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Studies on the Preparation of the "Ziegler Intermediate", a Key Intermediate in the Total Synthesis of Forskolin.

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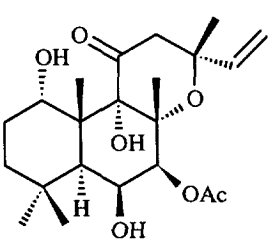
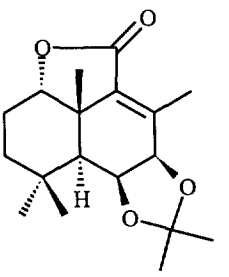
Abstract: Preparation of the "Ziegler key intermediate" 2 from lactone 3, readily obtained from hydroxy-β-ionone, was studied. In a first exploratory approach, lactones 11 and 13 were obtained but further transformations aimed at setting the ring junction were unsuccessful due to unexpected rearrangements. Through a straightforward synthetic sequence involving two new rearrangements, lactone 3 was converted to diosphenol 21 with the desired trans A/B ring junction. 21 was in turn transformed into the well-known acetonide 2 in a good yield. This constitutes a new formal total synthesis of forskolin. Copyright © 1996 Elsevier Science Ltd

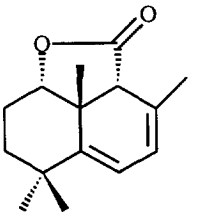
For some years, we have been interested in efficient chemical syntheses of forskolin **1**[1]. To date four approaches have been reported culminating in the total synthesis of this highly oxygenated diterpene.[2,3,4,5] In three of these syntheses, compound **2** (the "Ziegler intermediate") is the key precursor and various other approaches to the Ziegler Intermediate have thus constituted formal total syntheses of forskolin.[1,6]



Forskolin **1**



"Ziegler intermediate" **2**



3

Figure 1.

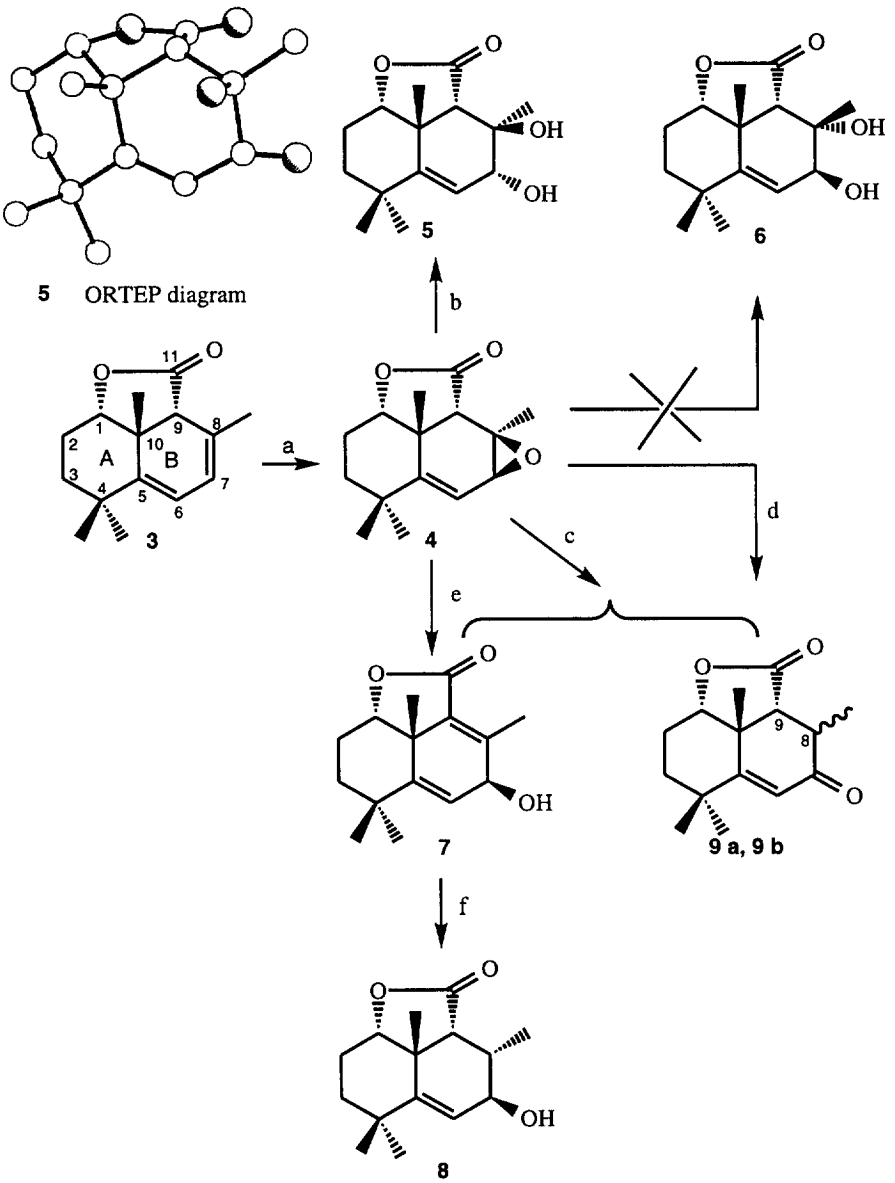
In our previous work we have described two different preparations of the intermediate tricyclic lactone **3**, first obtained by Koft[7] and used by Corey in his total synthesis,[4] in racemic[8] and optically pure form.[9] The latter uses as a key step the cyclisation of the acetylacetate of hydroxy-β-ionone promoted by cesium carbonate which proves to be straightforward and can be performed on a large scale (500g). This paper details further results aimed at the total synthesis of forskolin including the successful conversion of lactone **3** into the "Ziegler intermediate" **2**.[10]

Early synthetic planning.

We considered that the lactone **3** would be an attractive intermediate if conditions could be found to hydroxylate the two double bonds appropriately. In a first approach compound **3** was transformed by the use of m-chloroperbenzoic acid (m-CPBA) into the epoxide **4** as a single isomer in a 92% yield (fig. 2). Assignment of the stereochemistry of this epoxide **4** could not be deduced from the value of the coupling constant between H-6 and H-7 but was expected to be β corresponding to an approach of the reagent from the less hindered face of the molecule. We expected that stereocontrolled ring opening of the epoxide would give the *trans* diol **6** possessing the stereochemistry observed in forskolin. However, acidic treatment of epoxide **4** with $HClO_4$ in aqueous DMSO gave as the only product diol **5** (yield 77%) whose structure was confirmed by crystallographic studies. It appears that a selective opening of the protonated epoxide **4** takes place at C-7 leading to an allylic cation, which in turn undergoes a stereocontrolled solvolysis.

The assignment for the stereochemistry of **4** was further confirmed by exposure of the same epoxide to basic conditions. Treatment of **4** with 1 equivalent of DBU at room temperature or 1.2 equivalents of LDA at -78 °C (condition c) produced a mixture of three compounds **7**, **9a** and **9b**. The use of an excess of DBU (condition d) resulted in a 1:1 ratio of an isomeric mixture of **9a** and **9b**. The ^1H NMR spectrum of this mixture displayed a doublet at $\delta = 2.58\ ppm$ (J = 8 Hz) corresponding to H-9 of the isomer with an equatorial methyl group and a singlet at $\delta = 2.65\ ppm$ corresponding to H-9 the alternative isomer with an axial methyl group.

When epoxide **4** was treated with aqueous 6M NaOH (condition e), alcohol **7** was obtained as a single product in a 81% yield. The alcohol was transformed by $LiAlH_4$ reduction into lactone **8** in which the configuration of the 7-hydroxy group was assigned as β on the basis of the coupling constant between H-7 and H-8 (J = 10 Hz). Despite the fact that the configuration at C-7 in **5** was opposite to that required in forskolin, we nevertheless studied the anti-Markovnikov addition of water onto the Δ^5 double bond of this intermediate. However, classical strategies including hydroboration failed to give any reaction. It is important to note that the hydrogen atom at C-5 has to be introduced from the highly congested face of the molecule **5** which might explain its lack of reactivity. We turned therefore to an alternative method which involves the preparation of epoxide **10** followed by its reduction with Et_3SiH in the presence of a Lewis acid.

