Stereoselective Synthesis of the Naturally Occurring Lactones (−)-Osmundalactone and (−)-Muricatacine Using Ring-Closing Metathesis

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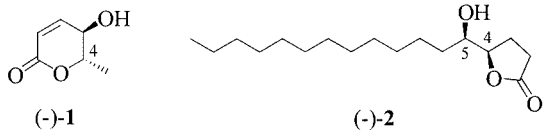
The stereoselective synthesis of the naturally occurring lactones osmundalactone (–)-**1** and muricatacin (–)-**2** is described. The key steps in each synthesis are the stereoselective addition of a Grignard reagent to a suitably protected α-hydroxy aldehyde and a ring-closing metathesis.

Introduction

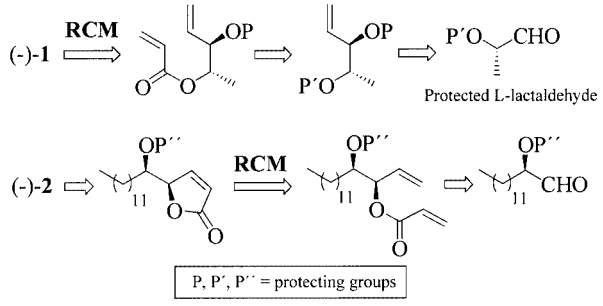
Lactone rings are a structural feature of many natural products.[1,2] A good deal of naturally occurring lactones, most particularly those that are α,β-unsaturated,[3] display pharmacologically important properties (e.g. antitumoural or else tumour-promoting activity). Osmundalactone (−)-**1**, for instance, is the aglycone part of the natural glycoside osmundalin[4] and occurs also in the free form[5] in the edible Japanese fern species *Osmunda japonic*a. Its enantiomer, (+)-**1**, has also been reported as a natural product.[6] Carcinogenic properties have not been unequivocally established for the aforementioned compounds but osmundalactone itself has been found to display antifeedant activity against larvae of some insect species.[5] Total syntheses of osmundalactone, as well as of its *cis*-diastereoisomer (4-*epi*-osmundalactone), have been published.[4,7−9] In addition, several O-substituted derivatives of osmundalactone or diastereoisomers thereof have been prepared, in some cases as intermediates in the synthesis of other natural products.[10−18]

A further naturally occurring lactone of pharmacological interest is muricatacin, isolated eleven years ago by McLaughlin and co-workers from seeds of *Annona muricata* and found to display cytotoxic activity against certain tumour cell lines.[19] The levorotatory natural material was shown to be a mixture of compound (−)-**2** (absolute configuration 4*R*, 5*R*) and its enantiomer, with a slight predominance of the former. Total syntheses of either enantiomer as well as of diastereoisomers thereof have been reported in the literature.[20−23]



Results and Discussion

Within our recently initiated program on the synthesis of naturally occurring lactones using ring-closing metathesis (RCM) reactions as one of the key steps,[24] we have devised stereoselective syntheses for the two aforementioned compounds. The retrosynthetic concept for both compounds is depicted in Scheme 1. Both syntheses rely upon the stereoselective addition of a vinylmetal reagent to a suitably pro-



Scheme 1

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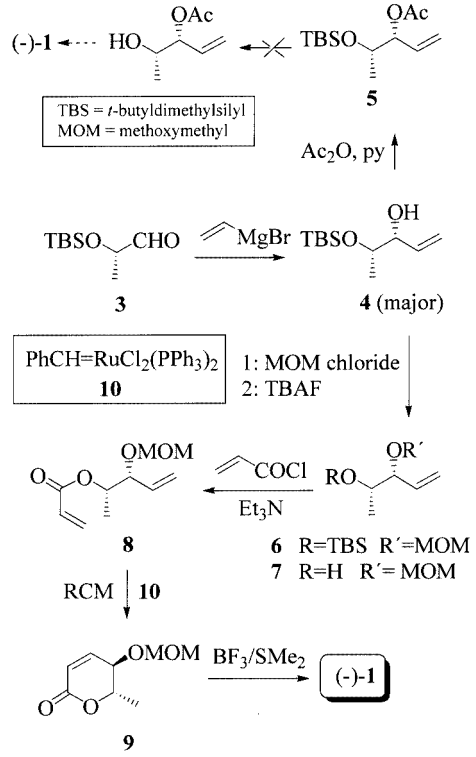
tected α-hydroxy aldehyde. The required adduct is the Felkin−Anh stereoisomer[25] in the case of osmundalactone but that predicted by Cram's α-chelation model[26] in the case of muricatacin. Consequently, the protecting groups P, P′ and P′′ were chosen with these purposes in mind.

