HETEROCYCLES, Vol. 88, No. 2, 2014, pp. 1101 - 1119. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 29th June, 2013, Accepted, 31st July, 2013, Published online, 8th August, 2013
DOI: 10.3987/COM-13-S(S)68

THE PAECILIN PUZZLE – ENANTIOSELECTIVE SYNTHESES OF THE PROPOSED STRUCTURES OF PAECILIN A AND B

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Dedicated to Professor Dr. Victor Snieckus on the occasion of his 77th birthday

Abstract – For the synthesis of the two diastereomers **3c** and **3d** of the proposed structure of paecilin B (**3**) phenol **19**, containing an alkenyl moiety, was treated with Pd(II) in the presence of the chiral BOXAX ligand **9b** to give **20** with 96% *ee*. A subsequent Sharpless dihydroxylation afforded two isomeric diols, which were further transformed into **31** and **32**. The final steps included removal of the silyl protecting group with simultaneous lactone formation, oxidation and cleavage of the methyl ether. For the preparation of the dimeric paecilin A (**1**) brominated intermediate **38** was treated with $(Bpin)_2$, S-Phos and $Pd(OAc)_2$. The spectroscopic data of the new compounds did not match those of the isolated natural products.

INTRODUCTION

The secondary metabolites paecilin A (**1**) and B (**3**) of the endophytic fungus *Paecilomyces sp*. have been isolated in 2007 by Guo *et al*.; however, the authors only published the constitution of these natural products, the absolute and relative configurations are still unknown.[1] Both paecilins have a chromanone skeleton and contain quaternary stereogenic centers as well as γ-lactone moieties. Paecilin A (**1**) is likely a dimer of paecilin B (**3**) with a 8,8'-biaryl connection. In an initial bioassay, paecilin A (**1**) and B (**3**) were tested using KB cell lines, but showed no pronounced cytotoxicity. However, several structurally related chromanones substituted with a γ-lactone moiety exhibit promising biological activities such as the dimer gonytolide A (**2**), which promotes the innate immune response.[2] Therefore, it seems reasonable to assume that **1** and **3** may also have some so far unknown bioactivities.

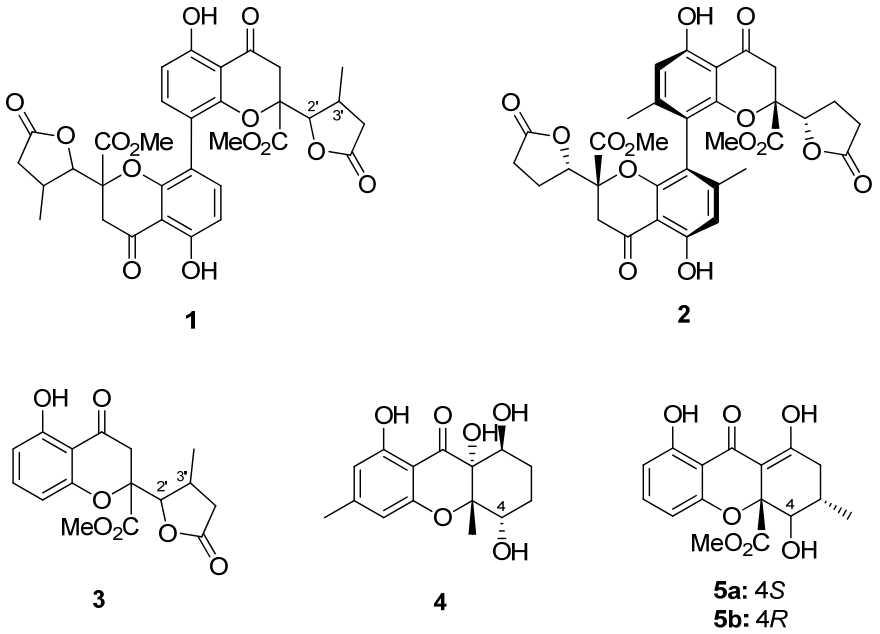


Figure 1. Paecilin A (**1**) and B (**3**), gonytolide A (**2**), diversonol (**4**) and blennolide A and B (**5**)

Paecilin B (**3**) contains three stereogenic centers, therefore it could exist in eight different stereoisomeric forms, the diastereomers **3a-d** and their enantiomers *ent*-**3a-d** (Figure 2). Though the absolute configuration of **3** is not known, a comparison with the natural products gonytolide A (**2**),[2] diversonol (**4**)[4] as well as blennolide A (**5a**) and blennolide B (**5b**)[3] would make it feasible to assume that paecilin B should have the relative and absolute configuration as depicted in **3a-d**. Recently, Porco *et al*. described a very nice synthesis of the two racemic diastereomers **3a** and **3b**; however, their spectroscopic data did not match those published for **3**.[3c] They therefore concluded that the natural product must be **3c**, **3d** or their respective enantiomers.

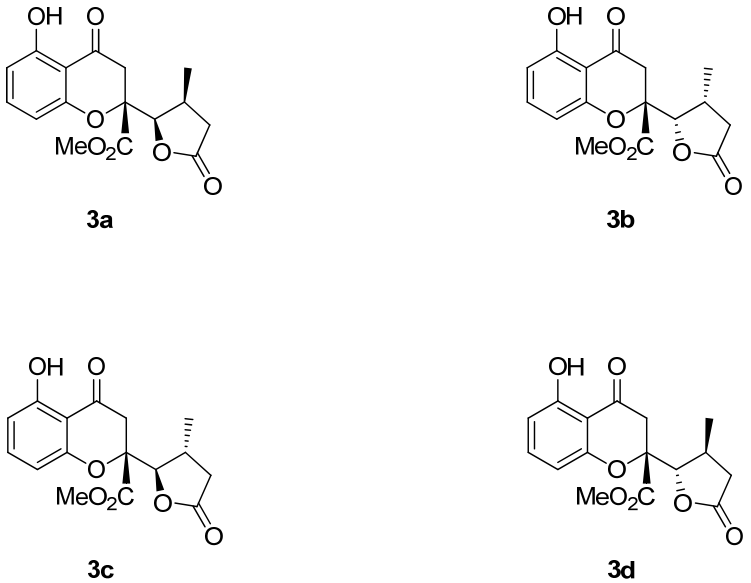
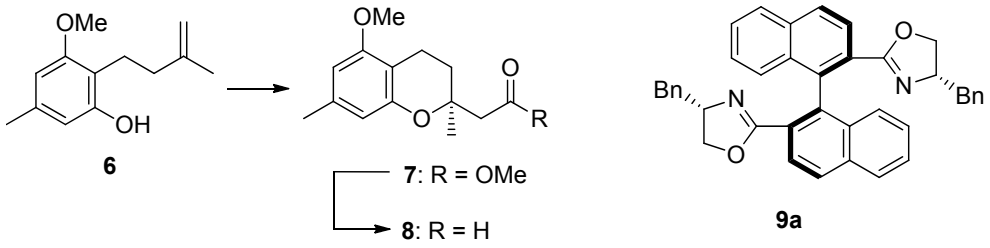


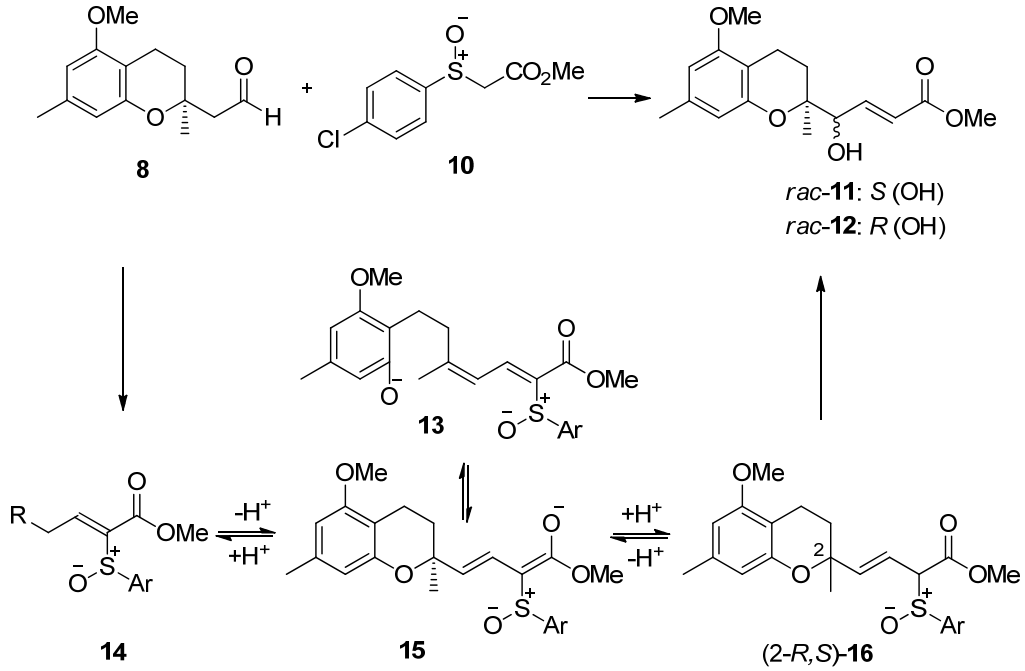
Figure 2. Possible diastereomers of paecilin B (**3a-d**)

