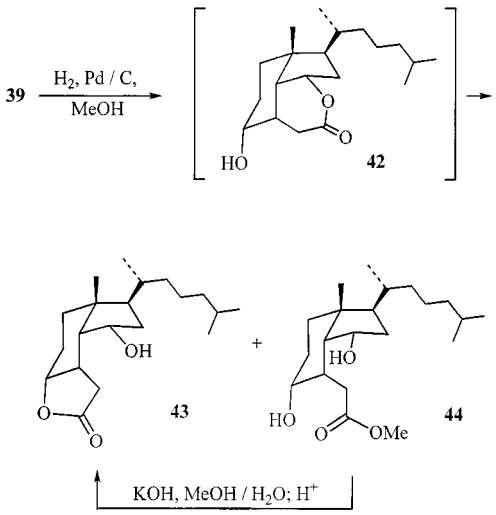
Figure 2. Global minimum energy conformations for **39** and **40**, as determined by molecular mechanics calculations (Chem-3D output); the arrows indicate the observed NOE enhancements

when compared to that of **40** indicated that no further reactions occurred during the hydrogenolysis. **41** was oxidized to 17,18-dihydro-3,9-di-*epi*-aplykurodinone B (**6**) with PDC (Scheme 8). The NOE difference NMR spectra of **6** afforded the same results as for **40**.



Scheme 8. Synthesis of **6**

On the other hand, hydrogenolysis of **39** under the same conditions furnished the five-membered lactone **43** (Scheme 9), together with the methyl ester **44**, as an inseparable mixture. Methanolysis of the **43** + **44** mixture and acidification resulted in the isolation of pure **43** whose structure was deduced by ^{1}H-NMR homonuclear decoupling and by the typical IR carbonyl stretching (ν_{max} = 1760 cm^{-1}).



Scheme 9. Formation of the five-membered lactone **43**

We interpret the different behaviour of lactone **39,** with respect to **40**, by considering that the six-membered lactone **42,** which is initially formed during the hydrogenolysis (Scheme 9), is more strained than **41** and thus isomerizes to the thermodynamically more stable five-membered lactone **43**. This isomerization has precedent[1] since it was shown that aplykurodins A (**1**) and B (**2**) smoothly isomerized to a five-membered lactone under acidic or basic conditions, or even during hydrogenation of the double bond of aplykurodin B (**2**).

Conclusions

Functionalization of the hydrindanone core of Grundmann ketone leading to the diol **27**, en route to aplykurodins, has been achieved in 14 steps and in 17% overall yield. Control of the lactonization reaction failed to give the target molecule 17,18-dihydro-3-*epi*-aplykurodinone B, affording only the unnatural epimer 17,18-dihydro-3,9-di-*epi*-aplykurodinone B (**6**).

Experimental Section

General: All reactions were carried out under dry argon using freshly distilled solvents unless otherwise noted. Tetrahydrofuran was distilled from sodium and benzophenone. Toluene and dichloromethane were distilled from calcium hydride. Glassware was flame-dried (0.05 Torr) before use. When necessary, compounds were dried by azeotropic removal of water with toluene under reduced pressure. Commercial reagents were purchased from Aldrich or Fluka and used without further purification. − Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized using UV light, spraying with H_2SO_4/$Ce(SO_4)_2$ solution and drying. Reaction temperatures were measured externally. − Flash chromatography was performed on Merck silica gel (60, particle size: 0.040−0.063 mm). Yields refer

to chromatographically and spectroscopically pure (^{1}H NMR) materials. − NMR spectra were recorded in $CDCl_3$ solutions with a Bruker AM-250 and DRX 400 spectrometers at room temp. Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ_H = 7.26, $^{13}CDCl_3$: δ_C = 77.0) − Optical rotations were recorded in $CHCl_3$ solutions with a JASCO DIP-1000 polarimeter − Mass spectra (E.I., 70 eV) were recorded with a VG TRIO 2000 mass spectrometer.

12: To a solution of Grundmann′s ketone **11** (1.72 g, 6.45 mmol) and hexamethyldisilazane (1.7 mL, 8.4 mmol) in dichloromethane (10 mL) at 0°C, lithium iodide (1.20 g, 7.92 mmol) and chlorotrimethylsilane (0.99 mL, 7.7 mmol) were added. The reaction mixture was stirred for 3 h, then quenched by addition of triethylamine (0.5 mL) and of a solution of $NaHCO_3$ (5% in water, 10 mL) and diluted with diethyl ether (5.0 mL). The organic layer was washed with water (3 × 15 mL), dried (Na_2SO_4), and concentrated in vacuo to give a residue (2.58 g) which was used in the next step without further purification. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.14 [9 H, s, $(CH_3)_3Si$], 0.86 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.87 (3 H, s, 12-CH_3), 0.92 (3 H, d, *J* = 6.4 Hz, 14-CH_3). − To a solution of crude trimethylsilyl ether (2.58 g, 7.70 mmol) in THF (8.0 mL) and pyridine (0.80 mL, 10.0 mmol) at −78°C, a solution of phenylselenyl chloride (1.90 g, 10.0 mmol) in THF (2.0 mL) was added dropwise. The mixture was stirred at −78°C for 0.5 h. The reaction was quenched by addition of a saturated solution of NaCl (15 mL), concentrated in vacuo to remove the excess of THF and extracted with dichloromethane (3 × 30 mL). The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash chromatography (silica gel 1−2% diethyl ether in petroleum ether) to give the phenylselenyl ketone (2.10 g 84%) as a colourless oil. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.93 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 1.17 (3 H, s, 12-CH_3), 7.24−7.46 (5 H, m, C_6H_5). − EIMS, *m*/*z*: 420 (Se^{80})/418 (Se^{78}) [M^+], 263, 245, 151, 43. − To a solution of the phenylselenyl ketone (7.10 g, 17.0 mmol) in dichloromethane (90 mL) at 0°C, pure *m*-chloroperbenzoic acid (4.80 g, 27.9 mmol) was added. The reaction mixture was stirred for 0.5 h and quenched by a satured solution of $NaHCO_3$ (2 × 20 mL). The organic layer was washed with water (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash chromatography (silica gel 1−5% diethyl ether in petroleum ether) to give **12** (3.67 g 83%) as a colorless oil. − $[\alpha]_D$ = −29 (*c* = 1.1, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.95 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 0.99 (3 H, s, 12-CH_3), 6.45 (1 H, dd, *J* = 3.4, 2.1 Hz, 9-H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.9, 18.7, 20.9, 22.5, 22.8, 23.7, 28.0, 33.7, 35.4, 36.0, 38.7, 39.4, 40.0, 48.4, 59.3, 135.4, 150.4, 200.3. − EIMS, *m*/*z*: 262 [M^+], 245, 177, 150.