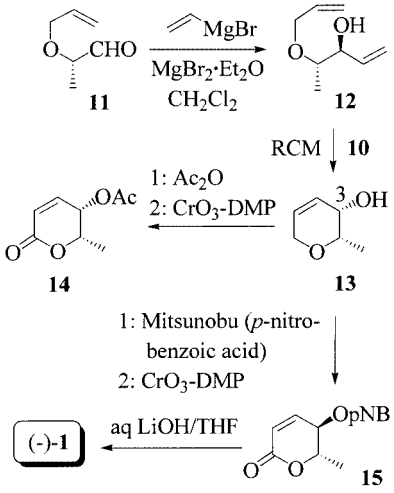
O-Silylated lactaldehydes have previously been shown in several instances to react with organometallic reagents predominantly in the Felkin−Anh sense.[8,16,27,28] We thus chose the silylated L-lactaldehyde **3** (Scheme 2) as a suitable starting material in our first approach to osmundalactone. The addition of a range of vinylmetal reagents was tried under numerous reaction conditions[8,29] but a diastereomeric ratio (*dr*) of about 85:15 was the highest value we were able to attain. Nonetheless, we carried on the projected reaction sequence with the mixture of stereoisomers as depicted in Scheme 2. We initially acetylated the allylic alcohol **4** (major diastereoisomer) with the aim of subsequently replacing the silyl group in **5** by the required acrylate moiety (Scheme 1). However, we were unable to desilylate **5** without a partial or total migration of the acetyl group.[30] In view of this, we protected the hydroxyl group of **4** as its MOM derivative **6**.[31] Desilylation of the latter, followed by acylation with acryloyl chloride yielded ester **8**. RCM of **8** was promoted by Grubbs' ruthenium catalyst **10**[32] in the presence of $Ti(OiPr)_4$ [33] and yielded the MOM derivative **9** of osmundalactone with a good yield. Final deprotection with BF_3/SMe_2 [34] provided (−)-**1**, the physical and spectroscopic data of which proved identical to those reported for (−)-osmundalactone.[4,8]

The fact that the diastereoselectivity of the vinylmetal addition step was not complete led us to undertake a second



Scheme 2. First approach to (−)-osmundalactone

approach in which the lactaldehyde precursor bears a sterically unencumbered, electron-donating protecting group.[35−37] The idea was to rely upon the high diastereoselectivity which often accompanies organometallic additions under Cram-type chelation control, even if this implied an extra step of configurational inversion. The O-allyl protecting group fulfilled the conditions required from such a protecting group and, at the same time, provided material for building up the oxygen-containing (dihydropyran) ring via RCM.[37] The missing lactone carbonyl was to be introduced later through allylic oxidation, as we have shown recently.[24]

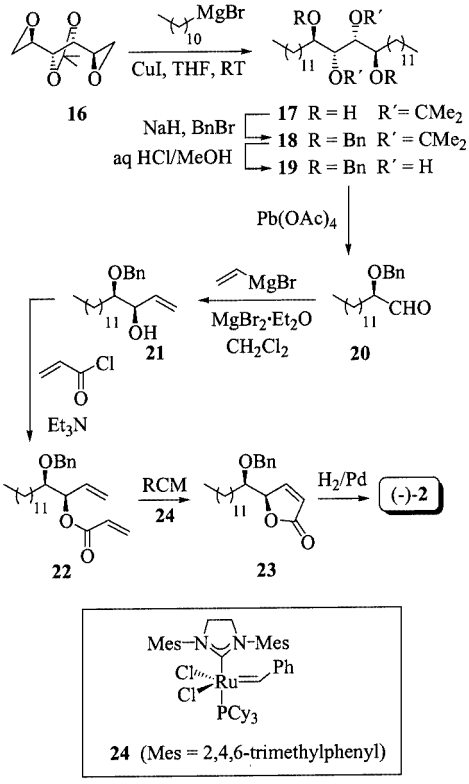


Scheme 3. Second approach to (−)-osmundalactone

Thus, *O*-allyl L-lactaldehyde **11**[37] (Scheme 3) was reacted with vinylmagnesium bromide. Provided that an excess of reagent and a bidentate Lewis acid ($MgBr_2$/diethyl ether) in a noncoordinating solvent (CH_2Cl_2) were used,[38] adduct **12** was obtained in 80% yield as a single stereoisomer (*dr* > 19:1). That **12** had in fact the configuration predicted by a Cram-like chelated transition state was shown through a chemical correlation. The RCM of **12** promoted by **10** yielded the sensitive dihydropyran **13**[37] which, by acetylation followed by allylic oxidation, gave 4-*epi*-osmundalactone acetate **14**, with spectroscopic data identical to those reported previously.[11]

The necessary configurational inversion at C-3 in **13** was cleanly achieved via a Mitsunobu reaction using *p*-nitrobenzoic acid (*p*-NBA).[39] The resulting *p*-nitrobenzoate was not isolated but directly subjected to allylic oxidation to form osmundalactone *p*-nitrobenzoate **15**. Saponification of the latter with lithium hydroxide in aqueous THF[40] afforded (−)-**1**.

For the synthesis of muricatacin, the chelation-controlled addition of a vinylmetal reagent to a suitably protected α-hydroxy tetradecanal was again required.[38] An O-benzyl was deemed an appropriate protecting group in this case, since it could be eliminated in the last step together with the projected olefin hydrogenation (Scheme 1). Consequently, (*R*)-2-benzyloxytetradecanal **20** was prepared in three steps from the known bisepoxide **16**[41] through the



Scheme 4. Synthesis of (−)-muricatacin

reaction sequence depicted in Scheme 4. Reaction of **20** with excess vinylmagnesium bromide in CH_2Cl_2 in the presence of $MgBr_2$/diethyl ether took place to yield alcohol **21** as a single diastereoisomer.[42] Acryloylation of **21** was achieved uneventfully to yield acrylate **22**. The RCM of **22** with catalyst **10** to yield the α,β-unsaturated lactone **23** proved very slow and low-yielding.[43] Fortunately, the recently described, second-generation ruthenium catalyst **24**[44] solved the problem: RCM of acrylate **22** in the presence of **24** furnished lactone **23** in good yield. Hydrogenation of **23** with a palladium catalyst took place with saturation of the C=C bond and concomitant cleavage of the benzyl group to afford muricatacin (−)-**2**, which showed the expected physical and spectroscopic data.[19]

Experimental Section

General Remarks: NMR spectra were measured in $CDCl_3$ solution at 25 °C (Varian Unity 500 or 400 NMR spectrometers). The residual solvent signals were taken as the reference (δ = 7.25 ppm for ^1H and 77.0 ppm for ^{13}C). Mass spectra were run either by the electron impact (EIMS, 70 eV), chemical ionization (CIMS, CH_4) or fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Reactions which required an inert atmosphere were carried out under argon with flame-dried glassware. Commercial reagents (Aldrich or Fluka) were used as received. Et_2O and THF were freshly distilled from sodium-benzophenone ketyl. Benzene and toluene were freshly distilled from sodium wire. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Unless detailed otherwise, "workup" means pouring the reaction mixture into brine, extraction with the indicated solvent, additional washing with 5% aq $NaHCO_3$, (if acids had been utilized in the reaction) or with 5% aq HCl (if bases had been utilized), then again with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination of the solvent under reduced pressure. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 60−200 μ) with the indicated eluent.