Recently, we have described the total syntheses of the tetrahydroxanthenones (–)-diversonol (*ent*-**4**)[4c] and (–)-blennolide A (*ent*-**5a**).[3b] For the synthesis of (–)-diversonol (*ent*-**4**) we employed an enantioselective domino Wacker/carbonylation/methoxylation reaction using BOXAX ligand **9a** to furnish ester **7** in 96% *ee* and 80% yield (Scheme 1).[4c,5]

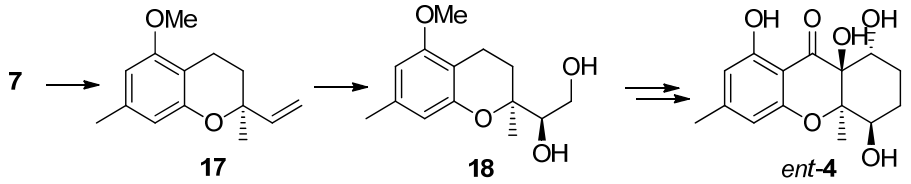
A: Enantioselective domino Wacker/carbonylation/methoxylation



B: Proposed pathway for the racemization



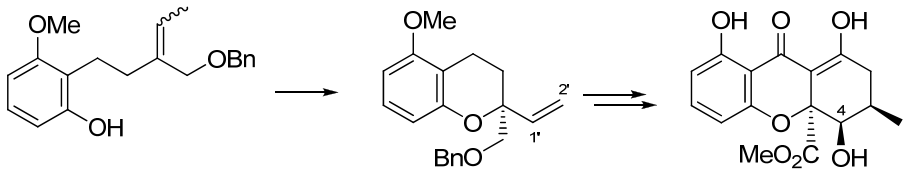
C: Sharpless dihydroxylation



Scheme 1. Enantioselective total synthesis of (–)-diversonol (*ent*-**4**)

Reduction of **7** to form aldehyde **8** set the stage for the direct introduction of the hydroxyl group at C-4 (numbering as in **4**) using a hydroxylating Knoevenagel condensation.[6] To our surprise, however, the steric integrity of the stereogenic center in **8** was lost in the course of the reaction to yield the racemic esters *rac*-**11** and *rac*-**12**. Most likely, a retro-1,6-Michael addition led to an opening of the chroman ring system and subsequent racemization via the intermediates **13**-**16**. We therefore sought alternative ways for the hydroxylation. In a revised strategy we introduced the C-4 hydroxy group via a Sharpless dihydroxylation[7] of readily accessible vinyl chroman **17**, which led to *ent*-**4** after 10 additional steps.

In a related approach we synthesized (–)-blennolide A (*ent*-**5a**) via an enantioselective domino Wacker/carbonylation/methoxylation reaction with 96% *ee* as described before and an enantioselective Wacker oxidation of the diastereomeric alkenyl phenols **19** (*E*/*Z* = 1:1.7) to give vinyl chroman **20** using catalytic amounts of palladium(II) trifluoracetate [Pd(OTFA)$_2$] and the chiral (*S*,*S*)-Bn-BOXAX ligand **9a** in methanol with however only 85% *ee* and 82% yield (Scheme 2).[3b]



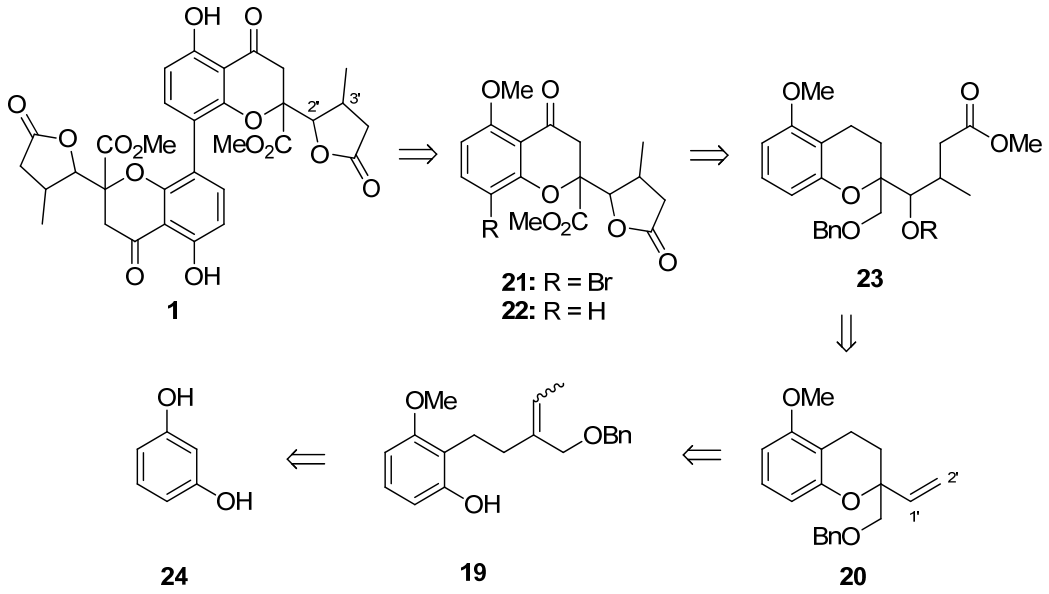
19 **20** *ent*-**5a**

Scheme 2. Enantioselective total synthesis of (–)-blennolide A (*ent*-**5a**)

Herein we report the syntheses of two diastereomers of the proposed structures of paecilin B (**3**) in their enantiomeric forms *ent*-**3c** and *ent*-**3d** and one diastereomer of the dimer paecilin A (**1**) using an enantioselective Wacker oxidation to finally solve the absolute and relative configuration of paecilin A (**1**) and paecilin B (**3**) and moreover to provide enough material for further biological studies.

RESULTS AND DISCUSSION

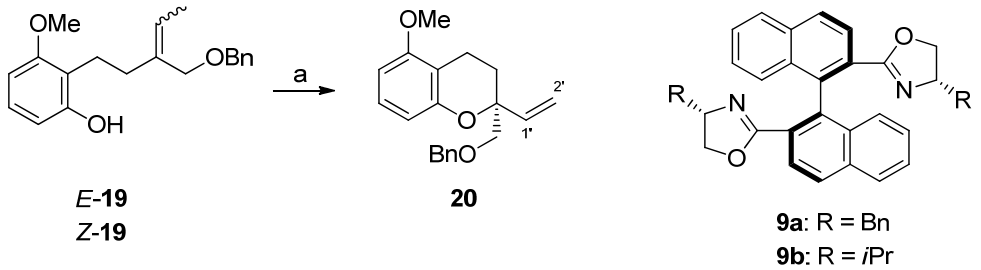
In accordance with the syntheses of *ent*-**4** and *ent*-**5a**, retrosynthetic analysis of the dimer paecilin A (**1**) leads to the methylated monomeric paecilin B (**22**) via halogenated intermediate **21**, from which **1** could be obtained via a Suzuki type coupling. Methylated paecilin B (**22**) should be accessible from **23** by benzylic oxidation and lactonization (Scheme 3). The latter could arise from intermediate **20**, employing a dihydroxylation and Wittig-Horner reaction followed by Michael addition.



Scheme 3. Retrosynthetic analysis of paecilin A (**1**)

Finally, for the synthesis of **20** an enantioselective Wacker oxidation of **19** was envisaged, which in turn can be synthesized from resorcinol (**24**) in six steps.

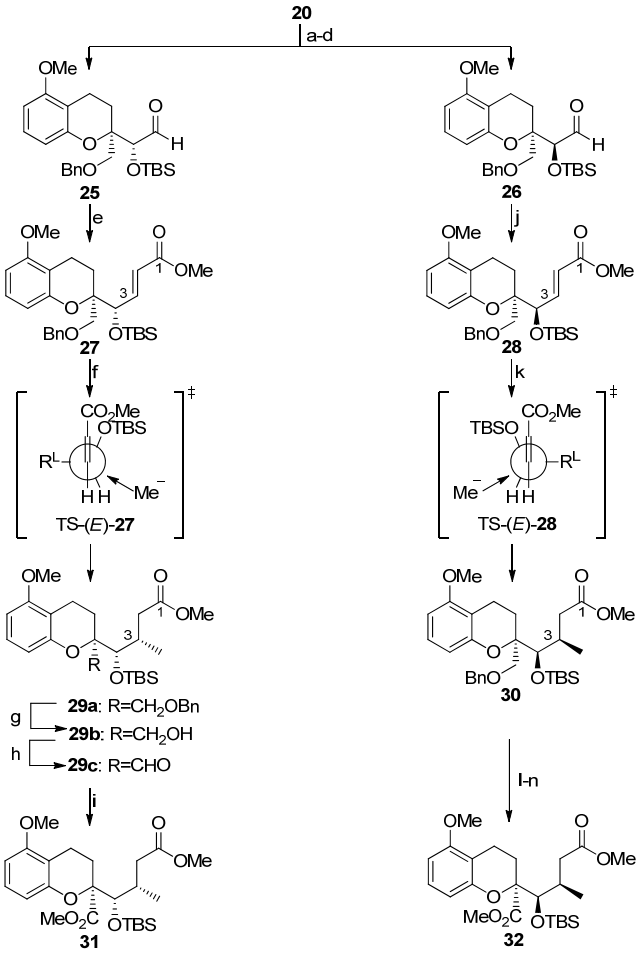
As already mentioned, an enantioselective Wacker oxidation of **19** to give **20** has been used by us for the synthesis of (-)-blennolide A (*ent*-**5a**)[3b] using the chiral (*S*,*S*)-Bn-BOXAX ligand (**9a**)[8] in methanol with 85% *ee* and 82% yield. Gratifyingly, the enantioselective Wacker oxidation of **19** could now be improved using (*S*,*S*)-*i*Pr-BOXAX (**9b**) instead of **9a**, which resulted in an enantioselectivity of 96% *ee* and an almost identical yield of 79% (Scheme 4).