13: To a solution of **12** (2.00 g, 7.60 mmol) in methanol (30 mL) at 0°C, $CeCl_3 \cdot 7\,H_2O$ (1.28 g, 3.42 mmol) and $NaBH_4$ (0.61 g, 22.0 mmol) were consecutively added. The reaction was stirred for 1 h and quenched by addition of HCl (1.0 N, 20 mL). The mixture was concentrated in vacuo to remove the excess methanol and extracted with diethyl ether (3 × 60 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash chromatography (silica gel, 15−40% diethyl ether in petroleum ether) to give **13** (1.60 g 80%) as a colorless oil. − $[\alpha]_D$ = −26 (*c* = 0.8, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.91 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 0.92 (3 H, s, 12-CH_3), 4.16 (1 H, m, 3-H), 5.44 (1 H, dd, *J* = 3.7, 1.8 Hz, 9-H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.1, 18.8, 21.6, 22.5, 22.8, 23.8, 28.0, 33.6, 35.3, 36.1, 36.7, 39.5, 41.7, 48.8, 59.3, 68.9, 117.0, 153.8. − EIMS, *m*/*z*: 264 [M^+], 249, 246, 152, 151.

14: To a suspension of NaH (60% in mineral oil, 0.012 g, 0.5 mmol) in THF (1.0 mL) at 0°C, was added a solution of **13** (0.053 g, 0.20 mmol) in THF (1.5 mL). After stirring for 0.5 h, BnBr (0.033 mL, 0.28 mmol) and tetrabutylammonium iodide (TBAI, 0.003 g, 0.007 mmol) were added. The resulting mixture was heated at reflux for 3 h and then quenched with a saturated solution of NH_4Cl (0.3 mL), concentrated in vacuo to remove the excess THF and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 10% diethyl ether in petroleum ether) to give **14** (0.064 g, 90%) as a colourless oil. − $[\alpha]_D$ = +10 (*c* = 0.9, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.91 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 0.92 (3 H, s, 12-CH_3), 3.95 (1 H, m, 3-H), 4.66 (2 H, s, OCH_2Ph), 5.57 (1 H, br. s, 9-H), 7.28−7.38 (5 H, m, C_6H_5). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.1, 18.8, 21.7, 22.5, 22.8, 23.8, 28.0, 33.1, 33.7, 35.5, 36.1, 39.5, 41.8, 48.8, 59.2, 70.8, 75.8, 118.1, 127.2 (× 3), 128.2 (× 2), 139.2, 150.8. − EIMS, *m*/*z*: 354 [M^+], 321, 263, 248, 197, 151.

15 and 16: To a solution of **14** (1.60 g, 4.50 mmol) in THF (5.0 mL) at 0°C, $BH_3 \cdot SMe_2$ (2.0 M in THF, 2.3 mL, 4.5 mmol) was slowly added. After 0.2 h the solution was warmed to room temp. and stirred for 3 h. The solution was then cooled at 0°C and absolute ethanol (10 mL), a solution of NaOH (3.0 M, 4.5 mL) and H_2O_2 (30% in water, 3.7 mL) were added in succession. The mixture was heated at reflux for 1 h, water was added (5.0 mL) and, after concentration in vacuo to remove the excess THF, was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; 10−20% diethyl ether in petroleum ether) to give **15** (0.94 g, 62%) and **16** (0.12 g, 8%) as colourless oils. − **15**: $[\alpha]_D$ = +13 (*c* = 0.9, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70 (3 H, s, 12-CH_3), 0.86 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.90 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 2.24 (1 H, dq, *J* = 12.0, 4.0 Hz, 4-H), 2.92 (1 H, br. s, O*H*), 3.65 (1 H, ddd, *J* = 12.5, 12.5, 5.0 Hz, 3-H), 4.12 (1 H, dt, *J* = 9.5, 7.0 Hz, 9-H), 4.45 (1 H, d, *J* = 12.5 Hz, OC*H*Ph), 4.70 (1 H, d, *J* = 12.5 Hz, OC*H*′Ph), 7.28−7.39 (5 H, m, C_6H_5). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.5, 18.3, 21.5, 22.5, 22.8, 23.7, 28.0, 31.7, 35.2, 35.9, 37.6, 39.3, 39.6, 44.9, 54.7, 61.7, 69.8, 73.4, 78.5, 127.5 (×2), 127.6, 128.4 (×2), 138.6. − EIMS, *m*/*z*: 354 [$M^+ - H_2O$], 287, 263, 196, 181, 151, 91. − **16**: $[\alpha]_D$= +15 (*c* = 0.9, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 0.90 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 1.02 (3 H, s, 12-CH_3), 3.33 (1 H, br. s, O*H*), 3.38 (1 H, dt, *J* = 12.5, 5.0 Hz, 3-H), 4.43 (1 H, dd, *J* = 10.0, 7.5 Hz, 9-H), 4.50 (1 H, d, *J* = 12.0 Hz, OC*H*Ph), 4.66 (1 H, d, *J* = 12.0 Hz, OC*H*′Ph), 7.28−7.39 (5 H, m, C_6H_5). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.1, 20.8, 22.6, 22.7, 25.3, 26.8, 28.0, 29.7, 33.7 (×2), 34.1, 38.8, 39.4, 43.6, 53.3, 55.6, 70.7, 71.7, 78.1, 127.4 (×2), 127.6, 128.4 (×2), 138.5. − EIMS, *m*/*z*: 354 [$M^+ - H_2O$], 287, 263.