(2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)pent-4-en-3-yl Acetate (5, ≈ 85:15 Mixture of Diastereoisomers): Allyl alcohol **4** (433 mg, ca. 2 mmol), prepared from **3** as a mixture of diastereoisomers according to the described procedure,[8] triethylamine (420 μL, ca. 3 mmol) and 4-(dimethylamino)pyridine (DMAP) (12 mg, ca. 0.1 mmol) were dissolved in dry CH_2Cl_2 (5 mL). After dropwise addition of acetic anhydride (285 μL, ca. 3 mmol), the reaction mixture was stirred overnight at room temp. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane/Et_2O, 9:1) afforded **5** (434 mg, mixture of diastereoisomers, 84%) as an oil: ^1H NMR (400 MHz, only signals of the major diastereoisomer): δ = 5.85 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1 H), 5.30−5.20 (m, 2 H), 5.06 (ddt, *J* = 7.2, 3.6 and 1 Hz, 1 H), 3.92 (dq, *J* = 3.6, 6.4 Hz, 1 H), 2.06 (s, 3 H), 1.09 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm.

(2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-(methoxymethoxy)pent-4-ene (6, Mixture of Diastereoisomers): *N*,*N*-Diisopropylethylamine (2.6 mL, 15 mmol) and chloromethyl methyl ether (760 μL, 10 mmol) were added dropwise sequentially to an ice-cooled solution of alcohol **4** (1.082 g, 5 mmol) in dry CH_2Cl_2 (10 mL). The resulting mixture was stirred overnight at room temp. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane/EtOAc, 9:1) provided compound **6** (1.12 g, 86%) as a colourless oil. IR: $\tilde{\nu}$ = 3080 cm^{-1}, 2956, 2930, 2887, 1472, 1463, 1375, 1255, 1153, 1104, 1007, 922, 834, 776, 739. ^1H NMR (500 MHz, only signals of the major diastereoisomer): δ = 5.75 (m, 1 H), 5.26 (m, 2 H), 4.71 (d, *J* = 6.5 Hz, 1 H), 4.59 (d, *J* = 6.5 Hz, 1 H), 3.84 (m, 2 H), 3.34 (s, 3 H), 1.16 (d, *J* = 6.5 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR (125 MHz, only signals of the major diastereoisomer): δ = 135.6, 118.6, 94.0, 81.7, 70.8, 55.4, 25.9, 19.6, 18.1, −4.6, −4.7 ppm. HR EIMS: *m*/*z* (%) = 229.1611 (2) [M^+ − OMe], 199 (21), 173 (58), 159 (100), 89 (34), 73 (36). Calcd. for $C_{13}H_{28}O_3Si$ − OMe: M = 229.1623.

(2*S*,3*R*)-3-(Methoxymethoxy)pent-4-en-2-ol (7, Mixture of Diastereoisomers): tetra-*n*-Butylammonium fluoride hydrate (6 mL of a 1 M solution in THF, 6 mmol) was added dropwise under argon to a solution of alcohol **6** (1.042 g, 4 mmol) in dry THF (15 mL). The reaction mixture was stirred overnight at room temp. Workup (extraction with Et_2O) and column chromatography on silica gel (hexane/EtOAc, 7:3) provided alcohol **7** (410 mg, 70%) as a colourless oil. IR: $\tilde{\nu}$ = 3450 (br, OH) cm^{-1}, 3079, 2978, 2934, 2890, 1450, 1425, 1404, 1373, 1153, 1099, 1020, 921. ^1H NMR (500 MHz, only signals of the major diastereoisomer): δ = 5.63 (m, 1 H), 5.20−5.10 (m, 2 H), 4.57 (d, *J* = 6.5 Hz, 1 H), 4.45 (d, *J* = 6.5 Hz, 1 H), 3.77 (dd, *J* = 7.7, 3.9 Hz, 1 H), 3.71 (m, 1 H), 3.23 (s, 3 H), 2.80 (br. s, 1 H), 1.00 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, only signals of the major diastereoisomer): δ = 133.9, 119.3, 93.9, 81.5, 69.0, 55.1, 17.7 ppm. HR EIMS: *m*/*z* (%) = 101.0601 (85) [M^+ − CHOHMe], 70 (100), 57 (95). Calcd. for $C_7H_{14}O_3$ − CHOHMe: M = 101.0602.