Scheme 4. Synthesis of **20**: a) 10 mol% [$Pd(OTFA)_2$], 10 mol% BOXAX ligand (**9a** and **9b**), *p*-benzoquinone, MeOH, 60 °C, 24 h, *E*/*Z*-**19** (*E*/*Z* = 1:1.7), for (*S*,*S*)-Bn-BOXAX (**9a**): 82%, 85% *ee*; for (*S*,*S*)-*i*Pr-BOXAX (**9b**): 79%, 96% *ee*

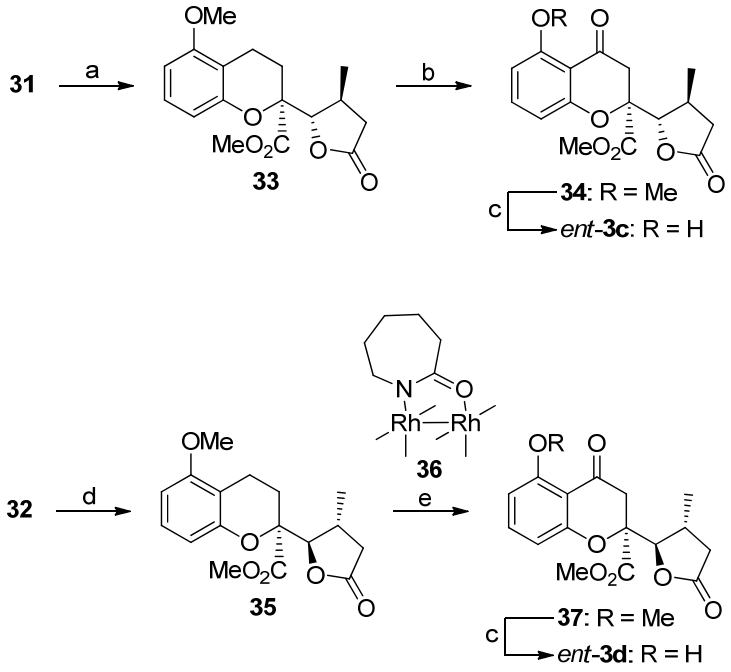
Sharpless dihydroxylation of **20** in which the desired hydroxyl groups at C-1' and C-2' (numbering as in **20**) were set up, was followed by a sequence of double TBS protection, chemoselective removal of the primary

silyl group and subsequent oxidation to give the aldehydes **25** and **26**, which could be readily separated by column chromatography (Scheme 5). In analogy to the preparation of **32** from **26** via **28** and **30**, with ester **32** being an intermediate in the enantioselective synthesis of (–)-blennolide A (*ent*-**5a**), diastereomer **31** was synthesized from **25** via **27** and **29** by a Wittig-Horner reaction followed by the introduction of a methyl group at C-3 (numbering as in **27**).



Scheme 5. Syntheses of **31** and **32**: a) AD-mix-α, $CH_3SO_2NH_2$, *t*BuOH/H_2O (1:1), rt, 4 d, 95%, (*syn*/*anti* = 1:2.4); b) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0 °C, 2.5 h, quant.; c) HF·pyridine, THF/pyridine, 0 °C, 1 h then rt, 26 h, 90% (9% diol); d) DMP, CH_2Cl_2, rt, 2 h, 94%; e) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C → rt, 2 h, 100%, (*E*/*Z* = 15.6:1); f) CuBr · Me_2S, MeLi, TMSCl, THF, –35 °C, 1 h, 94%; g) H_2 (1 atm), 10 mol% Pd/C, EtOAc, rt, 1 h, 100%; h) DMP, CH_2Cl_2, rt, 2 h, 92%; i) KOH, I_2, MeOH, rt, 4.5 h, 98%; j) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C → rt, 1.5 h, 100%, (*E*/*Z* = 4.5:1); k) CuBr · Me_2S, MeLi, TMSCl, THF, –35 °C, 1 h, 91%; l) H_2 (1 atm), 15 mol% Pd/C, MeOH, HOAc, rt, 26 h, 100%; m) DMP, CH_2Cl_2, rt, 2 h, 95%; n) KOH, I_2, MeOH, rt, 4 h, 100%; R^L = chromanyl.

Thus, the Wittig-Horner reaction of **25** with $(MeO)_2P(O)CH_2CO_2Me$ and sodium hydride in THF led to the corresponding α,β-unsaturated ester quantitatively with a very good selectivity (*E*/*Z* = 15.6:1). The *E*-diastereomer *E*-**27** was then subjected to a Michael addition using $CuBr \cdot Me_2S$, methyl lithium and TMSCl to yield **29a** in 94% yield as the exclusive diastereomer. This stereochemical outcome can be rationalized as a result of a Felkin-Anh transition state without any chelating effects.[9] The assigned relative configuration of **30** was confirmed by comparison of the NMR data of (–)-blennolide A (*ent*-**5a**) with the natural product (+)-blennolide A. In analogy we rationalized the relative configuration of **29a** using the same Felkin-Anh transition state model as for **30**. Subsequent hydrogenolysis of the benzyl group with palladium on charcoal and oxidation of the resulting primary alcohol using DMP and KOH/I_2 in methanol[10] led to the methyl ester **31** in 90% over 3 steps via **29b** and **29c**. Having successfully prepared the diastereomeric chromanes **31** and **32** the stage was set for the lactonization and benzylic oxidation.



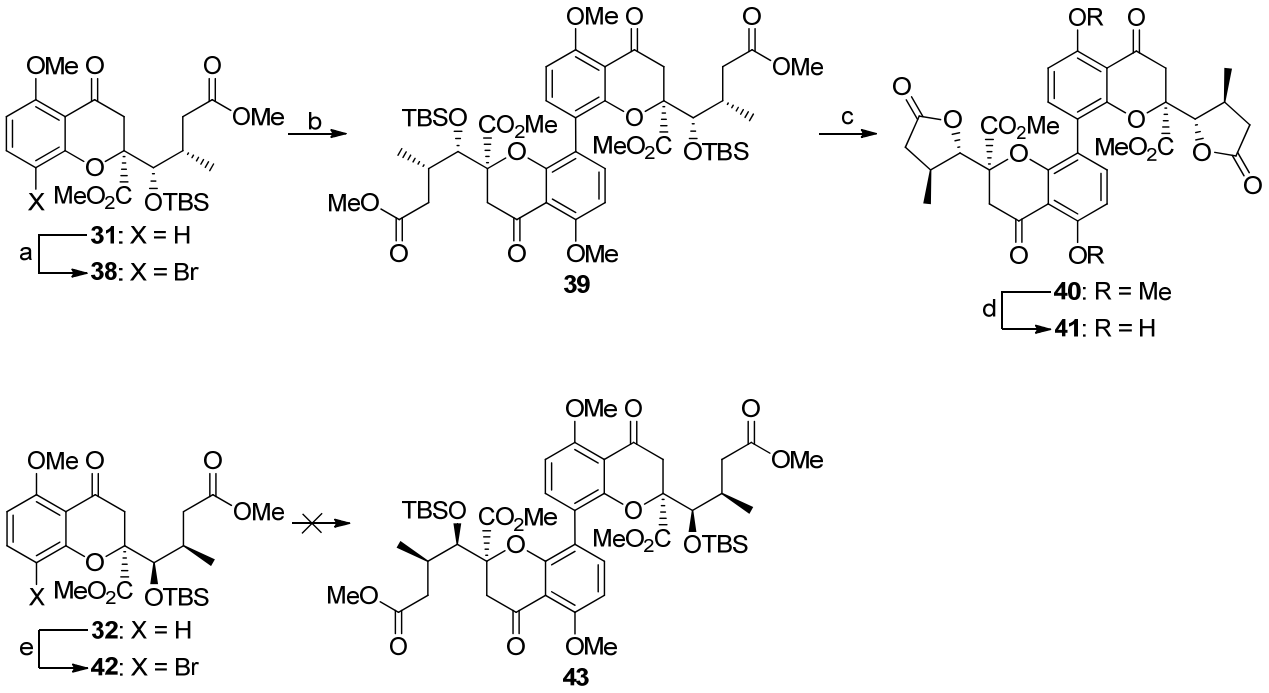
Scheme 6. Syntheses of γ-lactonyl chromanones *ent*-**3c** and *ent* -**3d**: a) TBAF·3 H_2O, THF, rt, 1 h, 86%; b) $KMnO_4$, 15% aq. $MgSO_4$-solution, acetone, ultrasound, 60 °C, 10 h, 68%, 73% brsm; c) BBr_3, CH_2Cl_2, –78 °C, 30 min, for *ent*-**3c**: 84%, for *ent*-**3d**: 83%; d) TBAF·3 H_2O, THF, rt, 100 min, 88%; e) $Rh_2(cap)_4$ (3 × 1.0 mol%), *t*BuOOH, $NaHCO_3$, DCE, 40 °C, 25.5 h, 63%.