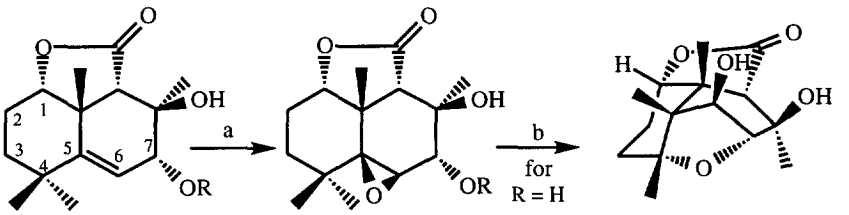


Reagents and conditions: a. m-CPBA (1.7 equiv.), CH_2Cl_2, 0 °C to r.t., 22h; b. $HClO_4$ (1.25 equiv.), DMSO, H_2O, r.t., 24h; c. DBU (1 equiv.), r.t. or LDA (1.2 equiv.), -78 °C; d. DBU (2 equiv.), PhH, 80 °C, 17h; e. NaOH (6M, 2 equiv.), THF, r.t., 24h; f. $LiAlH_4$ (1 equiv.), THF, r.t., 24h.

Figure 2.

m-CPBA treatment of diol **5** for 72 hours led indeed to a single epoxide **10** (yield 82%) assumed to have the geometry displayed in figure 3. Attempts to cleave reductively the epoxide ring in **10** led to a new compound

in an 80% yield for which ^{1}H and ^{13}C NMR studies suggested the rearranged structure **13**. In all the previously studied derivatives of this type, the signal for H-1 appears as a narrow triplet corresponding to an equatorial configuration on ring A. However, in the compound **13**, this signal appears as a doublet of doublets (J = 10 Hz, J = 6 Hz) in agreement with an axial configuration on ring A. Crystallographic studies confirmed that a rearrangement of the skeleton had occurred involving the migration of methyl group at C-4 and tetrahydrofuran ring formation between C-7 and C-4 (fig.3).

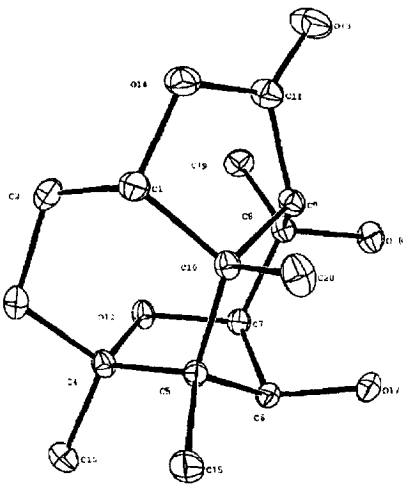


5 R = H
11 R = OAc

10 R = H
12 R = OAc

13

Reagents and conditions: a. m-CPBA, CH_2Cl_2, 72 h; b. BF_3•Et_2O, Et_3SiH, CH_2Cl_2, r.t.

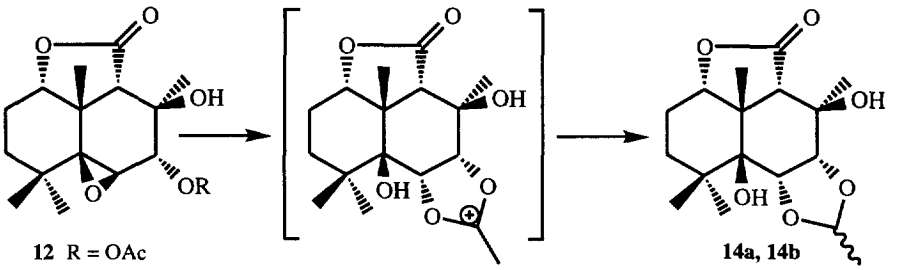


13 ORTEP diagram.

Figure 3.

The lack of reactivity of the Et_3SiH is clearly a consequence of the encumbered approach of this reagent on the opposite side of the Lewis acid activated epoxide. Support of this hypothesis was found when the same conditions were applied to the acetylated compound **12** which afforded a mixture of the acetals **14a** and **14b** (ratio 9:1) in an 80% yield, the structures of which were assigned from the NMR spectral data (fig. 4). In this surprising reaction the acetoxy group at C-7 plays the role of an internal nucleophile delivered from the face opposite to the activated epoxide leading to the intermediate acetoxonium which, in turn, is reduced by Et3SiH. This result is in agreement with the stereochemistry proposed for epoxide **12**.

Consequently, the construction of a *trans* A/B ring junction in tricyclic lactones appears as a major synthetic challenge. To avoid this potential difficulty, we embarked on an alternative strategy in which the *trans* ring junction was introduced in the early steps of the synthesis.

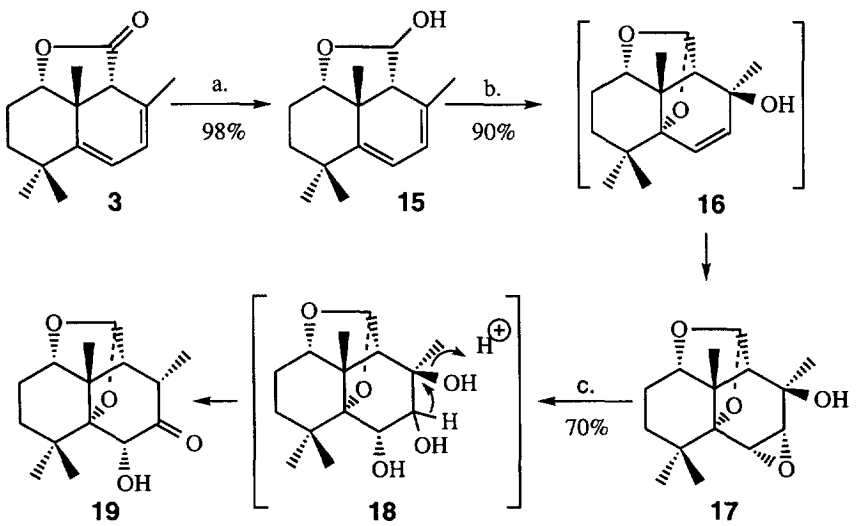


Reagents and conditions: $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, r.t.

Figure 4.

Second approach leading to the Ziegler intermediate.

The DIBAL-H reduction of lactone **3**, followed by prolonged exposure of the obtained lactol **15** to an excess (3 equiv.) of m-CPBA resulted in a tricyclic epoxide-alcohol **17** in a 90% overall yield (fig. 5). The α stereochemistry of this epoxide was supported by NOESY correlations observed between the angular 10-Me group and H-6β and H-7β (fig. 6).

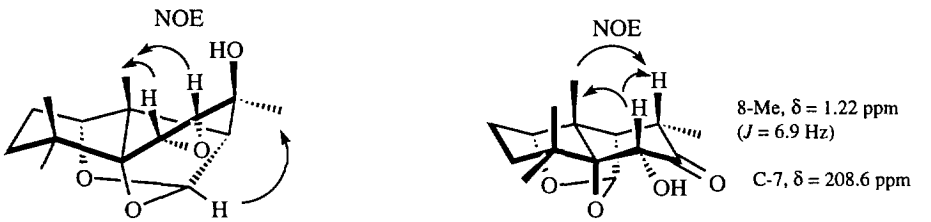


Reagents and conditions : a. DIBAL-H, THF, 0 °C; b. m-CPBA (3 equiv.), CH_2Cl_2, 48h; c. $HClO_4$ (1.3 equiv.), THF, 2.5h at 40 °C then 20h at r.t.

Figure 5.