(2*S*,3*R*)-3-(Methoxymethoxy)pent-4-en-2-yl Acrylate (8, Mixture of Diastereoisomers): Alcohol **7** (365 mg, ca. 2.5 mmol) was dissolved under argon in dry, ice-cooled CH_2Cl_2 (10 mL) and then treated

sequentially with triethylamine (700 μL, 5 mmol), DMAP (18 mg, 0.15 mmol) and acryloyl chloride (325 μL, 4 mmol). The reaction mixture was then allowed to reach room temp. and stirred overnight. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane/EtOAc, 8:2) furnished the oily ester **8** (350 mg, 70%). IR: $\tilde{\nu}$ = 3056 cm^{-1}, 2987, 2953, 2892, 1722, 1637, 1619, 1406, 1296, 1267, 1201, 1151, 1098, 1034, 986, 920, 810, 735. ^1H NMR (500 MHz, only signals of the major diastereoisomer): δ = 6.36 (dd, *J* = 17.2, 1 Hz, 1 H), 6.10 (dd, *J* = 17.2, 10.3 Hz, 1 H), 5.79 (dd, *J* = 10.3, 1 Hz, 1 H), 5.72 (m, 1 H), 5.35−5.25 (m, 2 H), 5.05 (dq, *J* = 4, 6.5 Hz, 1 H), 4.67 (d, *J* = 6.6 Hz, 1 H), 4.57 (d, *J* = 6.6 Hz, 1 H), 4.11 (dd, *J* = 7.3, 4 Hz, 1 H), 3.35 (s, 3 H), 1.25 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, only signals of the major diastereoisomer): δ = 165.3, 134.1, 130.5, 128.7, 119.4, 94.0, 78.5, 71.9, 55.3, 14.9 ppm. HR EIMS: *m*/*z* (rel. int.) = 169.0868 (4) [M^+ − OMe], 139 (29), 101 (75), 72 (40), 55 (100). Calcd. for $C_{10}H_{16}O_4$ − OMe: M = 169.0864.

(5*R*,6*S*)-5-Methoxymethoxy-6-methyl-5,6-dihydropyran-2-one (9): A solution of **8** (200 mg, 1 mmol) in dry, degassed CH_2Cl_2 (25 mL) was treated with Ti(O*i*Pr)$_4$ (300 μL, ca. 1 mmol) and heated under argon at reflux for 1 h. After this time, ruthenium catalyst **10** (41 mg, 0.05 mmol) was added to the solution. The reaction mixture was then stirred at reflux for 12 h. After this time, a second portion of catalyst (41 mg) was added, and the reflux was continued for a further 12 h. The mixture was cooled and filtered through celite, and the solvent was removed under reduced pressure. Column chromatography of the residue on silica gel (hexane/EtOAc, 7:3 and then 1:1) provided compound **9** (145 mg, 84%) as a slightly yellowish oil. $[\alpha]_D^{25}$ = −51 (*c* = 0.9, $CHCl_3$). IR: $\tilde{\nu}$ = 2982 cm^{-1}, 2933, 2846, 1732, 1446, 1388, 1237, 1151, 1102, 1080, 1042, 966, 916, 814. ^1H NMR (500 MHz): δ = 6.84 (dd, *J* = 10, 2.5 Hz, 1 H), 5.97 (br. d, *J* = 10.0 Hz, 1 H), 4.79 (d, *J* = 7.0 Hz, 1 H), 4.74 (d, *J* = 7.0 Hz, 1 H), 4.48 (dq, *J* = 8, 6.5 Hz, 1 H), 4.13 (br. d, *J* = 8.0 Hz, 1 H), 3.40 (s, 3 H), 1.43 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (125 MHz): δ = 162.7, 146.3, 121.0, 96.3, 77.3, 72.6, 55.9, 18.3 ppm. HR CIMS: *m*/*z* = 173.0807 [M + H^+]. Calcd. for $C_8H_{13}O_4$: M = 173.0813.

(5*R*,6*S*)-5-Hydroxy-6-methyl-5,6-dihydropyran-2-one, (−)-Osmundalactone (1): An ice-cooled solution of **9** (86 mg, ca. 0.5 mmol) in dry THF (7 mL) was treated under Ar successively with dimethyl sulfide (1.1 mL, 15 mmol) and freshly distilled $BF_3{\cdot}Et_2O$ (254 μL, ca. 2 mmol). The reaction mixture was then stirred in the ice bath for 30 min, quenched with satd. aq. $NaHCO_3$ and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane/EtOAc, 7:3, then 1:1) provided osmundalactone **1** (30 mg, 47%): $[\alpha]_D^{25}$ = −62 (*c* = 1.5, H_2O) {ref.[4] $[\alpha]_D^{22}$ = −70.62 (*c* = 2, H_2O)}. ^1H NMR (400 MHz): δ = 6.82 (dd, *J* = 9.8, 2.2 Hz, 1 H), 6.00 (dd, *J* = 9.8, 1.9 Hz, 1 H), 4.37 (dq, *J* = 8.8, 6.4 Hz, 1 H), 4.24 (br. dt, *J* = 8.8 and 2 Hz, 1 H), 1.49 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 162.9, 148.2, 120.9, 78.9, 67.8, 18.2 ppm. A certain proportion (15 mg, 24%) of the translactonization product (γ-lactone isomer) was also formed.