Both esters immediately cyclized upon exposure to tetrabutylammonium fluoride (TBAF · 3 H_2O) to give the desired lactones **33** and **35** in 86% and 88% yield, respectively (Scheme 6). To adress the benzylic oxidation of **33** and **35**, we used potassium permanganate,[11] dirhodium-tetrakiscaprolactamate

(**36**)/*tert*-butylhydroperoxide (*t*BuOOH)[12] and $Mn(OAc)_3$/*t*BuOOH[13] as oxidizing agents. Treatment of lactone **33** with potassium permanganate in an ultrasonic bath afforded chromanone **34** in 68% yield. For the synthesis of **37** from **35** the use of catalytic amounts of dirhodium-tetrakiscaprolactamate (**36**), $NaHCO_3$ and an excess of *t*BuOOH gave the highest yield with 63%. Finally, cleavage of the methyl ether moiety in **34** and **37** with BBr_3 in dichloromethane at –78 °C led to *ent*-**3c** and *ent*-**3d** in 84% and 83% yield, respectively. However, as was the case in the work of Porco *et al*.,[3c] the NMR data of compounds *ent*-**3c** and *ent*-**3d** were not in agreement with those reported for the natural product implying that the published structure of **3** is not correct or the natural product contained some impurities. Unfortunately, we were not able to compare our spectroscopic data with the original spectra, since Guo *et al*. did not reply to our request.

Significant differences in the ^{1}H- and ^{13}C-NMR spectra were found for 3-H_b, 2'-H, 4'-H_a and 4'-H_b with δ = 3.46 ppm (d, *J* = 17.1 Hz), 4.34 ppm (d, *J* = 3.6 Hz), 2.20 ppm (dd, *J* = 17.7, 3.9 Hz) and 2.99 ppm (dd, *J* = 17.7, 9.6 Hz) for **3c** and δ = 3.17 ppm (d, *J* = 17.1 Hz), 4.42 ppm (d, *J* = 3.9 Hz), 2.20 ppm (dd, *J* = 17.1, 3.9 Hz) and 2.87 ppm (dd, *J* = 17.1, 9.3 Hz) for **3d**. The corresponding signals of the natural product are δ = 3.53 ppm (d, *J* = 17.4 Hz), 4.97 ppm (d, *J* = 6.6 Hz), 2.41 ppm (dd, *J* = 17, 7 Hz) and 2.73 ppm (dd, *J* = 17, 7 Hz).

For the synthesis of the dimeric paecilin A (**1**) (Scheme 7) we have chosen a one pot borylation/Suzuki-Miyaura reaction.[14] In order to access the desired coupling partners, we halogenated diverse chromanes and chromanones and subjected them to Suzuki conditions. A bromination of **34** and **37** (= **22** without stereochemistry) to give **21** was not suitable, however bromination of **31** at C-8 with tetrabutylammonium tribromide ($TBABr_3$) provided **38** in 91% yield with high selectivity.[15] After considerable optimization, we were pleased to observe that reaction of **38** with 10 mol% $Pd(OAc)_2$, 25 mol% S-Phos, $(Bpin)_2$ and Cs_2CO_3 at 50 °C for 21 h led to the desired dimer **39** in 32% yield. In addition, 62% of the debrominated compound **31** and some starting material **38** were isolated. Desilylation of **39** using triethylamine trihydrofluoride ($NEt_3 \cdot 3$ HF) and cleavage of the methyl ether moieties with BBr_3 gave **41** in 66% yield over 2 steps. The brominated diastereomer **42**, which was obtained from **32** in 83% yield using $TBABr_3$, did not dimerize to **43** under various reaction conditions. This illustrates that the dimerization is a very sensitive transformation and even slight stereochemical variations impede the reaction. Comparison of the spectroscopic data of **41** again failed to match those published for paecelin A (**1**).



Scheme 7. Synthesis of **41**: a) $TBABr_3$, THF/H_2O (1:1), rt, 23 h, 91%; b) 10 mol% $Pd(OAc)_2$, 25 mol% S-Phos, $(Bpin)_2$, Cs_2CO_3, H_2O, THF, 50 °C, 21 h, 32% (+ 62% starting material **31**); c) $NEt_3 \cdot 3$ HF, 1,4-dioxane, 60 °C, 7 d, 98%; d) BBr_3, CH_2Cl_2, –78 °C, 30 min, 67%; e) $TBABr_3$, THF/H_2O (1:1), rt, 22 h, 83%.

CONCLUSION

For the structural determination of paecilin A (**1**) and B (**3**) we prepared the almost enantiopure homo dimer **41** and two diastereomeric monomers *ent*-**3c** and *ent*-**3d**. Their spectroscopic data however did not match the published information. The closest fit exists for **3b**, prepared by Porco *et al.,*[3c] in which only the signal for 3-H_b differs significantly with δ = 3.25 ppm (d, *J* = 17.3 Hz) instead of δ = 3.53 ppm (d, *J* = 17.3 Hz).

EXPERIMENTAL

Synthesis of the vinylchroman 20

(*S*)-2-(Benzyloxymethyl)-5-methoxy-2-vinylchroman (20): A solution of $Pd(OTFA)_2$ (121 mg, 365 µmol, 10 mol%) and (*S*,*S*)-*i*Pr-BOXAX (**9b**) (174 mg, 365 µmol, 10 mol%) in MeOH (3.6 mL) was stirred at rt for 30 min. After addition of a solution of phenol *E*/*Z*-1**9** (*E*/*Z* = 1:1.7, 1.14 g, 3.65 mmol, 1.00 eq.) in MeOH (5.4 mL) and *p*-benzoquinone (1.58 g, 14.6 mmol, 4.00 eq.) the mixture was heated at 60 °C for 24 h and then cooled to rt. Filtration over a pad of silica gel (15 × 6 cm, washing with petroleum ether/EtOAc = 10:1, TLC monitoring), evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 30:1) provided vinylchroman **20** as a colorless oil

(900 mg, 2.90 mmol, 79%, 96% *ee*). Analytical HPLC (column: *Daicel* Chiralcel® OD): wavelength: 205 nm, flow: 0.8 mL/min, eluent: *n*-hexane/*i*-PrOH = 99:1; t_R = 12.0 min, (–)-(*S*)-**20**, 98.0%; t_R = 17.0 min, (+)-(*R*)-**20**, 2.0%; 96% *ee*, α = 1.83. **Optical Rotation**: $[\alpha]_D^{23}$ –75.2 (*c* 0.19, $CHCl_3$). **TLC**: R_f = 0.35 (petroleum ether/EtOAc = 20:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.87–2.08 (m, 2 H, 3-H_2), 2.44 (ddd, *J* = 17.1, 10.8, 6.6 Hz, 1 H, 4-H_a), 2.73 (ddd, *J* = 17.1, 4.8, 3.9 Hz, 1 H, 4-H_b), 3.53 (d, *J* = 16.5 Hz, 1 H, CH_aOBn), 3.57 (d, *J* = 16.5 Hz, 1 H, CH_bOBn), 3.79 (s, 3 H, 5-OCH_3), 4.59 (d, *J* = 12.3 Hz, 1 H, OCH_aPh), 4.63 (d, *J* = 12.3 Hz, 1 H, OCH_bPh), 5.17 (dd, *J* = 10.8, 1.5 Hz, 1 H, 2'-H_a), 5.25 (dd, *J* = 17.4, 1.5 Hz, 1 H, 2'-H_b), 5.85 (dd, *J* = 17.4, 10.8 Hz, 1 H, 1'-H), 6.40 (d, *J* = 8.1 Hz, 1 H, 6-H), 6.58 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.06 (t, *J* = 8.1 Hz, 1 H, 7-H), 7.23–7.38 (m, 5 H, 5 × Ph-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 16.4 (C-4), 26.6 (C-3), 55.5 (5-OCH_3), 73.7 (OCH_2Ph), 75.6 (CH_2OBn), 78.8 (C-2), 101.6 (C-6), 109.8 (C-8), 110.8 (C-4a), 116.2 (C-2'), 126.9 (C-7), 127.5 (Ph-C_p), 127.6 (Ph-C_o), 128.3 (Ph-C_m), 137.8 (C-1'), 138.3 (Ph-C_i), 154.4 (C-8a), 157.5 (C-5) ppm. **IR** (film): ν(cm^{-1}) = 2934, 2856, 1592, 1468, 1409, 1345, 1315, 1267, 1250, 1193, 1167, 1096, 1028, 929, 773, 738, 698. **UV** (CH_3OH): λ_{max} (lg ε) = 204.0 nm (4.701), 271.5 (3.113), 279.0 (3.121). **MS** (ESI): *m*/*z* (%) = 643.3 (53) $[2M+Na]^+$, 333.2 (100) $[M+Na]^+$, 311.2 (25) $[M+H]^+$. Calcd for **$C_{20}H_{22}O_3$**: 311.1642 $[M+H]^+$, Found: 311.1641 $[M+H]^+$ (ESI-HRMS).