The proposed intermediate **16,** precursor to the epoxide **17**, can be isolated when only one equivalent of m-CPBA is used. An analogue of **16** (opposite configuration at C-8) has been obtained by Cha et al.[11] by the

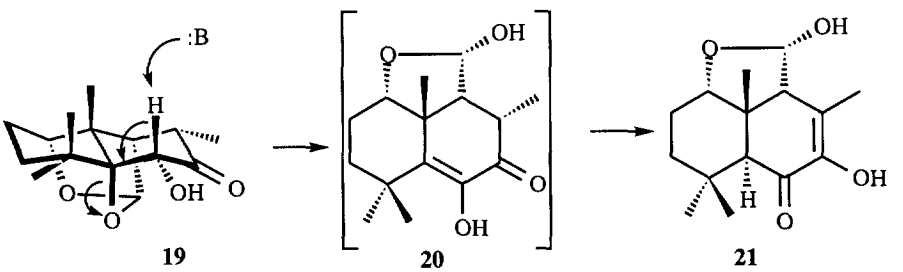
epoxidation of the lactol **15** with t-butylhydroperoxide in the presence of $VO(acac)_2$. In an attempt to open the epoxide **17** ring using aqueous acid ($HClO_4$/ H_2O in THF), epoxide **17** gave surprisingly the hydroxy-ketone **19**. The structure of the compound **19** has been supported by exhaustive homonuclear and heteronuclear 2D NMR studies; the stereochemistries of the 6-OH and 8-Me were assigned on the basis of NOESY correlations observed between H-6 and H-8, H-6 and the angular 10-Me as well as H-8 and 10-Me (fig. 6). We suppose that this reaction occurs through the conversion of the epoxide ring of **17** into an intermediate diol **18**,[12] which, by protonation of the tertiary 8-OH followed by hydride migration from position 7 to position 8, leads to compound **19** (fig. 5).



NOESY correlations observed on 17 **NOESY correlations observed on 19**

Figure 6.

Treatment of **19** with DBU as a base resulted in the formation of diosphenol **21** in 82% yield, through a second new reaction in which the abstraction of H-6 is expected to trigger the fragmentation of the tetrahydrofuran ring leading to intermediate diosphenol **20**, which, in turn, is transformed into the more stable diosphenol **21**. The hydrogen atom introduced at the ring junction was later confirmed to have the desired stereochemistry. It is worth noting that this fragmentation leads to a single lactol displaying a coupling constant of 5.2 Hz between H-9 and H-11.

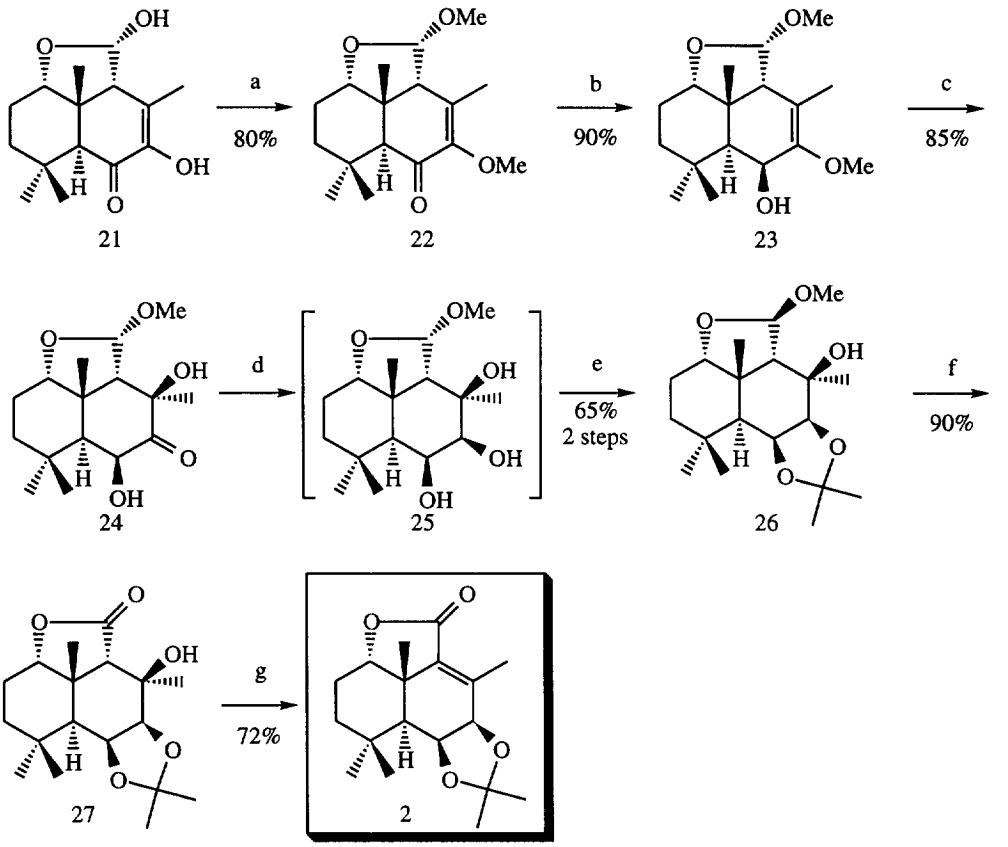


Reagents and conditions : DBU (3 equiv.), benzene, 80 °C.

Figure 7.

The final functional group adjustments were achieved by standard chemistry (fig.8). Methylation of the hydroxy groups of **21** (MeI, NaH, 3 equiv. in THF) followed by reduction (DIBAL-H, 1.5 equiv. in THF, 0 °C to room temperature, 2h) led to enol **23.** The ketodiol **24** was obtained by epoxidation of the latter with aqueous m-CPBA in ethanol (in the presence of 0.5 equiv. of Na_2CO_3). Reduction ($NaBH_4$ in ethanol, 0 °C) and protection of the triol **25** led to diacetal **26** in which the epimerisation of the 11-OMe group has occured. The ^1H NMR signal for H-11 in **26** was a singlet at $\delta = 4.99$ *ppm* in contrast to the doublet (J = 5 Hz)

observed for the same proton in **24**. Jones oxidation (CrO_3, H_2SO_4, 1.5 equiv., in acetone, 0 °C, 1h) and dehydration ($SOCl_2$, pyridine, 0 °C, 1h) produced the desired Ziegler intermediate **2** in 12% overall yield (not optimised) from lactone **3**. The ^1H and ^{13}C spectra of this sample were identical to those reported for an authentic sample.[2,3]



Reagents and conditions : a. MeI, NaH, (3 equiv.); b. DIBAL-H (1.5 equiv.), THF, 0 °C to r.t., 1h; c. m-CPBA (1 equiv.), Na_2CO_3 (0.5 equiv.), EtOH / H_2O (1:6), 0 °C to r.t., 2h; d. $NaBH_4$ (1 equiv.), EtOH, 0 °C, 1h; e. PTSA, 2,2 Dimethoxypropane, r.t., 18h; f. Jones reagent (1.5 equiv.), Acetone, r.t., 30 min.; g. $SOCl_2$ (12 equiv.), Pyridine, 0 °C, 1h.

Figure 8.

Conclusion.

This stategy which involves simple, stereo-controlled reactions and inexpensive reagents, allows an easy and straightforward preparation of a key intermediate in the total synthesis of forskolin. Modification of this strategy using the two key reactions of epoxide-alcohol rearrangement and tetrahydrofuran ring fragmentation is currently under investigation to reach forskolin in a minimum number of steps.

Experimental section.

Physical data and spectroscopic measurements

Melting points (mp) were determined on a REICHERT apparatus and are uncorrected.

^1H NMR spectra were recorded on a BRUKER WP 200 (200 MHz), or on a BRUKER AM 400 (400 MHz) instrument. The solvent and the instrument are given for each product. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform (7.27 ppm). Data are reported as follows: δ, chemical shift, multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet and m, multiplet), coupling constants (*J* in Hertz, Hz), integration and assignment.

^{13}C NMR spectra were recorded on the same instruments at 50.3 MHz and 100.6 MHz respectively. The chemical shifts are expressed in parts per million (ppm), reported from the central peak of deuterochloroform (77.14 ppm). J-modulated spin-echo technique (J-mod) experiments were used for evaluating CH multiplicities. When necessary, ^{13}C spectra were assigned with the aid of HETCOR experiments.