(2*S*,3*S*)-2-Allyloxypent-4-en-3-ol (12): A solution of aldehyde **11** (570 mg, 5 mmol), freshly prepared as reported previously,[37] and $MgBr_2$/diethyl ether (1.55 g, 6 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 1 h under argon at room temp. and then cooled to −78 °C. In a separate flask, the solvent was removed from a 1 M solution of vinylmagnesium bromide in THF (50 mL, 50 mmol) by a cycle of cooling to −78 °C, evaporation in vacuo and addition of dry CH_2Cl_2 (30 mL) to the residue (three repetitions). The suspension of vinylmagnesium bromide in CH_2Cl_2 obtained in this way was then added dropwise (15 min) from a syringe to the aforementioned solution of aldehyde **7**. The resulting mixture was stirred overnight at −40 °C. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane/EtOAc, 8:2) provided alcohol **12** (569 mg, 80%): colourless oil. $[\alpha]_D^{23}$ = +35 (*c* = 2, $CHCl_3$). ^1H NMR (500 MHz): δ = 5.92 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1 H), 5.81 (ddd, *J* = 17, 10.5, 6.5 Hz, 1 H), 5.36 (dt, *J* = 17.3, 1.5 Hz, 1 H), 5.28 (dq, *J* = 17.3, 1.5 Hz, 1 H), 5.22 (dt, *J* = 10.5, 1.5 Hz, 1 H), 5.18 (dq, *J* = 10.5, 1.5 Hz, 1 H), 4.14 (ddt, *J* = 12.5, 5.5, 1.5 Hz, 1 H), 3.95 (ddt, *J* = 12.5, 5.5, 1.5 Hz, 1 H), 3.91 (overlapped m, 1 H), 3.34 (dq, *J* = 6.5 and 6 Hz, 1 H), 1.13 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz): δ = 136.7, 134.7, 117.5, 117.1, 78.1, 76.6, 70.2, 15.7 ppm.

(2*S*,3*S*)-2-Methyl-3,6-dihydro-2*H*-pyran-3-ol (13): Alcohol **12** (142 mg, ca. 1 mmol) was dissolved in dry, degassed CH_2Cl_2 (60 mL), treated with catalyst **10** (41 mg, ca. 0.05 mmol) and heated at reflux for 24 h. Workup as above yielded dihydropyran **13**, which was sensitive towards chromatography on silica gel and was thus used in crude form in the next step: ^1H NMR (500 MHz): δ = 6.06 (complex m, 1 H), 5.93 (ddd, *J* = 10, 3.5, 1.5 Hz, 1 H), 4.20−4.10 (m, 2 H), 3.70−3.60 (m, 2 H), 1.30 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz): δ = 129.4, 127.0, 73.8, 65.8, 64.7, 16.5 ppm.

(5*S*,6*S*)-5-Acetoxy-6-methyl-5,6-dihydropyran-2-one, 4-*epi*-Osmundalactone Acetate (14): The crude RCM reaction mixture obtained above was evaporated to dryness, dissolved in CH_2Cl_2 (2 mL) and treated with Ac_2O (140 μL, ca. 1.5 mmol), triethylamine (280 μL, ca. 2 mmol) and DMAP (6 mg). The mixture was stirred under argon overnight at room temp. Workup (extraction with CH_2Cl_2) provided the crude acetylated derivative of **13** as a colourless oil, which was used as such in the next step. ^1H NMR (400 MHz): δ = 6.03 (ddd, *J* = 10, 3.5, 1.5 Hz, 1 H), 5.90 (complex m, 1 H), 4.96 (m, 1 H), 4.23 (ddd, *J* = 17, 3.5 and 2 Hz, 1 H), 4.12 (ddd, *J* = 17, 3.5 and 2 Hz, 1 H), 3.70 (dq, *J* = 2.5, 6.5 Hz, 1 H), 2.06 (s, 3 H), 1.17 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 170.8, 132.2, 122.7, 71.8, 66.5, 65.7, 20.9, 16.5 ppm.

A suspension of CrO_3 (600 mg, 6 mmol) in dry CH_2Cl_2 (5 mL) was cooled under argon to −20 °C and treated rapidly with 3,5-dimethylpyrazole (580 mg, 6 mmol). The resulting mixture was stirred at the same temp. for 20 min and then cooled to −30 °C. The acetylated derivative from above was dissolved in dry CH_2Cl_2 (2 mL) and added dropwise with a syringe to the oxidizing reagent. The reaction mixture was then stirred at −30 °C for 2 h. After this time, 5 M aqueous NaOH (2 mL) was added, the bath temperature was allowed to reach 0 °C and the stirring was continued for 1 h. The reaction mixture was then poured into diluted HCl, and the organic layer was washed with brine, dried on anhydrous Na_2SO_4, filtered, concentrated in a rotary evaporator and chromatographed on silica gel (hexane/EtOAc, 7:3). This afforded **14** (68 mg, 40% overall yield from **12**) as a colourless oil. ^1H NMR (400 MHz): δ = 6.90 (dd, *J* = 9.6, 5.8 Hz, 1 H), 6.16 (d, *J* = 9.6 Hz, 1 H), 5.13 (dd, *J* = 5.8, 2.8 Hz, 1 H), 4.63 (dq, *J* = 2.8, 6.5 Hz, 1 H), 2.07 (s, 3 H), 1.38 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 170.2, 162.9, 140.3, 124.8, 75.0, 63.7, 20.5, 15.9 ppm. HR CIMS: *m*/*z* = 171.0656 [M + H^+]. Calcd. for $C_8H_{11}O_4$: M = 171.0657.

Osmundalactone 4-Nitrobenzoate (15): Alcohol **12** (355 mg, 2.5 mmol) was subjected to RCM as described above. The crude reaction mixture containing **13** was concentrated to dryness, and the residue was dissolved under argon in dry THF (8 mL). Triphenylphosphane (918 mg, 3.5 mmol), 4-nitrobenzoic acid (1.17 g, 7 mmol) and DEAD (550 μL, 3.5 mmol) were then added successively. The reaction mixture was stirred for 6−8 h at room temp. (TLC monitoring). Workup (extraction with EtOAc) and rapid column chromatography on silica gel (hexane/EtOAc, 8:2) yielded the

p-nitrobenzoic ester, which was subjected as such to the allylic oxidation.