Syntheses of the lactonyl chromanones *ent*-3c and *ent*-3d

Methyl (*S*)-5-Methoxy-2-[(2*S*,3*S*)-3-methyl-5-oxotetrahydrofuran-2-yl]chroman-2carboxylate (33): A solution of chroman **31** (318 mg, 681 μmol, 1.00 eq.) in THF (9.5 mL) was treated with TBAF·3 H_2O (430 mg, 1.36 mmol, 2.00 eq.) at rt and the reaction mixture was stirred at rt for 1 h. After addition of silica gel (1.5 g) the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 4:1) furnished chroman **33** as a colorless foam (187 mg, 584 μmol, 86%). **TLC**: R_f = 0.22 (petroleum ether/EtOAc = 4:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.2 Hz, 3 H, 3'-CH_3), 2.11 (dd, *J* = 17.7, 3.6 Hz, 1 H, 4'-H_a), 2.19–2.34 (m, 3 H, 3-H_2, 4-H_a), 2.66–2.79 (m_c, 1 H, 3'-H), 2.81–2.93 (m, 1 H, 4-H_b), 3.02 (dd, *J* = 17.7, 9.3 Hz, 1 H, 4'-H_b), 3.72 (s, 3 H, $COOCH_3$), 3.77 (s, 3 H, 5-OCH_3), 4.44 (d, *J* = 3.0 Hz, 1 H, 2'-H), 6.41 (dd, *J* = 8.4, 0.9 Hz, 1 H, 6-H), 6.49 (dd, *J* = 8.4, 0.9 Hz, 1 H, 8-H), 7.05 (t, *J* = 8.4 Hz, 1 H, 7-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 16.5 (C-4), 20.8 (3'-CH_3), 25.5 (C-3), 30.3 (C-3'), 36.4 (C-4'), 52.8 ($COO\underline{C}H_3$), 55.4 (5-OCH_3), 82.1 (C-2), 87.7 (C-2'), 102.6 (C-6), 109.4 (C-8), 109.8 (C-4a), 127.3 (C-7), 153.8 (C-8a), 157.4 (C-5), 171.0 ($\underline{C}OOCH_3$), 176.5 (C-5') ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2949, 1777, 1757, 1731, 1605, 1591, 1467, 1449, 1440, 1344, 1284, 1272, 1247, 1171, 1131, 1086, 1018, 965, 773. **UV** (CH_3OH): λ_{max} (lg ε) = 272.0 nm (3.132), 279.0 (3.127). **MS** (ESI): *m*/*z* (%) = 663.3 (100) $[2M+Na]^+$, 343.1 (26) $[M+Na]^+$. Calcd for **$C_{17}H_{20}O_6$**: 343.1158 $[M+Na]^+$,

Found: 343.1152 $[M+Na]^+$ (ESI-HRMS).

Methyl (*S*)-5-Methoxy-2-[(2*R*,3*R*)-3-methyl-5-oxotetrahydrofuran-2-yl]chroman-2carboxylate (35): A solution of chroman **32** (900 mg, 1.93 mmol, 1.00 eq.) in THF (27 mL) was treated with TBAF·3 H_2O (1.22 g, 3.86 mmol, 2.00 eq.) at rt and the reaction mixture was stirred at rt for 100 min. After addition of silica gel (3.9 g) the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 4:1 → 3:1) furnished chroman **35** as a colorless foam (542 mg, 1.69 mmol, 88%). **TLC**: R_f = 0.19 (petroleum ether/EtOAc = 4:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.23 (d, J = 7.2 Hz, 3 H, 3'-CH_3), 1.76–1.90 (m, 1 H, 3-H_a), 2.12 (dd, J = 17.7, 3.9 Hz, 1 H, 4'-H_a), 2.22–2.41 (m, 2 H, 3-H_b, 4-H_a), 2.61–2.76 (m_c, 1 H, 3'-H), 2.81–2.92 (m, 1 H, 4-H_b), 2.90 (dd, J = 17.7, 9.3 Hz, 1 H, 4'-H_b), 3.70 (s, 3 H, $COOCH_3$), 3.77 (s, 3 H, 5-OCH_3), 4.45 (d, J = 3.3 Hz, 1 H, 2'-H), 6.42 (dd, J = 8.1, 0.6 Hz, 1 H, 6-H), 6.54 (dd, J = 8.1, 0.6 Hz, 1 H, 8-H), 7.07 (t, J = 8.1 Hz, 1 H, 7-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 16.2 (C-4), 21.2 (3'-CH_3), 25.0 (C-3), 29.7 (C-3'), 36.4 (C-4'), 52.9 (COO$\underline{C}H_3$), 55.4 (5-OCH_3), 81.8 (C-2), 89.0 (C-2'), 102.6 (C-6), 109.4 (C-8), 109.5 (C-4a), 127.5 (C-7), 153.6 (C-8a), 157.4 (C-5), 170.8 ($\underline{C}OOCH_3$), 176.1 (C-5') ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2956, 1772, 1751, 1733, 1606, 1591, 1470, 1347, 1268, 1248, 1170, 1145, 1082, 972, 769, 710, 514. **UV** (CH_3CN): λ_{max} (lg ε) = 203.0 nm (4.630), 273.0 (3.150), 279.0 (3.148), 300.0 (2.433). **MS** (ESI): *m*/*z* (%) = 663.3 (100) $[2M+Na]^+$, 343.1 (34) $[M+Na]^+$. Calcd for **$C_{17}H_{20}O_6$**: 343.1158 $[M+Na]^+$, Found: 343.1155 $[M+Na]^+$ (ESI-HRMS).

Methyl (*S*)-5-Methoxy-2-[(2*S*,3*S*)-3-methyl-5-oxotetrahydrofuran-2-yl]-4-oxochroman-2carboxylate (34): Method A (Mn-catalysed oxidation): A solution of chroman **33** (40.0 mg, 125 µmol, 1.00 eq.) and *tert*-butyl hydroperoxide (230 µL of a 5.5 M solution in decane, 1.25 mmol, 10.0 eq.) in EtOAc (0.45 mL) was treated with powdered molecular sieves 3 Å (45 mg) and the resulting mixture was stirred at rt for 30 min. After addition of $Mn(OAc)_3$·2 H_2O (6.70 mg, 25.0 µmol, 20 mol%) stirring was continued for 2 d before additional $Mn(OAc)_3$·2 H_2O (3.40 mg, 12.7 µmol, 10 mol%), *tert*-butyl hydroperoxide (115 µL of a 5.5 M solution in decane, 633 µmol, 5.06 eq.) and EtOAc (0.2 mL) were added. The mixture was stirred for further 24 h at rt and filtered over silica gel (eluting with EtOAc). After concentration *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 3:2) chromanone **34** was obtained as a colorless solid (29.3 mg, 87.6 µmol, 70%). Method B (Rh-catalysed oxidation): A solution of chroman **33** (40.0 mg, 125 µmol, 1.00 eq.) and dirhodium-tetrakiscaprolactamate (**36**) (410 µg, 625 nmol, 0.5 mol%) in dichloroethane (0.5 mL) was treated with $NaHCO_3$ (5.30 mg, 62.5 µmol, 0.50 eq.). *tert*-Butyl hydroperoxide (114 µL of a 5.5 M solution in decane, 625 µmol, 5.00 eq.) was added and the resulting deep-red solution was heated with stirring at 40 °C. After 3 h the mixture was treated with additional dirhodium-tetrakiscaprolactamate (**36**) (410 µg, 625 nmol, 0.5 mol%) and *tert*-butyl hydroperoxide