Mass spectra (MS) were obtained on a HEWLETT-PACKARD HP 5989B spectrometer *via* either direct introduction or gas chromatography (GC/MS) by coupling with a HEWLETT-PACKARD HP 5890 chromatograph. Ionisation was obtained either by electronic impact (EI) or chemical ionisation with ammonia (CI, NH_3) or methane (CI, CH_4). Mass spectral data are reported as m/z. High resolution mass spectra HRMS were recorded on ZAB.HFQ.VG apparatus.

Infrared spectra (IR) were obtained on a PERKIN-ELMER FT 1600 instrument using either NaCl salt plates (thin film) or NaCl cell (in the specified solvent) and are reported in terms of frequency of absorption (ν, cm^{-1}).

Microanalyses were performed by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, C.N.R.S., F-91198, Gif sur Yvette.

All reactions were monitored by thin-layer chromatography (TLC) carried out on E.MERCK Ref. 5549 or 5554 silica gel precoated silica gel 60F 254 plates. Visualisation was accomplished with UV light and then 7-10% ethanolic phosphomolybdic acid solution followed by heating.

Flash chromatography was performed on E. MERCK silica gel Si 60 (40-63 mm, Ref. 9385).

Solvents distillation

Tetrahydrofuran (THF), diethyl ether (Et_2O), benzene (PhH) and toluene were distilled from sodium-benzophenone. Dichloromethane (CH_2Cl_2) and amines were distilled from calcium hydride. Dimethylformamide (DMF) was distilled from magnesium sulfate under reduced pressure. Ethanol (EtOH) and methanol (MeOH) were distilled from the corresponding magnesium derivative.

Usual procedures

All air and/or water sensitive reactions were carried out under a nitrogen or argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. All corresponding glassware was oven dried (110 °C) and/or carefully dried in line with a flameless heat gun.

Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated.

The numbering sequence used for reporting NMR parameters is illustrated in figure 2.

(2aS*,3R*,4S*,8aS*,8bR*)-3,4-Epoxy-3,6,6,8b-tetramethyl-2a,6,7,8,8a,8b-hexahydro-2H-naphtho[1,8-bc]furan-2-one 4

Lactone **3** (930 mg, 4.0 mmol) was dissolved in dichloromethane (30 mL) and the solution was cooled to 0 °C. Technical 3-Chloroperoxybenzoic acid (70%, 1.5 g, 6.8 mmol) was slowly added. The mixture was allowed to warm to room temperature and was stirred for 22 hours. Potassium fluoride was added (780 mg, 13.4 mmol) and the mixture was filtered. The filtrate was washed with saturated aqueous sodium bicarbonate (2x10 mL) and with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and epoxide **4** (92% yield, 910 mg, 3.7 mmol) was obtained as a white crystalline solid. The product was used without further purification for the next step. **m.p.** 67 °C (pentane). **IR** (CCl_4, cm^{-1}) : 2960, 1754, 1674, 1253, 941. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.94 (d, H-6, J = 5.3 Hz, 1H), 4.20 (t, H-1, J = 2.2 Hz, 1H), 3.25 (d, H-7, J = 5.3 Hz, 1H), 2.77 (s, H-9, 1H), 2.2-2.0 (m, H-2, H-3, 4H), 1.72 (s, 3H), 1.48 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 174.8 (C-11), 150.1 (C-5), 120.1 (C-6), 82.6 (C-1), 61.1 (C-8), 55.0, 55.0 (C-7, C-9), 46.3, 35.1 (C-4, C-10), 32.8, 30.8, 28.2, 27.8, 20.7, 20.1 (C-2, C-3, 4 CH_3). **MS** m/z (EI) : 248 ($M^{+\cdot}$), 189, 166, 123. **HRMS** calc. for $C_{15}H_{20}O_3$ 248.1412, found 248.1406.

(2aS*,3R*,4R*,8aS*,8bR*)-3,4-Dihydroxy-3,6,6,8b-tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-naphtho[1,8-bc]furan-2-one 5

Epoxide **4** (320 mg, 1.3 mmol) was dissolved in a mixture DMSO/ water (60:40, 13 mL) and perchloric acid (31 mg, 0.31 mmol) was added. The mixture was stirred for 24 hours at room temperature. The solution was extracted with ethyl acetate (3x10 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (40:60). Diol **5** was obtained as a white crystalline solid (77% yield, 270 mg, 1.0 mmol). **m.p.** 144 °C (pentane/ diethyl ether 95:5). **IR** (CCl_4, cm^{-1}) : 3401, 2963, 1762, 1072.**^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.78 (d, H-6, J = 4.0 Hz, 1H), 4.22 (t, H-1, J = 4.6 Hz, 1H), 3.95 (d, H-7, J = 4.0 Hz, 1H), 2.59 (s, H-9, 1H), 2.1-1.2 (m, H-2, H-3, 4H), 1.52 (s, 3H), 1.49 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H).**^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 175.0 (C-11), 145.9 (C-5), 126.0 (C-6), 84.1 (C-1), 73.8 (C-8), 73.1 (C-7), 59.1 (C-9), 44.8, 35.2 (C-4, C-10), 34.0, 31.3, 29.0, 28.0, 22.7, 22.4 (C-2, C-3, 4 CH_3). **MS** m/z (EI) : 266 ($M^{+\cdot}$), 248, 219, 165, 149, 136, 108. **HRMS** calc. for ($M^{+\cdot}$) $C_{15}H_{22}O_4$ 266.1518, found 266.1510.

(4S*,8aS*,8bR*)-4-Hydroxy-3,6,6,8b-tetramethyl-4,6,7,8,8a,8b-hexahydro-naphtho[1,8bc]furan-2-one 7

To a solution of epoxide **4** (160 mg, 0.65 mmol) in THF (10 mL) was added aqueous 6M sodium hydroxide (0.22 mL, 1.3 mmol) and the mixture was stirred at room temperature for 24 hours. Aqueous 1M hydrochloric acid (1.3 mL, 1.3 mmol) was then added until the pH reaches 7. The mixture was extracted with diethyl ether (2x35 mL). The organic layers were separated and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (40:60). Alcohol **7** (yield 81%, 130 mg, 0.52 mmol) was obtained as a white crystalline solid. **m.p.** 82°C (pentane). **IR** (CCl_4, cm^{-1}) : 3495, 2962, 1760. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5. 84 (d, H-6, J = 5.3 Hz, 1H), 4.56 (d, H-7, J = 5.3 Hz, 1H), 4.34 (dd, H-1, J = 4.4 Hz, J = 12.3 Hz, 1H), 2.31 (s, 3H), 2.2-1.5 (m, H-2, H-3, 4H), 1.52 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 168.9 (C-11), 157.9, 148.5, 133.4 (C-5, C-8, C-9), 122.4 (C-6), 84.4

(C-1), 70.2 (C-7), 45.3, 35.2 (C-4, C-10), 36.3, 32.5, 32.3, 30.5, 28.0, 16.2 (C-2, C-3, C-4, C-10, $4CH_3$). **MS** m/z (EI) : 248 ($M^{+\cdot}$), 230, 215, 204, 189, 149, 69.

(2aR*,3R*,4S*, 8aS*, 8bR*)-4-Hydroxy-3,6,6,8b-tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-naphtho[1,8bc]furan-2-one 8

Alcohol **7** (50 mg, 0.2 mmol) was dissolved in dry tetrahydrofuran (10 mL). A 1M solution of lithium aluminium hydride in toluene (0.4 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 1.5 hours. After addition of H_2O (0.05 mL), 15% aqueous sodium hydroxide (0.05 mL) and again H_2O (0.15 mL), the aluminium and lithium salts were filtered and washed with ether (3x5 mL). The solution was concentrated under reduced pressure. The crude oily product was purified by chromatography on silica gel eluting with a mixture of ethyl acetate/ cyclohexane (40:60). Product **8** (yield 80%, 40 mg, 0.16 mmol) was obtained. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.65 (d, , J = 2.5 Hz, 1H); 4.18 (t, H-1, 1H); 4.12-4.20 (dd, H-7, J = 10 Hz, H = 2.5 Hz, 1H); 2.28 (d, H-9, J = 4 Hz, 1H); 1.98 (m, H-8, 1H);1.40 (d, J = 6 Hz, 3H); 1.38 (s, 3H); 1.18 (s, 3H); 1.10 (s, 3H).