The experimental procedure for the allylic oxidation with CrO_3-DMP was as described above for the synthesis of **14**. Reaction time: 4 h at −20 °C. Overall yield from **12**: 60% of lactone **15** as a yellowish oil, $[\alpha]_D^{23} = -108.5$ ($c = 2.4$, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 7.35−7.20 (m, 4 H), 6.90 (dd, $J = 9.8$, 3.8 Hz, 1 H), 6.21 (dd, $J = 9.8$ and 1 Hz, 1 H), 5.53 (ddd, $J = 6.5$, 3 and 1 Hz, 1 H), 4.80 (quint, $J = 6.5$ Hz, 1 H), 1.51 (d, $J = 6.5$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 163.7, 161.6, 151.0, 141.3, 134.1, 131.0, 123.8, 123.7, 76.4, 68.8, 18.5 ppm. HR EIMS: *m*/*z* = 277.0593 [M$^+$]. Calcd. for $C_{13}H_{11}NO_6$: M = 277.0586.

(−)-Osmundalactone (1): Lactone **15** (111 mg, 0.4 mmol) was dissolved in THF (5 mL). The solution was cooled in an ice bath and treated with lithium hydroxide (20 mg, ca. 0.8 mmol) dissolved in water (0.5 mL). The reaction mixture was stirred at 0 °C for 2−3 h (TLC monitoring!). Workup (extraction with Et_2O) and column chromatography on silica gel (hexane/EtOAc, 1:1) furnished osmundalactone **(−)-1** (36 mg, 70%).

(4*R*,5*R*)-4,5-Bis[(*R*)-1-hydroxytridecyl)]-2,2-dimethyl-1,3-dioxolane (17): Magnesium turnings (2.8 g, 115 mmol) were suspended under argon in dry THF (80 mL) at room temp. Several drops of 1,2-dibromoethane were then added to the suspension with a syringe until an effervescence started. A solution of *n*-undecyl bromide (25 mL, 112 mmol) in THF (80 mL) was then added dropwise with a syringe. The resulting mixture was stirred at 50 °C for 30 min.

In a separate flask, CuI (10.66 g, 56 mmol) was heated gently in vacuo until the solid turned light yellow. The flask was then cooled to −10 °C and filled with argon, followed by addition of dry Et_2O (100 mL). The previously prepared solution of *n*-undecylmagnesium bromide was then added dropwise with a syringe. The mixture was then stirred for 1 h at −10 °C, whereby it turned dark violet. Diepoxide **16** (2.6 g, 14 mmol) was dissolved in dry Et_2O (100 mL) and added dropwise to the solution of the organocopper reagent. After removing the cooling bath, the mixture was stirred for 12 h at room temperature. The reaction was then quenched with aqueous ammonium chloride and worked-up (extraction with Et_2O). Column chromatography on silica gel (hexane/EtOAc 9:1 to 8:2) afforded diol **17** (6.49 g, 93%) as a colourless oil. $[\alpha]_D^{23} = +12.4$ ($c = 0.3$, $CHCl_3$). IR: $\tilde{\nu}$ = 3350 (br) cm^{-1}, 3055, 2989, 2915, 2849, 1467, 1265, 1075, 738, 705. ^{1}H NMR (400 MHz): δ = 3.90 (br. s, 2 H), 3.65−3.50 (m, 4 H), 1.75 (m, 2 H), 1.55 (m, 2 H), 1.34 (s, 6 H), 1.35−1.20 (br. m, 40 H), 0.86 (t, $J = 7.0$ Hz, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 108.7, 83.2, 73.2, 34.3, 32.7, 32.0, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 26.8, 25.8, 25.2, 22.7, 14.1 ppm. HR EIMS: *m*/*z* (%) = 483.4432 (89) [M$^+$ − Me], 241 (71), 59 (100). Calcd. for $C_{31}H_{62}O_4$ − Me: M = 483.4413.

(4*R*,5*R*)-4,5-Bis[(*R*)-1-benzyloxytridecyl)]-2,2-dimethyl-1,3-dioxolane (18): A 60% commercial suspension of sodium hydride in mineral oil (1.45 g, equivalent to ca. 36 mmol of NaH) was stirred under argon with dry hexane. The suspension was then decanted and the supernatant liquid was removed with a syringe. This operation was repeated once more with dry THF. A solution of diol **17** (6 g, ca. 12 mmol) in dry THF (125 mL) was then added with a syringe. The solution was stirred at reflux for 1 h. Benzyl bromide (3.57 mL, 30 mmol) and tetra-*n*-butylammonium iodide (370 mg, 1 mmol) were then added to the reaction mixture, which was stirred for 12 h at reflux. Workup (extraction with Et_2O) and column chromatography on silica gel (hexane/EtOAc, 9:1) afforded **18** (6.92 g, 85%) as a colourless oil. $[\alpha]_D^{23} = +2.8$ ($c = 0.8$, $CHCl_3$). IR: $\tilde{\nu}$ = 3031 cm^{-1}, 2930, 2853, 1458, 1377, 1212, 1095, 732. ^{1}H NMR (500 MHz): δ = 7.45−7.30 (br. m, 10 H), 4.60 (m, 4 H), 4.12 (br. s, 2 H), 3.60 (br. s, 2 H), 1.75−1.50 (m, 6 H), 1.45 (s, 6 H), 1.40−1.25 (br. m, 38 H), 0.95 (t, $J = 7.0$ Hz, 6 H) ppm. ^{13}C NMR (125 MHz): δ = 138.8, 128.4, 127.9, 127.6, 109.4, 80.0, 79.9, 72.0, 32.0, 30.1, 29.8, 29.7, 29.6, 29.5, 27.5, 25.3, 22.7, 14.1 ppm. HR FABMS: *m*/*z* = 679.5634 [M + H$^+$]. Calcd. for $C_{45}H_{75}O_4$: M = 679.5665.