(114 µL of a 5.5 M solution in decane, 625 µmol, 5.00 eq.). Stirring was continued at 40 °C for 19 h before additional dirhodium-tetrakiscaprolactamate (**36**) (820 µg, 1.25 µmol, 1 mol%) and *tert*-butyl hydroperoxide (228 µL of a 5.5 M solution in decane, 1.25 mmol, 10.0 eq.) were added. After stirring at 40 °C for further 8 h the solids were removed by filtration over silica gel (eluting with EtOAc). After evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 3:2) chromanone **34** was obtained as a colorless solid (28.0 mg, 83.7 µmol, 67%). Method C ($KMnO_4$ oxidation): A suspension of chroman **33** (50.0 mg, 156 µmol, 1.00 eq.), potassium permanganate (99.0 mg, 624 µmol, 4.00 eq.), 15% aq. $MgSO_4$ solution (0.25 mL) and acetone (1 mL) in a sealed tube was kept for 4 h at 60 °C in ultrasonic bath. A second portion of potassium permanganate (99.0 mg, 624 µmol, 4.00 eq.), 15% aq. $MgSO_4$ solution (0.25 mL) and acetone (0.5 mL) was added before the irradiation was continued for 3 h at 60 °C. After addition of a third portion of potassium permanganate (150 mg, 949 µmol, 8.00 eq.) and 15% aq. $MgSO_4$ solution (0.38 mL) the reaction mixture was irradiated for further 3 h bei 60 °C, cooled to rt and passed through silica gel in column (6 × 3 cm, washing with EtOAc, TLC monitoring). After evaporation of the solvent *in vacuo* column chromatography on silica gel (petroleum ether/EtOAc = 3:2) furnished chromanone **34** as a colorless solid (35.5 mg, 106 µmol, 68%, 73% brsm). **Optical Rotation**: $[\alpha]_D^{24}$ –36.3 (*c* 0.60, $CHCl_3$). **TLC**: R_f = 0.24 (petroleum ether/EtOAc = 1:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 7.2 Hz, 3 H, 3'-CH_3), 2.18 (dd, *J* = 17.7, 4.2 Hz, 1 H, 4'-H_a), 2.71–2.85 (m_c, 1 H, 3'-H), 2.93 (d, *J* = 16.2 Hz, 1 H, 3-H_a), 2.98 (dd, *J* = 17.7, 9.3 Hz, 1 H, 4'-H_b), 3.35 (d, *J* = 16.2 Hz, 1 H, 3-H_b), 3.68 (s, 3 H, $COOCH_3$), 3.85 (s, 3 H, 5-OCH_3), 4.34 (d, *J* = 3.3 Hz, 1 H, 2'-H), 6.51 (dd, *J* = 8.4, 0.9 Hz, 1 H, 6-H), 6.58 (dd, *J* = 8.4, 0.9 Hz, 1 H, 8-H), 7.38 (t, *J* = 8.4 Hz, 1 H, 7-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 20.5 (3'-CH_3), 29.6 (C-3'), 36.3 (C-4'), 42.4 (C-3), 53.3 (COO<u>C</u>H_3), 56.2 (5-OCH_3), 84.1 (C-2), 86.5 (C-2'), 104.7 (C-6), 109.8 (C-8), 110.6 (C-4a), 136.4 (C-7), 160.3 (C-5), 161.0 (C-8a), 169.1 (<u>C</u>$OOCH_3$), 175.7 (C-5'), 187.4 (C-4) ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2973, 1779, 1747, 1694, 1601, 1578, 1471, 1441, 1291, 1259, 1199, 1164, 1012, 788, 742, 580, 529. **UV** (CH_3CN): λ_{max} (lg ε) = 214.0 nm (4.187), 265.0 (3.907), 327.0 (3.564). **MS** (ESI): *m*/*z* (%) = 691.2 (100) $[2M+Na]^+$, 357.1 (28) $[M+Na]^+$. Calcd for **$C_{17}H_{18}O_7$**: 357.0950 $[M+Na]^+$, Found: 357.0946 $[M+Na]^+$ (ESI-HRMS).

Methyl (*S*)-5-Methoxy-2-[(2*R*,3*R*)-3-methyl-5-oxotetrahydrofuran-2-yl]-4-oxochroman-2-carboxylate (37): A solution of chroman **35** (90.0 mg, 281 µmol, 1.00 eq.) and dirhodium-tetrakiscaprolactamate (1.84 mg, 2.81 µmol, 1 mol%) in dichloroethane (1.1 mL) was treated with $NaHCO_3$ (11.8 mg, 141 µmol, 0.50 eq.). *tert*-Butyl hydroperoxide (510 µL of a 5.5 M solution in decane, 2.81 mmol, 10.0 eq.) was added and the resulting deep-red solution was heated with stirring at 40 °C. After 4 h the mixture was

treated with additional dirhodium-tetrakiscaprolactamate (1.84 mg, 2.81 μmol, 1 mol%) and *tert*-butyl hydroperoxide (510 μL of a 5.5 M solution in decane, 2.81 mmol, 10.0 eq.). Stirring was continued at 40 °C for 15 h before additional dirhodium-tetrakiscaprolactamate (1.84 mg, 2.81 μmol, 1 mol%) and *tert*-butyl hydroperoxide (510 μL of a 5.5 M solution in decane, 2.81 mmol, 10.0 eq.) were added. After stirring at 40 °C for further 6.5 h the solids were removed by filtration over silica gel (eluting with EtOAc). After evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 1:1) chromanone **37** was obtained as a colorless solid (59.0 mg, 176 μmol, 63%). Mn-catalysed oxidation (51% yield, 64% brsm) and $KMnO_4$ oxidation (47% yield) were performed according to the described procedure for synthesis of **34**. **TLC**: R_f = 0.21 (petroleum ether/EtOAc = 1:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.25 (d, J = 6.9 Hz, 3 H, 3'-CH_3), 2.19 (dd, J = 17.1, 3.6 Hz, 1 H, 4'-H_a), 2.74–2.89 (m_c, 1 H, 3'-H), 2.88 (dd, J = 17.1, 9.3 Hz, 1 H, 4'-H_b), 2.93 (d, J = 16.2 Hz, 1 H, 3-H_a), 3.06 (d, J = 16.2 Hz, 1 H, 3-H_b), 3.68 (s, 3 H, $COOCH_3$), 3.88 (s, 3 H, 5-OCH_3), 4.41 (d, J = 3.6 Hz, 1 H, 2'-H), 6.54 (dd, J = 8.4, 0.9 Hz, 1 H, 6-H), 6.65 (dd, J = 8.4, 0.9 Hz, 1 H, 8-H), 7.41 (t, J = 8.4 Hz, 1 H, 7-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 21.0 (3'-CH_3), 29.8 (C-3'), 36.1 (C-4'), 41.6 (C-3), 53.4 ($COO\underline{C}H_3$), 56.2 (5-OCH_3), 84.1 (C-2), 87.7 (C-2'), 104.9 (C-6), 110.1 (C-8), 110.9 (C-4a), 136.8 (C-7), 160.5 (C-5), 161.2 (C-8a), 168.9 ($\underline{C}OOCH_3$), 175.4 (C-5'), 186.4 (C-4) ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 1767, 1755, 1674, 1601, 1574, 1471, 1440, 1336, 1257, 1178, 1100, 1076, 1001, 790, 742, 650, 576, 520. **UV** (CH_3CN): λ_{max} (lg ε) = 265.0 nm (3.995), 328.0 (3.677). **MS** (ESI): *m*/*z* (%) = 691.2 (100) $[2M+Na]^+$, 357.1 (40) $[M+Na]^+$. Calcd for **$C_{17}H_{18}O_7$**: 357.0950 $[M+Na]^+$, Found: 357.0945 $[M+Na]^+$ (ESI-HRMS).

Methyl (*S*)-5-Hydroxy-2-[(2*S*,3*S*)-3-methyl-5-oxotetrahydrofuran-2-yl]-4-oxochroman-2carboxylate (*ent*-3c): A solution of BBr_3 (7.78 mL of a 1.0 M solution in CH_2Cl_2, 7.78 mmol, 10.0 eq.) was added slowly to a stirred solution of chromanone **34** (260 mg, 778 μmol, 1.00 eq.) in CH_2Cl_2 (40 mL) at –78 °C. Stirring was continued for 30 min at –78 °C before being quenched with sat. aq. $NaHCO_3$ solution (7 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. After column chromatography on silica gel (petroleum ether/EtOAc = 2:1) chromanone ***ent*-3c** was obtained as a colorless solid (209 mg, 653 μmol, 84%). **Optical Rotation**: $[\alpha]_D^{24}$ –68.1 (*c* 1.20, $CHCl_3$). **TLC**: R_f = 0.31 (petroleum ether/EtOAc = 2:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.16 (d, J = 7.2 Hz, 3 H, 3'-CH_3), 2.20 (dd, J = 17.7, 3.9 Hz, 1 H, 4'-H_a), 2.76–2.90 (m_c, 1 H, 3'-H), 2.99 (dd, J = 17.7, 9.6 Hz, 1 H, 4'-H_b), 3.05 (d, J = 17.1 Hz, 1 H, 3-H_a), 3.46 (d, J = 17.1 Hz, 1 H, 3-H_b), 3.72 (s, 3 H, $COOCH_3$), 4.34 (d, J = 3.6 Hz, 1 H, 2'-H), 6.47 (dd, J = 8.4, 0.9 Hz, 1 H, 8-H), 6.52 (dd, J = 8.4, 0.9 Hz, 1 H, 6-H), 7.37 (t, J = 8.4 Hz, 1 H, 7-H), 11.42 (s_{br}, 1 H, 5-OH) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 20.5 (3'-CH_3), 29.6

(C-3'), 36.3 (C-4'), 40.5 (C-3), 53.5 (COO<u>C</u>H$_3$), 84.2 (C-2), 86.4 (C-2'), 107.4 (C-8, C-4a), 110.4 (C-6), 138.8 (C-7), 159.2 (C-8a), 161.8 (C-5), 169.0 (<u>C</u>OOCH$_3$), 175.5 (C-5'), 194.8 (C-4) ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2976, 2955, 1779, 1738, 1639, 1623, 1577, 1466, 1342, 1293, 1201, 1179, 1156, 1048, 1008, 840, 802, 728, 637, 579, 515. **UV** (CH$_3$CN): λ_{max} (lg ε) = 271.0 nm (3.930), 347.0 (3.485). **MS** (ESI): *m*/*z* (%) = 663.2 (100) [2M+Na]$^+$, 343.1 (31) [M+Na]$^+$. Calcd for **C$_{16}$H$_{16}$O$_7$**: 343.0794 [M+Na]$^+$, Found: 343.0796 [M+Na]$^+$ (ESI-HRMS).