(2aR*,8aS*,8bR*)-3,6,6,8b-Tetramethyl-2a,6,7,8,8a,8b-hexahydro-3H-naphtho[1,8bc]furan-2,4-dione 9a and 9b

Epoxide **4** (1.87 g, 7.5 mmol) was heated in benzene (100 mL) to 80 °C under argon and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.30 g, 15.1 mmol) was added. The mixture was stirred at 80 °C for 17 hours. Benzene was then removed under reduced pressure and replaced with dichloromethane. The solution was washed with 1M aqueous HCl. The organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and a column chromatography, eluting with a mixture of ethyl acetate/ cyclohexane (50:50) afforded a mixture (1:1) of diastereoisomeric α,β-unsaturated ketones **9a and 9b** (yield 43%, 820 mg, 3.3 mmol) as a colourless oil. **IR** (CCl_4, cm^{-1}) : 2939, 1776, 1672. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 6.02 and 5.98 (s, H-6, 1H), 4.27 and 4.25 (t, H-1, J = 2.6 Hz, 1H), 3.02 and 2.71 (q and dq, H-8, J = 8.1 Hz and J = 6.8 Hz, J = 1.1 Hz, 1H); 2.65 and 2.56 (s and d, H-9, J = 1.1 Hz, 1H), 2.2-1.9 (2H, m, H-2, H-3), 1.53 and 1.49 (s, 3H), 1.46 and 1.36 (d, J = 6.8 Hz and J = 8.1 Hz, 3H), 1.18 and 1.17 (s, 3H), 1.10 and 1.09 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 198.9 and 197.7 (C-7), 176.1 and 174.7 (C-11), 168.4 and 167.4 (C-5), 126.6 and 126.3 (C-6), 82.8 and 82.5 (C-1), 56.6 and 55.6 (C-9), 45.2 and 43.4, 36.4 and 36.3 (C-4, C-10) 38.0 and 36.8 (C-8) 33.8, 33.0, 30.4, 30.2, 27.2, 26.6, 25.3, 21.3, 21.0, 20.6, 18.2, 11.1 (C-2, C-3, 4 CH_3).

(2aS*,3R*,4R*,5R*,5aS*,8aS*,8bS*)-5,5a-Epoxy-3,4-dihydroxy-3,6,6,8b-tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-naphtho[1,8bc]furan-2-one 10

Diol **5** (210 mg, 0.79 mmol) was dissolved in dichloromethane (10 mL) and the solution was cooled to 0 °C. Technical 3-Chloroperoxybenzoic acid (70%, 428 mg, 1.74 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 72 hours. Potassium fluoride was added (200 mg, 3.44 mmol) and the mixture was filtered, the solid being washed with dichloromethane (10 mL). The filtrate was washed with aqueous sodium bicarbonate (2x5 mL) and with brine (5 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (40:60). Epoxide **10** (82% yield, 180 mg, 0.64 mmol) was obtained as a white crystalline solid. **m.p.** 145 °C (pentane/ ethyl ether 95:5). **IR** (CCl_4, cm^{-1}): 3501, 2941, 1760, 1072, 992. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 4.26 (d, H-7, J =

2.5 Hz, 1H), 3.91 (ls, H-1, 1H), 3.63 (d, H-6, J = 2.5 Hz, 1H), 2.42 (s, H-9, 1H), 2.12-2.00 (m, H-2, H-3, 4H), 1.55 (s, 3H), 1.48 (s, 3H), 1.13 (s, 3H), 0.77 (s, 3H). **^{13}C.NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 175.6 (C-11), 83.0 (C-1), 71.8, 65.6 (C-5, C-8), 70.4, 63.7, 58.5 (C-6, C-7, C-9), 43.1, 34.1 (C-4, C-10), 31.6, 27.5, 25.7, 23.4, 23.2, 20.0 (C-2, C-3, 4 CH_3). **HRMS** calc. for ($M^{+\cdot}$) $C_{15}H_{22}O_5$ 282.1467, found 282.1471.

(2aS*,3R*,4R*,8aS*,8bR*)-Acetic acid 3-hydroxy-3,6,6,8b-tetramethyl-2-oxo-2a,3,4,6,7,8,8a,8b-octahydro-2H-naphtho[1,8-bc]furan-4-yl ester 11

Diol **5** (250 mg, 0.93 mmol) was dissolved in acetic anhydride (4.1 mL) and pyridine (5 mL) was added under nitrogen atmosphere. The mixture was stirred at room temperature for 22 hours. After hydrolysis and usual work-up, the organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Acetate **11** (yield 90%, 260 mg, 0.84 mmol) was obtained and the product was used without further purification for the next step. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.60 (d, H-6, J = 3.5 Hz, 1H), 5.20 (d, H-7, J = 3.5 Hz, 1H), 4.18 (t, H-1, J = 4.0 Hz, 1H), 2.52 (s, H-9, 1H), 2.08 (s, 3H), 1.55 (s, 3H), 1.50 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H).

(2aS*,3R*,4R*,5R*,5aS*,8aS*,8bS*)-Acetic acid 5,5a-epoxy-3-hydroxy-3,6,6,8b-tetramethyl-2-oxo-2a,3,4,6,7,8,8a,8b-octahydro-2H-naphtho[1,8-bc]furan-4-yl ester 12

Acetate **11** (260 mg, 0.84 mmol) was dissolved in dichloromethane (10 mL) and the solution cooled to 0 °C. Technical 3-Chloroperoxybenzoic acid (70%, 455 mg, 1.85 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 72 hours. Potassium fluoride (215 mg, 3.7 mmol) was added and the mixture was filtered, the solid being washed with dichloromethane (10 mL). The filtrate was washed with aqueous sodium bicarbonate (2x5 mL) and with brine (5 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by chromatography eluting with a mixture of ethyl acetate/cyclohexane (40:60) and epoxy-acetate **12** (yield 85%, 230 mg, 0.71 mmol) was obtained. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.20 (d, H-7, J = 2.5 Hz, 1H), 4.27 (t, H-1, J = 2.2 Hz, 1H), 3.70 (s, OH, 1H), 3.55 (d, H-6, J = 2.5 Hz, 1H), 2.38 (s, H-9, 1H), 2.10 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.11 (s, 3H), 0.78 (s, 3H).

(2aS*,3R*,4R*,5R*,5aR*,6S*,8aS*,8bS*)-4,6-Epoxy-3,5-dihydroxy-3,5a,6,8b-tetramethyl-decahydro-naphtho[1,8-bc]furane-2-one 13

Epoxide **10** (70 mg, 0.25 mmol) was dissolved in dry dichloromethane (8 mL) in a three-necked flask under argon. Boron trifluoride etherate (70.5 mg, 0.5 mmol) and triethylsilane (87 mg, 0.75 mmol) were added dropwise and the mixture was stirred at room temperature for 4 hours. The solution was then diluted with dichloromethane (30 mL) and water (12 mL) was added. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography, eluting with a mixture of ethyl acetate/ cyclohexane (60:40). Tetracyclic lactone **13** (yield 80%, 57 mg, 0.20 mmol) was obtained as a white crystalline solid. **m.p.** 171 °C (pentane/ ethyl ether 95:5) **IR** (CCl_4, cm^{-1}) : 3400, 2928, 1753, 1145. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 4.59 (d, H-6, J = 5.5 Hz, 1H), 4.11 (dd, H-1, J = 2.5 Hz, J = 11.0 Hz, 1H), 3.76 (d, H-7, J = 5.5 Hz, 1H), 2.72 (s, H-9, 1H), 2.0-1.0 (m, H-2, H-3, 4H), 1.40 (s, 3H), 1.33 (s, 3H), 1.12 (s, 3H), 1.14 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 177.5 (C-11), 85.3 (C-1), 81.6, 75.0 (C-4, C-8), 78.6, 77.3 (C-6, C-7), 58.7 (C-9), 45.3 43.2

(C-5, C-10), 30.4, 30.1, 27.6, 26.2, 23.5, 15.5 (C-2, C-3, 4 CH_3). **MS** m/z (CI, NH_3) : 300 (MNH_4^+), 282, 265, 180.