(13*R*,14*S*,15*S*,16*R*)-13,16-Bis(benzyloxy)octacosane-14,15-diol (19): Compound **18** (6.79 g, 10 mmol) was dissolved in MeOH (50 mL) and treated with. 1 N HCl (10 mL). The mixture was then stirred at reflux for 12−18 h (TLC monitoring). Workup (extraction with Et_2O) and column chromatography on silica gel (hexane/EtOAc, 9:1) provided **19** (5.43 g, 85%) as a white solid. M.p. 62−64 °C. $[\alpha]_D^{23} = -4.6$ ($c = 0.1$, $CHCl_3$). IR: $\tilde{\nu}$ = 3400 (br) cm^{-1}, 3032, 2933, 2852, 1467, 1378, 1093, 900, 742. ^{1}H NMR (400 MHz): δ = 7.40−7.30 (br. m, 10 H), 4.63, 4.61 (AB system, $J = 11.5$ Hz, 2 H), 3.83 (d, $J = 4.7$ Hz, 2 H), 3.66 (m, 2 H), 1.70−1.40 (m, 6 H), 1.35−1.20 (br. m, 42 H), 0.88 (t, $J = 7.0$ Hz, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 138.4, 128.4, 127.9, 127.7, 82.2, 73.5, 70.9, 32.0, 31.1, 29.8, 29.7, 29.6, 29.5, 29.4, 25.4, 22.7, 14.1 ppm. HR FABMS: *m*/*z* = 639.5359 [M + H$^+$]. Calcd. for $C_{42}H_{71}O_4$: M = 639.5352.

(*R*)-2-Benzyloxytetradecanal (20): Lead tetraacetate (4 g, ca. 9 mmol) was added dropwise under argon to a solution of diol **19** (5.11 g, ca. 8 mmol) in dry benzene (70 mL). The mixture was stirred at room temp. for 4−5 h (TLC monitoring), then filtered through celite. The celite pad was washed three times with EtOAc. All organic layers were mixed, the volatiles removed under reduced pressure and the crude residue (4 g) was used directly in the next step. For analytical purposes, an aliquot of the residue was chromatographed on silica gel (hexane/EtOAc, 9:1) to give **20** as a gum (unstable). ^{1}H NMR (500 MHz): δ = 9.69 (d, $J = 1.5$ Hz, 1 H), 7.40−7.30 (br. m, 5 H), 4.72, 4.58 (AB system, $J = 11.7$ Hz, 2 H), 3.79 (td, $J = 6.5$, 1.5 Hz, 1 H), 1.73 (m, 2 H), 1.45 (m, 2 H), 1.40−1.25 (br. m, 18 H), 0.92 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (125 MHz): δ = 203.8, 137.3, 128.5, 128.2, 128.0, 83.5, 72.5, 32.0, 30.1, 29.7, 29.6, 29.5, 29.4, 24.8, 22.7, 14.1 ppm.

(3*R*,4*R*)-4-Benzyloxyhexadec-1-en-3-ol (21): A suspension of vinylmagnesium bromide in CH_2Cl_2 (100 mL) was prepared as described above from a commercial 1 M solution of vinylmagnesium bromide in THF (125 mL). In a separate flask, the previously obtained aldehyde **20** and $MgBr_2$/diethyl ether (3.36 g, ca. 13 mmol) were premixed at −78 °C in dry CH_2Cl_2 (100 mL) and stirred at this temp. for 1 h. The previously prepared suspension of vinylmagnesium bromide in the same solvent was then added dropwise with a syringe, and the reaction mixture was stirred for 12 h at the same temp. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane/EtOAc, 9:1) afforded **21** (3.32 g, 60% overall from **19**) as a colourless oil. $[\alpha]_D^{23} = -1.1$ ($c = 0.2$, $CHCl_3$). IR: $\tilde{\nu}$ = 3400 (br) cm^{-1}, 3032, 2925, 2854, 1459, 1070, 900. ^{1}H NMR (500 MHz): δ = 7.40−7.30 (br. m, 5 H), 5.90 (ddd, $J = 17.3$, 10.5 and 6 Hz, 1 H), 5.35 (dt, $J = 17.3$, 1.5 Hz, 1 H), 5.21 (dt, $J = 10.5$, 1.5 Hz, 1 H), 4.63, 4.55 (AB system, $J = 11.5$ Hz, 2 H), 4.08 (dt, $J = 6$ and 4.5 Hz, 1 H), 3.35 (dt, $J = 6$ and 5 Hz, 1 H), 2.50 (d, $J = 4.5$ Hz, 1 H), 1.70−1.40 (m, 6 H), 1.35−1.20 (br. m, 16 H), 0.88 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (125 MHz): δ = 138.4, 137.8, 128.5, 127.9, 127.8, 116.7, 82.4, 74.5, 72.7, 32.0, 30.5, 29.8, 29.7, 29.6, 29.5, 29.4, 25.2, 22.7, 14.1 ppm. HR EIMS: *m*/*z* (%) = 346.2858 (1) [M$^+$], 329 (2), 289 (15), 92 (100). Calcd. for $C_{23}H_{38}O_2$: M = 346.2872.