Methyl (*S*)-5-Hydroxy-2-[(2*R*,3*R*)-3-methyl-5-oxotetrahydrofuran-2-yl]-4-oxochroman2-carboxylate (*ent*-3d): A solution of BBr_3 (18.5 mL of a 1.0 M solution in CH_2Cl_2, 18.5 mmol, 10.0 eq.) was added slowly to a stirred solution of chromanone **37** (620 mg, 1.85 mmol, 1.00 eq.) in CH_2Cl_2 (90 mL) at –78 °C. Stirring was continued for 30 min at –78 °C before being quenched with sat. aq. $NaHCO_3$ solution (170 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. After column chromatography on silica gel (petroleum ether/EtOAc = 2:1) chromanone ***ent*-3d** was obtained as a pale-yellow foam (492 mg, 1.54 mmol, 83%). **Optical Rotation**: $[\alpha]_D^{23}$ –39.1 (*c* 1.02, $CHCl_3$). **TLC**: R_f = 0.61 (petroleum ether/EtOAc = 1:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.9 Hz, 3 H, 3'-CH_3), 2.20 (dd, *J* = 17.1, 3.9 Hz, 1 H, 4'-H_a), 2.74–2.89 (m_c, 1 H, 3'-H), 2.87 (dd, *J* = 17.1, 9.3 Hz, 1 H, 4'-H_b), 3.01 (d, *J* = 17.1 Hz, 1 H, 3-H_a), 3.17 (d, *J* = 17.1 Hz, 1 H, 3-H_b), 3.70 (s, 3 H, $COOCH_3$), 4.42 (d, *J* = 3.9 Hz, 1 H, 2'-H), 6.51 (d, *J* = 8.4 Hz, 1 H, 8-H), 6.54 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.39 (t, *J* = 8.4 Hz, 1 H, 7-H), 11.41 (s_{br}, 1 H, 5-OH) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 20.8 (3'-CH_3), 29.9 (C-3'), 36.0 (C-4'), 39.7 (C-3), 53.6 (COO<u>C</u>H$_3$), 84.2 (C-2), 87.5 (C-2'), 107.6 (C-4a), 107.6 (C-8), 110.6 (C-6), 139.0 (C-7), 159.1 (C-8a), 161.9 (C-5), 168.8 (<u>C</u>OOCH$_3$), 175.1 (C-5'), 193.9 (C-4) ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2957, 1784, 1738, 1646, 1626, 1579, 1461, 1354, 1228, 1202, 1171, 1051, 1008, 796, 731, 638. **UV** (CH_3OH): λ_{max} (lg ε) = 206.0 nm (4.246), 272.0 (3.945), 349.0 (3.471). **MS** (ESI): *m*/*z* (%) = 663.2 (100) [2M+Na]$^+$, 343.1 (20) [M+Na]$^+$. Calcd for **C$_{16}$H$_{16}$O$_7$**: 343.0794 [M+Na]$^+$, Found: 343.0790 [M+Na]$^+$ (ESI-HRMS).

Synthesis of the dimeric compound 41

Methyl (*S*)-8-Bromo-2-[(1*S*,2*S*)-1-(*tert*-butyldimethylsilyloxy)-4-methoxy-2-methyl-4oxo-butyl]-5-methoxy-4-oxochroman-2-carboxylate (38): *n*Bu_4NBr_3 (145 mg, 301 μmol, 1.02 eq.) was added to a solution of chromanone **31** (142 mg, 295 μmol, 1.00 eq.) in THF/H_2O (1:1, 1.4 mL) at rt and the reaction mixture was stirred for 23 h at rt. After concentration *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 3:1) chromanone **38** was obtained as a colorless oil (150 mg, 268 μmol, 91%).

Optical Rotation: $[\alpha]_D^{25}$ +12.5 (*c* 1.70, $CHCl_3$). **TLC**: R_f = 0.31 (petroleum ether/EtOAc = 2:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 0.10 (s, 3 H, $Si(CH_3)_a$), 0.15 (s, 3 H, $Si(CH_3)_b$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.11 (d, *J* = 6.9 Hz, 3 H, 2'-CH_3), 2.19 (dd, *J* = 16.5, 10.5 Hz, 1 H, 3'-H_a), 2.38–2.53 (m_c, 1 H, 2'-H), 2.88 (d, *J* = 16.2 Hz, 1 H, 3-H_a), 3.23 (dd, *J* = 16.5, 3.0 Hz, 1 H, 3'-H_b), 3.25 (d, *J* = 16.2 Hz, 1 H, 3-H_b), 3.64 (s, 3 H, 2-$COOCH_3$), 3.65 (s, 3 H, 4'-OCH_3), 3.86 (s, 3 H, 5-OCH_3), 4.00 (d, *J* = 2.1 Hz, 1 H, 1'-H), 6.43 (d, *J* = 9.0 Hz, 1 H, 6-H), 7.60 (d, *J* = 9.0 Hz, 1 H, 7-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = –4.2, –3.2 ($Si(CH_3)_2$), 18.5 ($SiC(CH_3)_3$), 19.9 (2'-CH_3), 26.1 ($SiC(\underline{C}H_3)_3$), 32.7 (C-2'), 36.6 (C-3'), 43.1 (C-3), 51.5 (4'-OCH_3), 53.1 (2-$COO\underline{C}H_3$), 56.3 (5-OCH_3), 78.1 (C-1'), 88.4 (C-2), 102.2 (C-8), 105.4 (C-6), 111.8 (C-4a), 139.1 (C-7), 157.8 (C-8a), 159.4 (C-5), 170.2 (2-$\underline{C}OOCH_3$), 173.6 (C-4'), 188.2 (C-4) ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2953, 2931, 1735, 1639, 1587, 1471, 1436, 1315, 1251, 1099, 1054, 832, 776, 734, 528. **UV** (CH_3CN): λ_{max} (lg ε) = 194.0 nm (4.426), 268.0 (3.813), 336.0 (3.592). **MS** (ESI): *m*/*z* (%) = 1141.3 (100) $[2M+Na]^+$, 1063.4 (9) $[2M–Br+Na]^+$, 583.1 (29) $[M+Na]^+$, 561.2 (48) $[M+H]^+$, 481.3 (6) $[M–Br+H]^+$. Calcd for **$C_{24}H_{35}BrO_8Si$**: 581.1182 $[M+Na]^+$, Found: 581.1177 $[M+Na]^+$ (ESI-HRMS).

Dimethyl (2*S*,2'*S*)-2,2'-bis[(1*S*,2*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-2-methyl-4-oxobutyl]-5,5'-dimethoxy-4,4'-dioxo-[8,8'-bichroman]-2,2'-dicarboxylate (39): A solution of chromanone **38** (127 mg, 227 µmol, 1.00 eq.) in THF (8.5 mL) was added to a mixture of $Pd(OAc)_2$ (5.10 mg, 22.7 µmol, 10 mol%), S-Phos (23.3 mg, 56.8 µmol, 25 mol%), Cs_2CO_3 (148 mg, 454 µmol, 2.00 eq.), bis(pinacolato)diboron (115 mg, 454 µmol, 2.00 eq.) and water (16.4 µL, 16.4 mg, 908 µmol, 4.00 eq.) at rt and the reaction mixture was stirred at 50 °C for 21 h. The catalyst was removed by filtration over silica gel (washing with EtOAc) and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 2:1 → 1:1) provided biaryl **39** as a colorless solid (35.0 mg, 36.5 µmol, 32%) and a inseparable mixture of chromanonen **31** and **38** as a pale-yellow oil (77.0 mg, 141 µmol, 62%, **31**:**38** = 1:5). **Optical Rotation**: $[\alpha]_D^{26}$ –24.6 (*c* 0.92, $CHCl_3$). **TLC**: R_f = 0.11 (petroleum ether/EtOAc = 2:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 0.06 (s, 6 H, 2 × $Si(CH_3)_a$), 0.09 (s, 6 H, 2 × $Si(CH_3)_b$), 0.84–0.96 (m, 24 H, 2 × $SiC(CH_3)_3$, 2''-CH_3, 2'''-CH_3), 1.88 (dd, *J* = 16.8, 10.8 Hz, 2 H, 3''-H_a, 3'''-H_a), 2.05–2.22 (m, 2 H, 2''-H, 2'''-H), 2.38 (d, *J* = 16.8 Hz, 2 H, 3''-H_b, 3'''-H_b), 2.87 (dd, *J* = 15.6 Hz, 2 H, 3-H_a, 3'-H_a), 3.25 (d, *J* = 15.6 Hz, 2 H, 3-H_b, 3'-H_b), 3.47 (s, 6 H, 4''-OCH_3, 4'''-OCH_3), 3.63 (s_{br}, 6 H, 2-$COOCH_3$, 2'-$COOCH_3$), 3.85 (d, *J* = 1.8 Hz, 2 H, 1''-H, 1'''-H), 3.92 (s, 6 H, 5-OCH_3, 5'-OCH_3), 6.55 (d, *J* = 9.0 Hz, 2 H, 6-H, 6'-H), 7.54 (d, *J* = 9.0 Hz, 2 H, 7-H, 7'-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = –4.4, –3.4 ($Si(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), 19.1 (2''-CH_3, 2'''-CH_3), 26.1 ($SiC(\underline{C}H_3)_3$), 32.9 (C-2'', C-2'''), 35.7 (C-3'', C-3'''), 43.3 (C-3, C-3'), 51.1 (4''-OCH_3, 4'''-OCH_3), 52.9 (2-$COO\underline{C}H_3$, 2'-$COO\underline{C}H_3$), 56.0 (5-OCH_3, 5'-OCH_3), 78.1 (C-1'', C-1'''), 87.6 (C-2, C-2'), 104.0 (C-6, C-6'), 110.8