(3aS*,5aS*,6R*,6aR*,9aS*,9bS*,9cS*)-6,9b-Dihydroxy-1,1,6,8,9c-pentamethyl-decahydro-4,7,9-trioxa-cyclopenta[c]acenaphthylen-5-one 14a and 14b

Epoxy-acetate **12** (50 mg, 0.15 mmol) was dissolved in dry dichloromethane (5 mL). Boron trifluoride etherate (37.7 µL, 0.30 mmol) and triethylsilane hydride (73.3 µL, 0.46 mmol) were slowly added under nitrogen. The mixture was stirred at room temperature for 22 hours. The solution was then diluted with dichloromethane (30 mL) and water was added (10 mL). After usual work-up, the organic layer was dried over $MgSO_4$, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography, eluting with a mixture of ethyl acetate/ cyclohexane (60:40). A mixture (90:10) of acetonides **14a** and **14b** (yield 80%, 40 mg, 0.12 mmol) was obtained. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) for the major isomer : 4.85 (d, H-12, *J* = 5.0 Hz, 1H), 4.27 (d, H-6, *J* = 7.5 Hz, 1H), 4.21 (bs, H-1, 1H), 4.00 (dd, H-7, *J* = 7.5 Hz, *J* = 2.5 Hz, 1H), 2.40 (d, H-9, *J* = 2.5 Hz, 1H), 1.70 (s, 3H), 1.52 (s, 3H), 1.38 (d, *J* = 5.0 Hz, 3H), 1.10 (s, 6H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) for the major isomer : 174.2 (C-11), 101.4 ($CH_3\underline{C}HO_2$), 83.6 (C-1), 81.1, 79.5 (C-6,C-7), 72.8, 72.6 (C-8, C-5), 59.0 (C-9), 45.6, 38.1 (C-4, C-10), 31.1, 27.9, 27.0, 24.2, 23.9, 20.9 (C-2, C-3, 4 CH_3), 17.5 ($\underline{C}H_3CHO_2$).

(2S*,2aR*,8aS*,8bR*)-3,6,6,8b-Tetramethyl-2a,6,7,8,8a,8b-hexahydro-2H-naphtho[1,8-bc]furan-2-ol 15

To a solution of lactone **3** (1.71 g, 7.4 mmol) in 8 mL of THF at 0 °C was added a 1.5 M solution of DIBAL-H in toluene (6.4 mL, 9.6 mmol, 1.30 equiv.). The resulting solution was stirred at 0 °C for 1 h and quenched at -78 °C by successive addition of MeOH (1 mL) and a saturated aqueous Rochelle salt solution (16 mL). The mixture was allowed to warm to 20 °C and stirred at this temperature for 1h, then extracted with diethyl ether (4 x 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford lactol **15** (99% yield, 1.70 g, 7.26 mmol) which was used without further purification. **m.p.** 97 °C. **IR** (CCl_4, cm^{-1}) : 3403, 1658, 1448, 1364, 1051, 1004, 986, 946, 882. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.68 (m, H-6, H-7, 2 H), 5.06 (dd, H-11, *J* = 6.5 Hz, *J* = 4.7 Hz, 1H), 4.22 (t, H-1, *J* = 2.6 Hz, 1H), 3.89 (d, OH, *J* = 4.7 Hz, 1H), 2.03 (d, H-9, *J* = 6.5 Hz, 1H), 1.86 (se, H-2, H-3, $C\underline{H}_3$, 5 H), 1.52 (td, H-3, *J* = 13.1 Hz, *J* = 4.5 Hz, 1H), 1.18 (dt, H-2, *J* = 13.1 Hz, *J* = 3.4 Hz, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 144.6, 131.3 (C-5, C-8), 119.2, 117.6 (C-6, C-7), 103.7 (C-11), 84.6 (C-1), 62.0 (C-9), 44.5 (C-10), 34.8 (C-4), 33.9, 30.8, 28.6, 24.1, 22.8, 22.0 (C-2, C-3, 4 CH_3).

(2S*,2aS*,3R*,4R*,5S*,5aR*,8aS*,8bS*)-3,6,6,8b-Tetramethyl-5a-hydroxy-4,5-epoxy-decahydronaphtho[1,8-bc]furan-2-ol, 2-5a anhydro 17

To a solution of lactol **15** (1.6 g, 7.1 mmol) in dichloromethane (70 mL) was added technical 3-Chloroperoxybenzoic acid (70%, 5.2 g, 21.2 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight and then potassium fluoride (4.0 g, 23.3 mmol) was added. The suspension was filtered and the filtrate was successively washed with a saturated aqueous Na_2CO_3 solution (30 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (30:70) gave epoxide **17** (yield 90%, 1.70 g, 6.39 mmol) as a crystalline solid. **m.p.** 139 °C. **IR** (CCl_4, cm^{-1}) : 3443, 2960, 2932, 2876, 1552, 982, 946, 923, 890. **NMR ^{1}H** δ ($CDCl_3$, 400 MHz, ppm) : 4.90 (s, H-11, 1 H), 3.96 (t, H-1, *J*

= 1.5 Hz, 1H), 3.22 (d, H-6 or H-7, J = 3.8 Hz, 1H), 3.03 (d, H-7 or H-6, J = 3.8 Hz, 1H), 2.02 (td, H-3, J = 13.2 Hz, J = 4.8 Hz, 1H), 1.90 (s, H-9, 1H), 1.76 (m, H-2, 2H), 1.43 (s, 3H), 1.31 (s, 3H), 1.13 (se, 5H), 1.07 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 98.6 (C-11), 79.9 (C-1), 67.6 (C-5 or C-8), 63.1 (C-9), 54.8, 51.8 (C-6, C-7), 47.5 (C-8 or C-5), 34.8 (C-10), 30.2 (C-3), 27.0 (C-4), 21.9 (C-2), 26.3, 25.3, 21.6, 13.4 (4 CH_3). **MS** m/z (CI, NH_3) : 284 (MNH_4^+), 267 (MH^+), 249, 203. **HRMS** calc. for $C_{15}H_{22}O_4$ 266.151806, found 266.15169.

(2S*,2aR*,3S*,5R*,5aR*,8aS*,8bS*)-5,5a-Dihydroxy-4-one-3,6,6,8b-tetramethyl-decahydronaphtho[1,8-bc]furan-2-ol, 2-5a anhydro 19

To a solution of epoxide **17** (0.50 g, 1.9 mmol) in THF (20 mL) was added perchloric acid (70% in water, 0.21 mL, 2.6 mmol) at room temperature. The resulting solution was stirred at 40 °C for 2.5 h and stirred at room temperature for 18 h. The solution was diluted with water (25 mL) and then extracted with ethyl acetate (4x15 mL). The combined extracts were washed with brine (30 mL) and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (20:80) gave ketone **19** (yield 70%, 0.35 g, 1.26 mmol) as a crystalline solid. **m.p.** 117 °C. **IR** (CCl_4, cm^{-1}) : 3472, 2975, 2934, 2880, 1724, 1386, 986, 947, 932. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.08 (s, H-11, 1H), 4.48 (dd, H-6, J = 4.1 Hz, J = 1.2 Hz, 1H), 4.01 (d, H-1, J = 3.0 Hz, 1H), 3.65 (d, OH, J = 4.1 Hz, 1H), 2.60 (m, H-8, 1H), 2.23 (d, H-9, J = 4.3 Hz, 1H), 1.97 (td, H-3, J = 13.8 Hz, J = 4.5 Hz, 1H), 1.80-1.60 (m, H-2, 2H), 1.45 (s, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.20 (s, 3H), 1.12 (s, 3H), 1.00 (m, H-3, 1H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 208.6 (C-7), 100.6 (C-11), 87.8 (C-5), 82.4 (C-1), 78.1 (C-6), 60.4 (C-9), 47.5 (C-10), 39.0 (C-8), 35.8 (C-4), 31.9 (C-3), 21.6 (C-2), 28.8, 22.0, 14.5, 12.9 (4 CH_3). **MS** m/z (CI, NH_3) : 284 (MNH_4^+), 267 (MH^+). **HRMS** calc. for $C_{15}H_{22}O_4$ 266.15106, found 266.151695. **Anal.** calc. for $C_{15}H_{22}O_4$ C : 67.65, H : 8.33, found C : 67.55, H : 8.48.