(3*R*,4*R*)-4-Benzyloxyhexadec-1-en-3-yl Acrylate (22): Alcohol **21** (2.77 g, 8 mmol) was dissolved under argon in dry, ice-cooled CH_2Cl_2 (25 mL) and then treated with acryloyl chloride (1 mL, ca. 12 mmol), triethylamine (2.8 mL, 20 mmol) and DMAP (48 mg, 0.4 mmol). The

reaction mixture was then stirred at 0 °C for 3 h. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane/EtOAc, 8:2) furnished the ester **22** (2.25 g, 70%) as a colourless oil. $[\alpha]_D^{23} = +28.1$ ($c = 0.3$, $CHCl_3$). IR: $\tilde{\nu} = 3066\ cm^{-1}$, 30312, 2925, 2854, 1728, 1635, 1456, 1404, 1377, 1362, 1294, 1264, 1189, 1111, 1046, 984, 896, 808, 735, 697. ^1H NMR (400 MHz): $\delta = 7.40-7.25$ (br. m, 5 H), 6.44 (dd, $J = 17.3$, 1.5 Hz, 1 H), 6.17 (dd, $J = 17.3$, 10.4 Hz, 1 H), 5.90 (ddd, $J = 17.1$, 10.5 and 6 Hz, 1 H), 5.85 (dd, $J = 10.4$, 1.5 Hz, 1 H), 5.52 (ddt, $J = 7$, 6 and 1.5 Hz, 1 H), 5.33 (dt, $J = 17.3$, 1.5 Hz, 1 H), 5.27 (dt, $J = 10.4$, 1.5 Hz, 1 H), 4.69, 4.59 (AB system, $J = 11.5$ Hz, 2 H), 3.52 (dt, $J = 7$ and 5.5 Hz, 1 H), 1.55−1.35 (br. m, 4 H), 1.35−1.20 (br. m, 18 H), 0.89 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz): $\delta = 165.3$, 138.4, 133.1, 131.1, 128.5, 128.3, 128.0, 127.7, 118.0, 79.7, 75.4, 72.8, 32.0, 30.4, 29.6 (several overlapped signals), 25.4, 22.7, 14.1 ppm. HR FAB MS: $m/z = 401.3039$ [M + H$^+$]. Calcd. for $C_{26}H_{41}O_3$: M = 401.3055.

(5*R*)-5-[(*R*)-1-Benzyloxytridecyl]-5*H*-furan-2-one (23): Acrylate **22** (1 g, 2.5 mmol) and ruthenium complex **24** (105 mg, 5% mol) were dissolved under argon in dry, degassed toluene (100 mL) and heated at 80 °C for 24−30 h (TLC monitoring!). Once the starting material had been consumed, the volatiles were removed under reduced pressure, and the residue was chromatographed on silica gel (hexane/EtOAc, 7:3) to give lactone **23** (745 mg, 80%) as a colourless oil. $[\alpha]_D^{23} = +3.7$ ($c = 0.3$, $CHCl_3$). IR: $\tilde{\nu} = 3065\ cm^{-1}$, 3032, 2929, 2853, 1757, 1600, 1496, 1455, 1377, 1351, 1159, 1087, 1028, 892, 821, 748. ^1H NMR (500 MHz): $\delta = 7.40$ (br. d, $J = 5.8$ Hz, 1 H), 7.40−7.30 (br. m, 5 H), 6.16 (dd, $J = 6$ and 1.5 Hz, 1 H), 5.10 (d, $J = 5.0$ Hz, 1 H), 4.69, 4.60 (AB system, $J = 11.5$ Hz, 2 H), 3.64 (dt, $J = 6$ and 5 Hz, 1 H), 1.80−1.40 (m, 6 H), 1.35−1.20 (br. m, 16 H), 0.87 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (125 MHz): $\delta = 172.8$, 153.9, 137.9, 128.5, 128.0, 122.7, 84.6, 78.9, 73.4, 32.0, 30.6, 29.8, 29.7, 29.6, 29.5, 29.4, 25.6, 22.7, 14.1 ppm. HR EIMS: m/z (%) = 372.2666 (1) [M$^+$], 289 (3), 91 (100). Calcd. for $C_{24}H_{36}O_3$: M = 372.2664.

(−)-Muricatacin (2): A solution of lactone **23** (75 mg, ca. 0.2 mmol) was dissolved in EtOH (3 mL) and stirred for 48 h under H_2 (1 atm) in the presence of 20% palladium hydroxide on carbon (Pearlman's catalyst) (5 mg). After filtration through celite and removal of all volatiles under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc, 7:3) to yield muricatacin (−)-**2** (50 mg, 89%) as a white solid. M.p. 68−70 °C {ref.[21] m.p. 67−68 °C}. $[\alpha]_D^{23} = -19.5$ ($c = 2.1$, $CHCl_3$) {ref.[19] $[\alpha]_D^{20} = -16.1$, ref.[21] $[\alpha]_D^{20} = -23.3$}. IR: $\tilde{\nu} = 3400$ (br) cm^{-1}, 2928, 2855, 1769, 1466, 1377, 1189, 909. ^1H NMR (400 MHz): $\delta = 4.40$ (dt, $J = 7.5$, 4.6 Hz, 1 H), 3.55 (dt, $J = 7$ and 4.6 Hz, 1 H), 2.60 (ddd, $J = 17.8$, 10 and 5 Hz, 1 H), 2.57 (dd, $J = 17.8$, 9.3 Hz, 1 H), 2.30−2.05 (m, 2 H), 1.70 (br. s, 1 H), 1.50 (m, 2 H), 1.40−1.20 (br. m, 20 H), 0.87 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (125 MHz): $\delta = 177.1$, 82.9, 73.7, 33.0, 31.9, 29.6, 29.5, 29.4, 29.3, 28.7, 25.4, 24.1, 22.7, 14.1 ppm. HR CIMS: m/z (%) = 285.2429 (1) [M + H$^+$], 267 (100). Calcd. for $C_{17}H_{33}O_3$: M = 285.2430.

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