(C-4a, C-4a'), 118.0 (C-8, C-8'), 139.4 (C-7, C-7'), 158.7 (C-8a, C-8a'), 159.8 (C-5, C-5'), 171.0 (2-$\underline{C}OOCH_3$, 2'-$\underline{C}OOCH_3$), 173.2 (C-4", C-4'"), 189.1 (C-4, C-4') ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2923, 1728, 1690, 1593, 1572, 1474, 1255, 1166, 1119, 1099, 1039, 827, 772. **UV** (CH_3CN): λ_{max} (lg ε) = 193.0 nm (4.679), 247.0 (4.261), 338.0 (3.818). **MS** (ESI): *m*/*z* (%) = 981.4 (100) $[M+Na]^+$. Calcd for **$C_{48}H_{70}O_{16}Si_2$**: 981.4100 $[M+Na]^+$, Found: 981.4095 $[M+Na]^+$ (ESI-HRMS).

Dimethyl (2*S*,2'*S*)-5,5'-Dimethoxy-2,2'-bis[(2*S*,3*S*)-3-methyl-5-oxotetrahydrofuran-2-yl]4,4'-dioxo-[8,8'-bichroman]-2,2'-dicarboxylate (40): $NEt_3 \cdot 3$ HF (120 µL, 118 mg, 730 µmol, 25.0 eq.) was added to a solution of biaryl **39** (28.0 mg, 29.2 µmol, 1.00 eq.) in 1,4-dioxane (1 mL) at rt and the reaction mixture was stirred at 60 °C for 3 d. After a second addition of $NEt_3 \cdot 3$ HF (120 µL, 118 mg, 730 µmol, 25.0 eq.) stirring was continued for further 4 d at 60 °C before being quenched by carefully addition of sat. aq. $NaHCO_3$ solution (8 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 1:5) furnished compound **40** as a colorless foam (19.0 mg, 28.5 µmol, 98%). **Optical Rotation**: $[\alpha]_D^{25}$ +11.4 (*c* 0.47, $CHCl_3$). **TLC**: R_f = 0.12 (petroleum ether/EtOAc = 1:3). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 7.2 Hz, 6 H, 3"-CH_3, 3'"-CH_3), 1.55–1.86 (m, 4 H, 4"-H_2, 4'"-H_2), 2.47–2.65 (m_c, 2 H, 3"-H, 3'"-H), 2.74 (d, *J* = 15.9 Hz, 2 H, 3-H_a, 3'-H_a), 3.42 (d, *J* = 15.9 Hz, 2 H, 3-H_b, 3'-H_b), 3.60 (s_{br}, 6 H, 2-$COOCH_3$, 2'-$COOCH_3$), 3.90 (s, 6 H, 5-OCH_3, 5'-OCH_3), 4.28 (s_{br}, 2 H, 2"-H, 2'"-H), 6.61 (d, *J* = 8.7 Hz, 2 H, 6-H, 6'-H), 7.13–7.29, 7.43–7.64 (2 × m, 2 H, 7-H, 7'-H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 21.0 (3"-CH_3, 3'"-CH_3), 29.6 (C-3", C-3'"), 35.3 (C-4", C-4'"), 42.3 (C-3, C-3'), 52.5 (2-COO$\underline{C}H_3$, 2'-COO$\underline{C}H_3$), 56.4 (5-OCH_3, 5'-OCH_3), 84.2 (C-2, C-2'), 85.9 (C-2", C-2'"), 104.0 (C-6, C-6'), 110.6 (C-8, C-8'), 118.1 (C-4a, C-4a'), 138.2 (C-7, C-7'), 158.4 (C-8a, C-8a'), 159.6 (C-5, C-5'), 167.9 (2-$\underline{C}OOCH_3$, 2'-$\underline{C}OOCH_3$), 176.9 (C-5", C-5'"), 188.0 (C-4, C-4') ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2958, 1783, 1748, 1684, 1569, 1474, 1254, 1160, 1091, 1011, 749. **UV** (CH_3CN): λ_{max} (lg ε) = 194.0 nm (4.628), 254.0 (4.251), 336.0 (3.899). **MS** (ESI): *m*/*z* (%) = 1355.4 (71) $[2M+Na]^+$, 689.2 (100) $[M+Na]^+$, 667.2 (60) $[2M+H]^+$. Calcd for **$C_{34}H_{34}O_{14}$**: 689.1846 $[M+Na]^+$, Found: 689.1841 $[M+Na]^+$ (ESI-HRMS).

Dimethyl (2*S*,2'*S*)-5,5'-Dihydroxy-2,2'-bis[(2*S*,3*S*)-3-methyl-5-oxotetrahydrofuran-2-yl]4,4'-dioxo-[8,8'-bichroman]-2,2'-dicarboxylate (41): A solution of BBr_3 (590 µL of a 1.0 M solution in CH_2Cl_2, 590 µmol, 19.9 eq.) was added slowly to a stirred solution of biaryl **40** (19.0 mg, 29.7 µmol, 1.00 eq.) in CH_2Cl_2 (3 mL) at –78 °C. The resulting solution was stirred for 30 min at –78 °C before being quenched with sat. aq. $NaHCO_3$ solution (10 mL) at –78 °C. The organic layer was separated and the aqueous layer

was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. After column chromatography on silica gel (petroleum ether/EtOAc = 1:1) biaryl **41** was obtained as a colorless foam (12.7 mg, 19.9 μmol, 67%). **Optical Rotation**: $[\alpha]_D^{24}$ +78.3 (*c* 0.64, $CHCl_3$). **TLC**: R_f = 0.28 (petroleum ether/EtOAc = 1:1). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.9 Hz, 6 H, 3"-CH_3, 3'"-CH_3), 1.82 (dd, *J* = 18.0, 3.6 Hz, 2 H, 4"-H_a, 4'"-H_a), 2.06 (dd, *J* = 18.0, 9.0 Hz, 2 H, 4"-H_b, 4'"-H_b), 2.39–2.57 (m_c, 2 H, 3"-H, 3'"-H), 3.03 (d, *J* = 17.4 Hz, 2 H, 3-H_a, 3'-H_a), 3.59 (d, *J* = 17.4 Hz, 2 H, 3-H_b, 3'-H_b), 3.76 (s_{br}, 6 H, 2-$COOCH_3$, 2'-$COOCH_3$), 4.26 (d, *J* = 3.0 Hz, 2 H, 2"-H, 2'"-H), 6.60 (d, *J* = 8.7 Hz, 2 H, 6-H, 6'-H), 7.47–7.82 (m, 2 H, 7-H, 7'-H), 11.61 (s_{br}, 2 H, 5-OH, 5'-OH) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 20.7 (3"-CH_3, 3'"-CH_3), 29.7 (C-3", C-3'"), 35.4 (C-4", C-4'"), 40.5 (C-3, C-3'), 53.5 (2-COO<u>C</u>H_3, 2'-COO<u>C</u>H_3), 84.9 (C-2, C-2'), 85.9 (C-2", C-2'"), 107.5 (C-4a, C-4a'), 109.9 (C-6, C-6'), 115.0 (C-8, C-8'), 140.8 (C-7, C-7'), 156.4 (C-8a, C-8a'), 161.6 (C-5, C-5'), 168.9 (2-<u>C</u>$OOCH_3$, 2'-<u>C</u>$OOCH_3$), 175.3 (C-5", C-5'"), 195.3 (C-4, C-4') ppm. **IR** (neat): $\tilde{\nu}$ (cm^{-1}) = 2960, 1787, 1748, 1646, 1465, 1343, 1152, 1008, 733. **UV** (CH_3CN): λ_{max} (lg ε) = 196.0 (4.534), 256.0 (4.361), 359.0 (3.756). **MS** (ESI): *m/z* (%) = 1299.3 (100) $[2M+Na]^+$, 661.2 (59) $[M+Na]^+$. Calcd for **$C_{32}H_{30}O_{14}$**: 661.1533 $[M+Na]^+$, Found: 661.1530 $[M+Na]^+$ (ESI-HRMS).

ACKNOWLEDGEMENTS

We thank the Deutsche Forschungsgemeinschaft (DFG), the state of Lower Saxony, the VW-foundation and the Fonds of the Chemical Industry for generous support. S.J. thanks the CaSuS Program and J.R.R. thanks the Konrad Adenauer Stiftung for Ph.D. scholarships, J.H. thanks the Dorothea Schlözer Fellowship Programme and B.G. thanks the Alexander von Humboldt Foundation for postdoctoral scholarships.

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