18: To a solution of **12** (0.050 g, 0.19 mmol) in methanol (2.0 mL) at 0°C, sodium hydroxide (0.004 g, 0.095 mmol) and hydrogen peroxide (30% wt. 0.57 mmol) were added. The reaction mixture was stirred for 3 h at room temp., quenched with water (3.0 mL), concentrated in vacuo to remove the excess methanol and extracted three times with diethyl ether. The crude material was used in the next step without further purification. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (9 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3 and 14-CH_3), 1.12 (3 H, s, 12-CH_3), 2.34 (1 H, dd, *J* = 16.8, 8.2 Hz, 4-

H), 2.55 (1 H, dt, J = 16.8, 4.4, Hz, 4-H′), 3.48 (1 H, d, J = 2.6 Hz, 9-H).

20: To a solution of **15** (1.09 g, 2.9 mmol) in dichloromethane (5.0 mL), *i*Pr_2EtN (3.1 mL, 18 mmol) and MEMCl (1.6 mL, 15 mmol) were added. The mixture was stirred at room temp. for 3 h, quenched with a saturated solution of $NaHCO_3$ (5.0 mL) and extracted with dichloromethane (3 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 15−20% diethyl ether in petroleum ether) to give **20** (1.20 g, 91%) as a colourless oil. − $[\alpha]_D$ = +6 (c = 0.9, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.68 (3 H, s, 12-CH_3), 0.86 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.89 (3 H, d, J = 6.4 Hz, 14-CH_3), 2.20 (1 H, m, 4-H), 3.35 (3 H, s, OCH_3), 3.41−3.65 (5 H, m, OCH_2CH_2O and 3-H, overlapping), 3.97 (1 H, ddd, J = 9.5, 9.5, 4.8 Hz, 9-H), 4.43 (1 H, d, J = 11.9 Hz, OCHPh), 4.65 (1 H, d, J = 11.9 Hz, OCH'Ph), 4.66 (1 H, d, J = 7.0 Hz, OCHO), 4.72 (1 H, d, J = 7.0 Hz, OCH'O), 7.28−7.39 (5 H, m, C_6H_5). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.4, 18.5, 21.4, 22.5, 22.8, 23.9, 28.0, 32.1, 35.0, 36.0, 37.3, 39.4 (×2), 45.0, 54.1, 58.9, 60.0, 66.7, 69.7, 71.7, 77.3, 78.9, 95.3, 127.1, 127.5 (×2), 128.1 (×2), 139.2. − EIMS, *m*/*z*: 371 [M^+ − $CH_3OCH_2CH_2OCH_2$-], 355, 265, 249, 248, 207.

21: To a solution of **20** (1.21 g, 2.60 mmol) in absolute ethanol (10 mL), palladium on activated carbon (10% wt., 0.121 g) was added. The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was then stirred vigorously under hydrogen for 1.5 h, filtered through a pad of silica gel and concentrated in vacuo to give **21** (0.98 g 100%) as a colourless oil. − $[\alpha]_D$= +95 (c = 0.8, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70 (3 H, s, 12-CH_3), 0.86 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.88 (3 H, d, J = 6.4 Hz, 14-CH_3), 2.02 (1 H, dq, J = 12.4, 3.7 Hz, 4-H), 3.11 (1 H, br. s, OH), 3.39 (3 H, s, OCH_3), 3.54−3.81 (5 H, m, OCH_2CH_2O and 3-H, overlapping), 4.14 (1 H, m, 9-H), 4.72 (1 H, d, J = 7.0 Hz, OCHO), 4.78 (1 H, d, J = 7.0 Hz, OCH'O). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.5, 18.4, 21.3, 22.5, 22.8, 23.8, 28.0, 35.2, 35.3, 35.9, 36.0, 39.4, 39.6, 43.9, 54.6, 59.0, 60.4, 67.4, 70.1, 71.8, 78.7, 94.6. − EIMS, *m*/*z*: 281 [M^+ − CH_3OCH_2-CH_2OCH_2], 265, 247, 207, 105.

22: To a solution of **21** (0.98 g, 2.6 mmol) in CH_2Cl_2 (3.0 mL), 4-Å molecular sieves (1.40 g) and PDC (2.00 g, 5.20 mmol) were consecutively added. After 2 h, the reaction mixture was diluted with diethyl ether (7.0 mL). Filtration through a short pad of Celite and $CaSO_4$ (10% w/w) afforded a solution which was concentrated in vacuo and purified by flash chromatography (silica gel, 40% diethyl ether in petroleum ether) to give **22** (0.92 g, 97%) as a colourless oil. − $[\alpha]_D$ = +60 (c = 1.4, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.63 (3 H, s, 12-CH_3), 0.85 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.91 (3 H, d, J = 6.4 Hz, 14-CH_3), 2.60 (1 H, d, J = 9.1 Hz, 8-H), 3.39 (3 H, s, OCH_3), 3.59−3.81 (4 H, m, OCH_2CH_2O), 4.35 (1 H, m, 9-H), 4.69 (1 H, d, J = 7.0 Hz, OCHO), 4.75 (1 H, d, J = 7.0 Hz, OCH'O). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.5, 18.4, 22.5, 22.8, 23.7, 23.9, 28.0, 35.3, 35.8 (×2), 39.2, 39.3, 41.2, 50.0, 54.9, 58.9, 66.7, 67.5, 71.7, 71.8, 94.6, 210.0. − EIMS, *m*/*z*: 293 [M^+ − $CH_3OCH_2CH_2O$], 279, 263, 249, 151.

23: To a solution of **22** (0.360 g, 0.980 mmol) in THF (1.5 mL) at −78°C, lithium bis(trimethylsilyl)amide [LiN$(TMS)_2$, 1.0 M in THF, 2.5 mL, 2.5 mmol] was added. After 1 h, *N*-phenyltrifluoromethanesulfonimide (0.875 g, 2.45 mmol), dissolved in THF (1.5 mL), was added and, after an additional 0.4 h, the reaction mixture was warmed to room temp. After 2 h at room temp., the reaction was quenched by addition of NH_4Cl (5% in water), concentrated in vacuo to remove the excess THF and extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 5−15% diethyl ether in petroleum ether) to give **23** (0.446 g, 90%) as a colourless oil. − $[\alpha]_D$ = +13 (c = 0.6, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (3 H, s, 12-CH_3), 0.88 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.92 (3 H, d, J = 6.4 Hz, 14-CH_3), 2.63 (1 H, dq, J = 10.6, 3.4 Hz, 8-H), 3.39 (3 H, s, OCH_3), 3.55 (2 H, m, OCH_2CH_2O), 3.69 (1 H, m, OCH$_2$CHO), 3.81 (1 H, m, OCH$_2$CH'O), 4.00 (1 H, dt, J = 10.6, 7.1, Hz, 9-H), 4.73 (1 H, d, J = 7.0 Hz, OCHO), 4.78 (1 H, d, J = 7.0 Hz, OCH'O), 5.60 (1 H, dd, J = 7.0, 3.4 Hz, 4-H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.6, 18.4, 22.5, 22.8, 23.6, 23.7, 27.9, 34.9, 35.7, 35.8, 37.5, 39.4, 44.3, 52.4, 54.9, 58.9, 67.3, 71.7, 76.2, 95.9, 116.7, 149.1. − EIMS, *m*/*z*: 395 [M^+ − $CH_3OCH_2CH_2O$-CH_2O], 394, 281, 245, 149, 105.