(2S*,2aR*,5aS*,8aS*,8bR*)-2,4-Dihydroxy-3,6,6,8b-tetramethyl-2,2a,5a,6,7,8,8a,8b-octahydro-naphtho[1,8-bc]furan-5-one 21

To a solution of ketone **19** (0.40 g, 1.5 mmol) in anhydrous benzene (5 mL) was added DBU (0.72 mL, 4.8 mmol) at room temperature. The resulting solution was refluxed for 18 h, cooled to room temperature and quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with ethyl acetate (4 x 7 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate / cyclohexane (50:50) gave diosphenol **21** (yield 82%, 0.33 g, 1.28 mmol) as a crystalline solid. **m.p.** 158 °C. **IR** (CCl_4, cm^{-1}) : 3607, 3456, 2932, 2873, 1739, 1708, 1687, 1663, 1385, 1264, 1011. **^{1}H NMR** δ (400 MHz, $CDCl_3$, ppm) : 5.95 (s, 7-OH, 1H), 5.54 (d, H-11, J = 5.2 Hz, 1H), 4.08 (t, H-1, J = 5.8 Hz, 1H), 3.50 (se, 11-OH, 1H), 2.64 (s, H-5, 1H), 1.88 (s, 3H), 1.78 (m, H-2, 2H), 1.48 (td, H-3, J = 13.2, J = 5.2 Hz, 1H), 1.17 (m, H-3, 1H), 1.11 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 195.7 (C-6), 143.5 (C-8), 119.1 (C-7), 100.8 (C-11), 81.8 (C-1), 64.0 (C-9), 53.6 (C-5), 49.1 (C-10), 35.7 (C-3), 21.4 (C-2), 20.9 (C-4),, 32.1, 21.1, 18.5, 15.5 (4 CH_3). **MS** m/z (CI, NH_3) : 284 ($M\text{-}NH_4^+$), 267 (MH^+), 266 , 249. **Anal.** calc. for $C_{15}H_{22}O_4$ C : 67.65, H : 8.33, found C : 67.14, H : 8.26.

(2S*,2aR*,5aS*,8aS*,8bR*)-2,4-Dimethoxy-3,6,6,8b-tetramethyl-2,2a,5a,6,7,8,8a,8b-octahydro-naphtho[1,8-bc]furan-5-one 22

To a solution of diosphenol **21** (0.20 g, 0.75 mmol) in THF (8 mL) was added sodium hydride (60% dispersion in mineral oil, 0.09 g, 2.25 mmol) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and methyl iodide was added (0.14 mL, 2.25 mmol). After 18 h at room temperature, the reaction was quenched by addition of methanol (2 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (20:80) gave product **22** (yield 80%, 0.17 g, 0.57 mmol) as a colourless oil. **IR** (CCl_4, cm^{-1}) : 2993, 2932, 2834, 1729, 1690, 1637, 1441, 1379, 1321, 1279, 1214, 1101, 1001. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 4.99 (d, H-11, J = 5.0 Hz, 1H), 3.93 (t, H-1, J = 2.6 Hz, 1H), 3.61 (s, OMe, 3H), 3.43 (s, OMe, 3H), 2.56 (s, H-5, 1H), 2.30 (d, H-9, J = 5.0 Hz, 1H), 1.79 (se, 4H), 1.70 (m, 1H), 1.43 (m, 1H), 1.13 (m, 1H), 1.11 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 195.9 (C-6), 148.8 (C-8), 133.6 (C-7), 107.3 (C-11), 81.5 (C-1), 63.1 (C-9), 59.6 (OMe), 56.0 (OMe), 55.0 (C-5), 48.0 (C-10), 35.7 (C-3), 27.9 (C-4), 21.3 (C-2), 31.8, 20.8, 18.1, 15.7 (4 CH_3). **MS** m/z (CI, NH_3) : 312 (MNH_4^+), 295 (MH^+), 263.

(2S*,2aR*,5S*,5aS*,8aS*,8bR*)-2,4-Dimethoxy-3,6,6,8b-tetramethyl-2a,5,5a,6,7,8,8a,8b-octahydro-2H-naphtho[1,8-bc]furan-5-ol 23

To a solution of ketone **22** (0.1 g, 0.34 mmol) in THF (4 mL) at 0 °C was added a 1.5 M solution of DIBAL-H in toluene (0.34 mL, 0.51 mmol). The resulting solution was stirred at 0 °C for 1 h and quenched at -78 °C by successive addition of methanol (1 mL) and a saturated aqueous Rochelle salt solution (10 mL). The mixture was allowed to warm to 20 °C and stirred at this temperature for 1h, then extracted with ethyl acetate (4 x 5 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (10:90) gave alcohol **23** (yield 80%, 0.81 g, 0.27 mmol) as a colourless oil. **IR** (cm^{-1}) : 3478, 2928, 1682, 1450, 1100, 1041, 1013. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 4.61 (d, H-11, J = 5.0 Hz, 1H), 4.47 (s, H-6, 1H), 3.85 (t, H-1, J = 2.5 Hz, 1H), 3.60 (s, 3H), 3.37 (s, 3H), 2.07 (d, H-9, J = 5.0 Hz, 1H), 1.79 (m, 2H, H-2), 1.64 (s, 3H), 1.37 (d, H-5, J = 3.4 Hz, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.10 (m, 2 H, H-3), 0.98 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 151.0 (C-8), 114.9 (C-7), 109.4 (C-11), 83.4 (C-1), 64.9 (C-6), 63.3 (C-9), 58.0 (OMe), 55.9 (OMe), 46.7 (C-5), 42.8 (C-10), 37.3 (C-3), 33.3 (C-4), 22.0 (C-2), 31.7, 22.9, 19.7, 14.9 (4 CH_3). **MS** m/z (CI, NH_3) : 314 (MNH_4^+), 297 (MH^+), 296, 265. **HRMS** calc. for $C_{17}H_{28}O_4$: 296.198756, found : 296.198781.

(2S*,2aS*,3R*,5S*,5aS*,8aS*,8bR*)-3,5-Dihydroxy-2-methoxy-3,6,6,8b-tetramethyl-octahydro-naphtho[1,8-bc]furan-4-one 24

Method A : To a solution of alcohol **23** (0.14 g, 0.46 mmol) in anhydrous pyridine (6 mL) was added osmium tetroxide (0.13 g, 0.51 mmol). The resulting mixture was stirred for 4 h at room temperature and the osmium ester was hydrolysed by the addition of a saturated aqueous solution of sodium sulphite (10 mL). The mixture was stirred vigorously at room temperature overnight and then extracted with dichloromethane (4x8 mL). The combined extracts were successively washed with a 1N aqueous HCl solution (2x10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (10:90) gave ketone **24** (yield = 58%, 0.08 g, 0.27 mmol) as a crystalline solid.