24: To a solution of **23** (0.260 g, 0.510 mmol) in THF (2.5 mL), LiCl (0.100 g, 2.30 mmol), $Pd(PPh_3)_4$ (0.020 g, 0.014 mmol) and $Bu_3SnCH{=}CH_2$ (0.18 mL, 0.62 mmol) were consecutively added. The reaction mixture was heated at reflux for 4 h, then quenched with water (3.0 mL), concentrated in vacuo to remove the excess THF and extracted with petroleum ether. The organic layer was washed with a solution of NH_4OH (10% in water, 5.0 mL), brine (5.0 mL) and finally dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 5−10% diethyl ether in petroleum ether) to give **24** (0.152 g, 80%) as a colorless oil. − $[\alpha]_D$ = +86 (c = 0.7, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.67 (3 H, s, 12-CH_3), 0.85 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.91 (3 H, d, J = 6.4 Hz, 14-CH_3), 2.31 (1 H, dq J = 10.6, 3.4 Hz, 8-H), 3.37 (3 H, s, OCH_3), 3.53 (2 H, m, OCH_2CH_2O), 3.73 (2 H, m, OCH$_2$CH_2O), 3.92 (1 H, m, 9-H), 4.70 (1 H, d, J = 7.0 Hz, OCHO), 4.78 (1 H, d, J = 7.0 Hz, OCH'O), 4.82 (1 H, dd, J = 10.7, 2.2 Hz, 1-H), 5.27 (1 H, dd, J = 17.3, 2.2 Hz, 1-H′), 5.73 (1 H, dd, J = 6.8, 3.2 Hz, 4-H), 6.36 (1 H, dd, J = 17.3, 10.7 Hz, 2-H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.2, 18.5, 22.4, 22.7, 23.8, 24.4, 27.9, 35.8, 35.9, 36.3, 36.9, 39.3, 42.1, 52.6, 55.6, 58.9, 67.4, 71.7, 77.2, 95.1, 111.7, 121.8, 136.9, 137.1. − EIMS, *m*/*z*: 273 [M^+ − $CH_3OCH_2CH_2OCH_2O$], 272, 257, 159.

25: To a solution of the diene **24** (0.140 g, 0.340 mmol) in dichloromethane (6.0 mL), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP, 0.002 g) was added. The reaction mixture was cooled at −78°C, irradiated with a 400-W incandescent lamp and bubbled with oxygen. After 2 h, the mixture was concentrated in vacuo and the crude residue was purified by flash chromatography (silica gel, 10−25% diethyl ether in petroleum ether) to give **25** (0.132 g, 87%) as a colourless oil. − $[\alpha]_D$ = +62 (c = 0.2, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.81 (3 H, s, 12-CH_3), 0.86 (9 H, d, J = 6.6 Hz, 19-CH_3, 20-CH_3, and 14-CH_3), 2.68 (1 H, m, 8-H), 3.37 (3 H, s, OCH_3), 3.55 (2 H, m, OCH_2CH_2O), 3.74 (2 H, m, OCH$_2$-CH_2O), 4.02 (1 H, ddd, J = 8.9, 8.9, 3.9 Hz, 9-H), 4.40 (1 H, br. d, J = 16.0 Hz, 1-H), 4.75 (1 H, d, J = 7.0 Hz, OCHO), 4.81 (1 H, d, J = 7.0 Hz, OCH'O), 4.93 (1 H, br. d, J = 16.0 Hz, 1-H′), 5.08 (1 H, m, 4-H), 5.77 (1 H, br. s, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 17.9, 19.9, 22.4, 22.7, 23.2, 23.9, 27.9, 35.6 (×2), 37.5, 39.3, 40.9, 53.1, 54.8, 59.0, 67.6, 71.4, 71.7, 77.2, 76.5, 78.4, 95.2, 116.3, 137.9. − EIMS, *m*/*z*: 410 [M^+], 304, 286, 105.

26: To a solution of **25** (0.137 g, 0.330 mmol) in absolute ethanol (10 mL), PtO_2 (0.014 g) and $NaNO_2$ (0.007 g, 0.10 mmol) were added. The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was stirred vigorously under hydrogen for 3 h. It was then filtered through a pad of silica gel and

Celite (1:1) and concentrated in vacuo to give **26** (0.138 g, 100%) as a colourless oil. − $[\alpha]_D$ = +68 (*c* = 0.6, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.55 (3 H, s, 12-CH_3), 0.86 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.90 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 2.76 (1 H, br. d, *J* = 10.2 Hz, 8-H), 3.42 (3 H, s, OCH_3), 3.55−3.63 (3 H, m, OCH_2C*H*O), 3.80 (1 H, m, OCH_2C*H*O), 4.06 (1 H, dd, *J* = 12.4, 5.4 Hz, 1-H), 4.21 (1 H, ddd, *J* = 10.2, 10.2, 5.1 Hz 9-H), 4.38 (1 H, dd, *J* = 12.4, 9.0 Hz, 1-H′), 4.71 (1 H, d, *J* = 7.4 Hz, OC*H*O), 4.73 (1 H, br. s, 4-H), 4.77 (1 H, d, *J* = 7.4 Hz, OC*H*′O), 5.58 (1 H, bdd, *J* = 9.0, 5.4 Hz, 2-H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.3, 18.5, 22.5, 22.8, 23.8, 28.0, 29.7 (× 2), 35.0, 35.8, 36.1, 39.4, 45.2, 54.3, 57.7, 59.1, 64.0, 67.8, 72.3, 74.8, 77.2, 94.5, 122.7, 140.8. − EIMS, *m*/*z*: 394 [M^+ − H_2O], 289, 288, 273, 245, 175.