Method B : To a solution of alcohol **23** (0.03 g, 0.10 mmol) in water (6 mL) and ethanol (1 mL) was added technical 3-Chloroperoxybenzoic acid (0.03 g, 0.10 mmol) and solid sodium carbonate (5.0 mg, 0.05 mmol) at 0 °C. The resulting mixture was stirred for 2 h at room temperature and water was added (10 mL). The aqueous phase was extracted with dichloromethane (4x8 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (30:70) gave ketone **24** (yield 85%, 0.028 g, 0.009 mmol) as a crystalline solid. **m.p.** 149 °C. **IR** (CCl_4, cm^{-1}) : 3604, 3513, 2932, 2870, 1741, 1723, 1379, 1033. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 5.30 (d, H-11, *J* = 3.0 Hz, 1H), 4.80 (dd, H-6, *J* = 6.0, *J* = 1.8 Hz, 1H), 3.77 (t, H-1, *J* = 2.7 Hz, 1H), 3.35 (s, 3H), 2.99 (d, 6-OH, *J* = 1.9 Hz, 1H), 2.63 (d, H-5, *J* = 6.0 Hz, 1H), 1.80 (m, H-2, H-9, 3H), 1.63 (m, H-3, 1H), 1.41 (s, 3H), 1.17 (m, H-3, 1H), 1.15 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 214.4 (C-7), 103.9 (C-11), 82.1 (C-1), 73.8 (C-8), 73.2, 69.0 (C-6, OMe), 55.5 (C-5), 46.7 (C-9), 44.3 (C-10), 39.0, 21.7 (C-2, C-3), 33.9 (C-4), 31.4, 25.4, 22.8, 21.2 (4 CH_3).

(2S*,2aS*,3R*,4S*,5S*,5aS*,8aS*,8bR*)-2-Methoxy-3,6,6,8b-tetramethyl-decahydro-naphtho[1,8-bc]furan-3,4,5-triol 25

^{1}H NMR δ (400 MHz, $CDCl_3$, ppm) : 4.97 (d, H-11, *J* = 6.0 Hz, 1H), 4.40 (se, H-6, 1H), 3.80 (t, H-1, *J* = 2.5 Hz, 1H), 3.62 (d, H-7, *J* = 3.8 Hz, 1H), 3.41 (s, 3H), 1.95 (d, H-9, *J* = 6 Hz, 1H), 1.79 (m, H-2, 2H), 1.47 (s, 3H), 1.38 (s, 3H), 1.28 (s, H-5, 1H), 1.23 (m, H-3, 2H), 1.10 (s, 3H), 1.00 (s, 3H).

(3aS*,5R*,5aS*,6R*,6aS*,9aS*,9bS*,9cS*)-5-Methoxy-1,1,6,8,8,9c-hexamethyl-decahydro-4,7,9-trioxa-cyclopenta[c]acenaphthylen-6-ol 26

To a solution of ketone **24** (0.060 g, 0.20 mmol) in ethanol (15 mL) was added sodium borohydride (0.008 g, 0.20 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C, quenched by the addition of a 1N aqueous HCl solution (0.5 mL) and concentrated *in vacuo* to give a residue which was dissolved in 2,2-dimethoxypropane (2 mL) and to which was added a catalytic amount of *p* -toluenesulfonic acid. The resulting solution was stirred for 18 h at room temperature, and diethyl ether (20 mL) was added. The solution was successively washed with a saturated aqueous sodium carbonate solution (10 mL) and brine (8 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture ethyle acetate/ cyclohexane (30:70) gave product **26** (yield = 65%, 0.044 g, 0.13 mmol) as a white crystalline solid. **m.p.** 97 °C. **IR** (CCl_4, cm^{-1}) : 3569, 2937, 1381, 1207, 1101, 1056. **^{1}H NMR** δ (200 MHz, $CDCl_3$, ppm) : 4.99 (s, H-11, 1H), 4.58 (dd, H-6, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 3.92 (d, H-7, *J* = 8.1 Hz, 1H), 3.75 (t, H-1, *J* = 8 Hz, 1H), 3.32 (s, 3H), 1.97 (s, H-9, 1H), 1.93 (m, 1H), 1.88 (d, H-5, *J* = 2.0 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.38 (m, 2 H), 1.34 (s, 3H), 1.30 (s, 3H), 1.14 (m, 1H), 1.00 (s, 3H), 0.98 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 108.0 (C-14), 106.5 (C-11), 86.0 (C-1), 80.4, 73.0 (C-6, C-7), 70.6 (C-8), 60.1 (C-5), 54.4 (OCH_3), 42.2 (C-10), 39.8 (C-9), 34.9 (C-3), 29.8 (C-4), 24.1 (C-2), 30.7, 28.1, 28.0, 27.1, 26.0, 23.1 (6 CH_3). **MS** m/z (EI) : 340 ($M^{+\cdot}$), 325, 309, 180. **HRMS** calc. for $C_{19}H_{32}O_5$ 340.22497, found 340.22513.

(3aS*,5aS*,6R*,6aS*,9aS*,9bS*,9cS*)-6-Hydroxy-1,1,6,8,8,9c-hexamethyl-decahydro-4,7,9-trioxa-cyclopenta[c]acenaphthylen-5-one 27

Jones reagent (0.077 mL, 0.15 mmol) was added dropwise to a stirred solution of lactol **26** (0.035 g, 0.10 mmol) in acetone (5 mL) at 0 °C. After 1 h, the reaction was quenched by the addition of water (10 mL)

and extracted with dichloromethane (4x5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with ethyl acetate, gave lactone **27** (yield = 90%, 30 mg, 0.09 mmol) as a white crystalline solid. **m.p.** 125 °C. **IR** (CCl_4, cm^{-1}) : 3539, 2932, 1752, 1373, 1266, 1205, 1060, 1039. **^{1}H NMR** δ (400 MHz, $CDCl_3$, ppm) : 4.65 (dd, H-6, *J* = 8.2, *J* = 2.9 Hz, 1H), 4.16 (d, H-7, *J* = 8.2 Hz, 1H), 4.02 (t, H-1, *J* = 4.8 Hz, 1H), 2.93 (s, 8-OH, 1H), 2.49 (s, H-9, 1H), 2.00-1.80 (m, 2 H), 1.74 (d, H-5, *J* = 2.9 Hz, 1H), 1.57 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 1.23 (m, 2H), 1.12 (s, 3H), 1.04 (s, 3H). **^{13}C NMR** δ (50.3 MHz, $CDCl_3$, ppm) : 178.4 (C-11), 108.4 (C-14), 86.8 (C-1), 80.0, 72.2 (C-6, C-7), 69.2 (C-8), 59.8 (C-5), 40.4 (C-9), 40.2 (C-10), 35.8 (C-3), 32.4 (C-4), 22.4 (C-2), 31.1, 29.2, 25.3, 25.2, 24.1, 23.1 (6 CH_3).

(3aS*,6aR*,9aS*,9bS*,9cS*)-1,1,6,8,8,9c-Hexamethyl-2,3,3a,5,6a,9a,9b,9c-octahydro-1H-4,7,9-trioxa-cyclopenta[c]acenaphthylen-5-one 2

Freshly distilled thionyl chloride (0.060 mL, 0.80 mmol) was added to a stirred solution of lactone **27** (0.020 g, 0.062 mmol) in pyridine (0.5 mL) at 0 °C. After 1 hour, the mixture was diluted with dichloromethane (15 mL) and the resulting solution was successively washed with 1 N aqueous HCl (6 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/ cyclohexane (20:80) gave Ziegler's intermediate **2** (yield 72%, 0.014 g, 0.045 mmol) as a white crystalline solid. **m.p.** 100 °C (lit. 99-101 °C, Ziegler,[2] 110-111 °C, Ikegami[2]). **^{1}H NMR** δ (400 MHz, $CDCl_3$, ppm) : 4.62 (dd, H-6, *J* = 7.4 Hz, *J* = 2.9 Hz, 1H), 4.58 (d, H-7, *J* = 7.4 Hz, 1H), 4.09 (dd, H-1, *J* = 11.5 Hz, *J* = 5.8 Hz, 1H), 2.29 (s, 3H), 1.93-1.60 (m, 2 H), 1.52 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.31 (m, 2H), 1.20 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** δ (100.6 MHz, $CDCl_3$, ppm) : 169.0 (C-11), 144.6 (C-8), 136.7 (C-9), 109.2 (C-14), 87.5 (C-1), 79.3, 73.2 (C-6, C-7), 51.6 (C-5), 40.4 (C-10), 36.1 (C-3), 32.2 (C-4), 25.1 (C-2), 31.1, 28.3, 26.3, 26.3, 22.9, 17.9 (6 CH_3).

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