27: To a solution of **26** (1.27 g, 3.08 mmol) in ethyl acetate (40 mL), platinum on carbon (5% wt., 0.420 g) and $NaNO_2$ (0.130 g, 1.88 mmol) were added. The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was then stirred vigorously under hydrogen for 2 h. It was then filtered through a pad of silica gel and Celite (1:1), concentrated in vacuo and the crude residue was purified by flash chromatography (silica gel, 2−5% methanol in chloroform) to give **27** (1.10 g, 86%) as a colorless oil. − $[\alpha]_D$ = +57 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (3 H, s, 12-CH_3), 084 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.89 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 3.37 (3 H, s, OCH_3), 3.55 (2 H, m, OCH_2CH_2O), 3.65 (2 H, m, 1-H_2), 3.77 (3 H, m, OCH_2CH_2O and 9-H, overlapping), 3.94 (1 H, br. s, 4-H), 4.63 (1 H, d, *J* = 7.1 Hz, OC*H*O), 4.73 (1 H, d, *J* = 7.1 Hz, OC*H*′O-). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 18.5, 22.5, 22.7, 23.7, 27.9, 29.5, 32.6, 34.4, 35.3, 36.0, 36.7, 38.4, 39.4, 43.3, 51.5, 53.7, 59.0, 60.9, 67.5, 67.8, 72.0, 79.0, 95.2. − EIMS, *m*/*z*: 396 [M^+ − H_2O].

28: To a solution of **27** (0.595 g, 1.44 mmol) in CH_2Cl_2 (20 mL), pyridine (0.3 mL, 3.7 mmol), pivaloyl chloride (0.9 mL, 7.1 mmol) and dimethylaminopyridine (DMAP, 0.010 g, 0.08 mmol) were consecutively added. After 1.5 h, the reaction mixture was quenched by addition of a solution HCl (2.0 N, 5.0 mL). The organic layer was washed with a saturated solution of $CuSO_4$ (10 mL) and brine (10 mL) and then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 2−5% methanol in chloroform) to give **28** (0.564 g 79%) as a colorless oil. − $[\alpha]_D$ = +41 (*c* = 1.2, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (3 H, s, 12-CH_3), 0.85 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.90 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 1.18 [9 H, s, (CH_3)$_3$C], 3.38 (3 H, s, OCH_3), 3.54 (2 H, m, OCH_2-CH_2O), 3.70 (2 H, m, OCH_2CH_2O), 3.78 (1 H, ddd, *J* = 8.5, 8.5, 3.5 Hz, 9-H), 3.92 (1 H, br. s, 4-H), 4.14 (2 H, dd, *J* = 7.3, 5.3 Hz, 1-H_2), 4.66 (1 H, d, *J* = 7.1 Hz, OC*H*O), 4.74 (1 H, d, *J* = 7.1 Hz, OC*H*′O). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 18.5, 22.5, 22.7, 23.8, 27.2 (× 3), 28.0, 28.1, 29.6, 34.3, 35.3, 36.0, 36.7, 37.7, 39.4, 43.2, 51.7, 53.8, 59.0, 62.9, 66.8, 67.8, 71.9, 77.2, 79.0, 95.2, 178.5. − EIMS, *m*/*z*: 498 [M^+], 480 [M^+ − H_2O].

29: To a solution of **28** (0.040 g, 0.081 mmol) in CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.08 g) and PDC (0.061 g, 0.162 mmol) were added. After 2 h, the reaction mixture was diluted with diethyl ether (4.0 mL). Filtration through a short pad of Celite and $CaSO_4$ (10% w/w) afforded a solution which was concentrated in vacuo. The crude residue was used without further purification. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.89 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 0.97 (3 H, s, 12-CH_3), 1.12 [9 H, s, (CH_3)$_3$C], 3.37 (3 H, s, OCH_3), 3.51 (2 H, m, OCH_2CH_2O), 3.68 (2 H, m, OCH_2CH_2O), 3.85 (1 H, m, *J* = 9-H), 3.92 (1 H, br. s, 4-H), 4.01 (1 H, m, 1-H), 4.20 (1 H, m, 1-H′), 4.64 (1 H, d, *J* = 7.1 Hz, OC*H*O), 4.75 (1 H, d, *J* = 7.1 Hz, OC*H*′O).

30: To a solution of **29** (0.040 g, 0.081 mmol) in methanol (2.0 mL) at 0°C, $CeCl_3 \cdot 7\,H_2O$ (0.029 g, 0.078 mmol) and $NaBH_4$ (0.003 g) were added. The reaction mixture was stirred for 1 h, quenched by addition of HCl (1.0 N, 1.0 mL) and concentrated in vacuo to remove the excess methanol. The aqueous layer was extracted with diethyl ether (3 × 3 mL) and the organic phase was dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash chromatography (silica gel, 15−30% ethyl acetate in petroleum ether) to give **30** (0.040 g 100% two steps) as a colourless oil. − $[\alpha]_D$ = +118 (*c* = 1.5 $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75 (3 H, s, 12-CH_3), 0.85 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.87 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 1.17 [9 H, s, (CH_3)$_3$C], 3.38 (4 H, m, OCH_3 and 4-H, overlapping), 3.54 (2 H, m, OCH_2-CH_2O), 3.70 (2 H, m, OCH_2CH_2O), 3.81 (1 H, ddd, *J* = 8.9, 8.9, 3.9 Hz, 9-H), 4.29 (2 H, m, 1-H_2), 4.66 (1 H, d, *J* = 7.1 Hz, OC*H*O), 4.73 (1 H, d, *J* = 7.1 Hz, OC*H*′O), 7.32 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 18.3, 22.4, 22.6, 23.6, 27.1 (× 3), 27.7, 27.8, 31.1, 35.1, 35.8, 37.4, 37.5, 39.3, 40.6, 43.2, 53.1, 56.2, 58.9, 63.0, 67.7, 71.7, 74.5, 77.2, 78.3, 95.1, 178.6. − EIMS, *m*/*z*: 498 [M^+], 480 [M^+ − H_2O].

31: To a suspension of NaH (60% in mineral oil, 0.016 g, 0.70 mmol) in THF (1.0 mL), at 0°C, was added a solution of alcohol **30** (0.04 g, 0.08 mmol) in THF (1.0 mL). After stirring for 0.5 h, BnBr (0.06 mL, 0.048 mmol) and TBAI (some crystals) were added. The resulting mixture was heated at reflux for 2 h and then quenched with a saturated solution of NH_4Cl (0.3 mL), concentrated in vacuo to remove the excess THF and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 5−15% ethyl acetate in petroleum ether) to give **31** (0.030 g, 65%). − $[\alpha]_D$ = +24 (*c* = 0.9 $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75 (3 H, s, 12-CH_3), 0.85 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.88 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 1.17 (9 H, s, (CH_3)$_3$C), 3.20 (1 H, ddd, *J* = 10.4, 10.4, 5.6 Hz, 4-H), 3.38 (3 H, s, OCH_3), 3.53 (2 H, m, OCH_2CH_2O), 3.69 (2 H, m, OCH_2CH_2O), 3.84 (1 H, ddd, *J* = 7.2, 7.2, 4.0 Hz, 9-H), 4.10 (1 H, m, 1-H), 4.25 (1 H, m, 1-H′), 4.43 (1 H, d, *J* = 11.7 Hz, C*H*Ph), 4.63 (1 H, d, *J* = 11.7 Hz, C*H*′Ph), 4.67 (1 H, d, *J* = 7.1 Hz, OC*H*O), 4.73 (1 H, d, *J* = 7.1 Hz, OC*H*′O), 7.30−7.34 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 15.1, 18.3, 22.4, 22.6, 23.6, 27.1 (× 3), 27.8, 28.1, 35.1, 35.8, 37.3, 37.4, 38.6, 39.3,43.0, 53.1, 56.8, 58.8, 63.3, 65.7, 67.6, 71.0, 71.7, 78.6, 81.9, 95.2, 127.3, 127.7 (× 2), 128.1 (× 2), 138.6, 178.2. − EIMS, *m*/*z*: 588 [M^+], 396, 376.

32: To a suspension of NaH (60% in mineral oil, 0.70 g, 2.90 mmol) in THF (1.0 mL) at 0°C, was added a solution of **28** (0.80 g, 1.60 mmol) in THF (1.5 mL). After stirring for 0.5 h, BnBr (1.1 mL, 9.2 mmol) and TBAI (0.030 g, 0.075 mmol) were added. The resulting mixture was refluxed for 2 h and then quenched with a saturated solution of NH_4Cl (0.3 mL), concentrated in vacuo to remove the excess THF and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 5−20% ethyl acetate in petroleum ether) to give **32** (0.581 g, 62%) as a colorless oil. − $[\alpha]_D$ = +7 (*c* = 1.2, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (3 H, s, 12-CH_3), 0.86 (6 H, d, *J* = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.90 (3 H, d, *J* = 6.4 Hz, 14-CH_3), 1.18 [9 H, s, (CH_3)$_3$C], 3.38 (3 H, s, OCH_3), 3.53 (3 H, m, OCH_2-CH_2O and 4-H, overlapping), 3.71 (2 H, m, OCH_2CH_2O), 3.76 (1 H, ddd, *J* = 7.3, 7.3, 3.6 Hz, 9-H), 3.98 (2 H, m, 1-H_2), 4.31 (1 H,

d, J = 11.7 Hz, C*H*Ph), 4.59 (1 H, d, J = 11.7 Hz, C*H*′Ph), 4.67 (1 H, d, J = 7.1 Hz, OC*H*O), 4.74 (1 H, d, J = 7.1 Hz, OC*H*′O), 7.30−7.34 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 18.5, 22.5, 22.8, 23.7, 24.4, 27.2 (×3), 27.9, 28.0, 34.6, 35.4, 36.0, 36.8, 37.2, 39.5, 43.0, 52.2, 53.5, 59.0, 62.6, 67.7, 70.3, 71.9, 73.9, 77.2, 79.2, 95.2, 127.2, 127.5 (× 2), 128 (× 2), 139.2, 178.5. − EIMS, *m*/*z*: 588 [M^+], 396, 376.

33: A solution of **32** (0.530 g, 0.736 mmol) in trifluoroacetic acid and dichloromethane (1:1 ratio, 20 mL) was left to react overnight. The organic phase was washed with a $NaHCO_3$ solution (10% in water, 10 mL), then brine (10 mL) and finally dried (Na_2SO_4) and concentrated in vacuo. The crude trifluoroacetate was dissolved in chloroform (3.0 mL), and absolute ethanol (5.0 mL) and a solution of NH_4OH (33% in water, 1.0 mL) were added. After 2 h, the organic phase was concentrated in vacuo and the residue was purified by flash chromatography (silica gel, 5−10% ethyl acetate in petroleum ether) to give 33 (0.368 g, 82%) as a colourless oil.

33: $[\alpha]_D$ = −6 (c = 1.1, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (3 H, s, 12-CH_3), 0.87 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.91 (3 H, d, J = 6.4 Hz, 14-CH_3), 1.19 [9 H, s, $(CH_3)_3$C], 3.55 (1 H, br. s, 4-H), 3.89 (1 H, m, 9-H), 4.04 (2 H, m, 1-H_2), 4.32 (1 H, d, J = 11.7 Hz, C*H*Ph), 4.61 (1 H, d, J = 11.7 Hz, C*H*′Ph), 7.30−7.34 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 18.5, 22.6, 22.8, 23.7, 24.5, 27.2 (× 3), 28.0, 28.5, 34.7, 35.3, 36.1, 37.1, 39.5, 40.5, 44.0, 53.4, 55.1, 62.7, 70.3, 73.5, 74.8, 127.3, 127.5 (× 2), 128.2 (× 2), 138.6, 178.7. − EIMS, *m*/*z*: 500 [M^+], 482 [$M^+ - H_2O$].

34: To a solution of **33** (0.279 g, 0.588 mmol) in CH_2Cl_2 (5.0 mL), 4-Å molecular sieves (0.4 g) and PDC (0.442 g, 1.18 mmol) were added. After 2 h, the reaction mixture was diluted with diethyl ether (7.0 mL). Filtration through a short pad of Celite and $CaSO_4$ (10% w/w) afforded a solution which was concentrated in vacuo and purified by flash chromatography (silica gel, 10−15% diethyl ether in petroleum ether) to give **34** (0.220 g, 79%) as a colourless oil. − $[\alpha]_D$ = −2 (c = 1.0, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (3 H, s, 12-CH_3), 0.85 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.99 (3 H, d, J = 6.4 Hz, 14-CH_3), 1.19 [9 H, s, $(CH_3)_3$C], 3.60 (1 H, br. q, J = 2.3 Hz, 4-H), 4.07 (2 H, m, 1-H_2), 4.32 (1 H, d, J = 11.7 Hz, C*H*Ph), 4.59 (1 H, d, J = 11.7 Hz, C*H*′Ph), 7.30−7.34 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 18.8, 19.3, 22.3, 22.5, 23.5, 24.0, 25.6, 27.1 (× 3), 27.8, 33.8, 34.3, 35.1, 35.8, 39.1, 41.5, 42.3, 51.1, 58.1, 62.2, 70.3, 73.3, 127 (× 3), 128.2 (× 2), 138.6, 178.5, 215.8. − EIMS, *m*/*z*: 498 [M^+].

35 and 36: To a solution of MeONa in methanol (1 M, 3.5 mL) was added **34** (0.129 g, 0.259 mmol). After 2 h, the reaction mixture was diluted with diethyl ether (5.0 mL). Filtration through a short pad of silica gel afforded a solution which was concentrated in vacuo and purified by flash chromatography (silica gel, 10−40% ethyl acetate in petroleum ether) to give **35** (0.034 g, 32%) and **36** (0.072 g, 67%) as colourless oils. − **35**: $[\alpha]_D$ = −28 (c = 0.5, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.86 (3 H, s, 12-CH_3), 0.86 (3 H, d, J = 6.4 Hz, 14-CH_3), 3.49 (1 H, br. s, 4-H), 3.64 (1 H, m, 1-H), 3.71 (1 H, m, 1-H′), 4.33 (1 H, d, J = 12.0 Hz, C*H*Ph), 4.56 (1 H, d, J = 12.0 Hz, C*H*′Ph), 7.22−7.36 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 21.4, 22.5, 22.7, 24.9 (× 2), 25.4, 28.0, 31.8 (× 2), 32.4, 33.0, 37.5, 39.1, 41.9, 50.3, 53.7, 61.5, 69.9, 75.0, 126.7 (× 2), 127.1, 128.2 (× 2), 139.0, 221.3. − EIMS, *m*/*z*: 414 [M^+], 396 [$M^+ - H_2O$]. − **36**: $[\alpha]_D$= −2 (c = 0.9, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (3 H, s, 12-CH_3), 0.86 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.99 (3 H, d, J = 6.4 Hz, 14-CH_3), 2.45 (1 H, d, J = 10.2 Hz, 8-H), 3.56 (1 H, m, 1-H), 3.61 (1 H, br. s, 4-H), 3.68 (1 H, m, 1-H′), 4.32 (1 H, d, J = 11.7 Hz, C*H*Ph), 4.60 (1 H, d, J = 11.7 Hz, C*H*′Ph), 7.28−7.36 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 19.0, 22.5, 22.7, 23.6, 24.1, 27.9, 30.8, 33.9, 34.5, 35.3, 36.0, 39.3, 41.7, 42.6, 51.3, 58.6, 60.9, 70.4, 74.7, 127.6 (× 2), 128.3 (× 3), 138.6, 216.9. − EIMS, *m*/*z*: 414 [M^+], 396 [$M^+ - H_2O$].

37 and 38: To a solution of **35** (0.024 g, 0.058 mmol) in diethyl ether (1.0 mL) at 0°C, was added $LiAlH_4$ (1.0 M in THF, 0.12 mL, 0.12 mmol). The reaction mixture was stirred for 1 h and quenched with diethyl ether (0.5 mL) and NH_4OH (0.1 mL, 10% aqueous solution). Filtration through a short pad of Celite and concentration in vacuo gave a crude material, which was used without further purification. − **37** and **38**: ^{1}H NMR (400 MHz, $CDCl_3$, peak integration not reported): δ = 0.86 (d, J = 6.6 Hz, 19-CH_3 and 20-CH_3, **37** and **38**), 0.87 (d, J = 6.4 Hz, 14-CH_3, **38**), 0.93 (d, J = 6.4 Hz, 14-CH_3, **37**), 1.04 (s, 12-CH_3, **37** and **38**), 3.57 (br. s, 4-H, **38**), 3.62 (m, 1-H_2 and 4-H, **37**), 3.63 (m, 1-H, **38**), 3.75 (m, 1-H′, **38**), 4.02 (br. s, 9-H, **37**), 4.29 (d, J = 11.7 Hz, C*H*Ph, **38**), 4.37 (d, J = 11.7 Hz, C*H*Ph, **37**), 4.62 (d, J = 11.7 Hz, C*H*′Ph, **38**), 4.72 (d, J = 11.7 Hz, C*H*′Ph, **37**), 4.73 (dd, J = 16.0, 7.8 Hz, 9-H, **38**) 7.28−7.36 (m, C_6H_5, **37** and **38**).

39 and 40: The mixture of **37** and **38** (0.025 g) was dissolved in benzene (0.5 mL) and $RuCl_2(PPh_3)_3$ (0.034 g, 0.035 mmol) was added. The reaction mixture was stirred overnight. Filtration through a short pad of silica gel and concentration in vacuo gave a crude product which was purified by flash chromatography (silica gel, 10−20% ethyl acetate in petroleum ether) to give **39** (0.014 g, 73%) and **40** (0.0025 g, 13%) as colourless oils. − **39**: IR ($CHCl_3$): $\tilde{\nu}$ = 1736 cm^{-1} (C=O). − $[\alpha]_D$ = +6 (c = 0.9, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.92 (3 H, d, J = 6.4 Hz, 14-CH_3), 0.96 (3 H, s, 12-CH_3), 2.01 (1 H, m, 10-Hβ), 2.09 (1 H, m, 8-H), 2.36 (1 H, m, 2-H), 2.39 (1 H, br. s, 3-H), 2.56 (1 H, m, 2-H′), 3.53 (1 H, br. s, 4-H), 4.46 (1 H, d, J = 11.7 Hz, C*H*Ph), 4.53 (1 H, d, J = 11.7 Hz, C*H*′Ph), 4.84 (1 H, ddd, J = 8.0, 8.0, 4.4 Hz, 9-H), 7.28−7.36 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 22.5, 22.8, 23.0, 24.4, 24.8, 28.0, 31.3, 33.0, 33.4, 34.1, 35.3, 35.5, 37.5, 39.4, 43.2, 47.3, 51.4, 70.2, 75.2, 80.3, 127.5, 127.6 (× 2), 128.3 (× 2), 174.0. − EIMS, *m*/*z*: 412 [M^+]. − **40**: $[\alpha]_D$ = +41 (c = 0.2, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.91 (3 H, d, J = 6.4 Hz, 14-CH_3), 1.11 (3 H, s, 12-CH_3), 1.42 (1 H, m, 5-Hα), 1.44 (1 H, m, 8-H), 1.97 (1 H, dq, J = 14.0, 3.0 Hz, 5-Hβ), 2.13 (1 H, dt, J = 11.1, 5.6, 5.6 Hz, 10-Hα), 2.21 (1 H, m, 3-H), 2.55 (1 H, dd, J = 17.2, 9.1 Hz, 2-Hβ), 2.97 (1 H, dd, J = 17.2, 5.0 Hz, 2-Hα), 3.53 (1 H, br. s, 4-H), 4.29 (1 H, d, J = 11.7 Hz, C*H*Ph), 4.62 (1 H, d, J = 11.7 Hz, C*H*′Ph), 4.68 (1 H, ddd, J = 10.8, 10.8, 5.8 Hz, 9-H), 7.28−7.36 (5 H, m, C_6H_5). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2, 22.3, 22.5, 22.7, 23.7, 24.4, 28.0, 31.0, 31.7, 33.3, 33.4, 34.6, 35.3, 37.3, 39.4, 50.5, 54.8, 70.8, 73.6, 79.0, 127.4 (×2), 127.7, 128.5 (×2), 138.2, 174.0. − EIMS, *m*/*z*: 412 [M^+].

41: To a solution of **40** (0.003 g, 0.0078 mmol) in methanol (0.5 mL), was added palladium on carbon (10% wt., 0.003 g). The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was then stirred vigorously under hydrogen for 2 h. It was then filtered through a pad of Celite and concentrated in vacuo. The residue (0.003 g) was used in the next step without further purification. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.92 (3 H, d, J = 6.4, 14-CH_3), 1.10 (3 H, s, 12-CH_3), 2.60 (1 H, dd, J = 17.0, 9.2 Hz, 2-H), 2.95 (1 H, dd, J = 17.0, 5.2 Hz, 2-H′), 3.90 (1 H, br.

s, 4-H), 4.69 (1 H, ddd, J = 10.9, 10.9, 5.8 Hz, 9-H), 7.28−7.36 (5 H, m, C_6H_5). − EIMS, m/z: 322 [M^+].

6: To a solution of **41** (0.003 g) in CH_2Cl_2 (0.5 mL), PDC (0.005 g, 0.013 mmol) and 4-Å molecular sieves (0.005 g) were added. After 2 h, the reaction mixture was diluted with diethyl ether (7.0 mL). Filtration through a short pad of Celite and $CaSO_4$ (10% w/w) afforded a solution which was concentrated in vacuo to give **6** (0.002 g, 66% two steps) as a colourless oil. − $[\alpha]_D$ = +6 (c = 0.3, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.93 (3 H, d, J = 6.4 Hz, 14-CH_3), 1.35 (3 H, s, 12-CH_3), 1.75 (1 H, ddd, J = 14.3, 14.3, 4.8, 6-H), 1.94 (1 H, dt, J = 14.3, 5.3 Hz, 6-H′), 2.10 (1 H, dd, J = 11.0, 8.6 Hz, 10-Hα), 2.25 (1 H, m, 10-Hβ), 2.31 (1 H, m, 5-H), 2.56 (1 H, m, 5-H′), 2.62 (1 H, dd, J = 18.2, 8.6 Hz, 2-H), 2.90 (1 H, ddd, J = 8.6, 8.6, 4.6 Hz, 3-H) 3.33 (1 H, dd, J = 18.2, 4.6 Hz, 2-H′), 4.06 (1 H, m, 9-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 22.4, 22.5, 22.7, 24.5, 28.0, 28.1, 33.4, 33.8, 34.9, 36.6, 38.4, 39.4, 39.6, 40.4, 52.1, 54.8, 78.8, 171.5, 209.4. − EIMS, m/z: 320 [M^+].

43: To a solution of **39** (0.014 g, 0.034 mmol) in methanol (2.0 mL), was added palladium on carbon (10% wt., 0.010 g). The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was then stirred vigorously under hydrogen for 3 h. It was then filtered through a pad of Celite and concentrated in vacuo. The crude residue was purified by flash chromatography (silica, gel 5−25% ethyl acetate in petroleum ether) to give a residue (0.009 g) containing an inseparable mixture of **43** and **44**. To a solution of the residue in MeOH (0.25 mL), 10% aqueous solution of KOH (0.25 mL) was added. The solution was stirred for 1 h at room temp. The methanol was evaporated by flushing with N_2, and the resulting solution was neutralized with 2 N HCl. The white precipitate was extracted with Et_2O and the lactone **43** (0.006 g, 55%) was recovered. − IR: $\tilde{\nu}$ = 1760 cm^{-1}(C=O). − $[\alpha]_D$ = +8 (c = 0.3, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (6 H, d, J = 6.6 Hz, 19-CH_3 and 20-CH_3), 0.95 ((3 H, s, 12-CH_3), 0.96 (3 H, d, J = 6.4, 14-CH_3), 2.53 (1 H, m, 18.2, 8.6 Hz, 2-H), 2.72 (1 H, m, 2-H′) 3.33 (1 H, br. s, 3-H), 4.67 (1 H, dd, J = 15.1,7.5 Hz, 9-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 22.5, 22.8, 23.9 (×2), 25.1, 28.0, 29.7, 31.5, 32.3, 33.2, 33.7, 36.1, 39.5, 39.9, 50.0, 53.7, 71.2, 79.3, 178.2. − EIMS, m/z: 320 [M^+].

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