CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201204037

Enantioselective Total Synthesis of (−)-Diversonol

Lutz F. Tietze,* Stefan Jackenkroll, Christian Raith, Dirk A. Spiegl, Johannes R. Reiner, and Maria Claudia Ochoa Campos[a]

Dedicated to Professor George M. Sheldrick on the occasion of his 70th birthday

Abstract: For the synthesis of (−)-diversonol (*ent*-**1**), an enantioselective domino-Wacker/carbonylation/methoxylation reaction and an enantioselective Wacker oxidation were used to give the chroman in high yield and 96% and 93% *ee*, respectively. Dihydroxylation at the vinyl moiety using the Sharpless procedure and a Wittig–Horner reaction followed by hydrogenation, benzylic oxidation, and an intramolecular acylation provided the tetrahydroxanthenone, from which *ent*-**1** is accessible in a few steps. Furthermore, the synthesis of the diastereomeric diversonol *rac*-1,9a-*epi*-diversonol (*rac*-**41**) is also described.

Keywords: asymmetric catalysis · domino reactions · palladium · total synthesis · Wacker oxidation

Introduction

Diversonol (**1**) is a fungal metabolite and has been isolated from different fungi such as *Penicillium diversum*[1a] and *Microdiplodia sp.*[1b] Its absolute configuration was determined by Krohn et al. using CD-spectroscopy combined with TDDFT ECD calculations[1b] and the first total syntheses of the racemic as well as the enantiopure compound were described by Bräse et al.;[2a,b,c] another access to *rac*-**1** was published by Nicolaou and Li (Figure 1).[2d] The bioactivity of diversonol (**1**) seems to be not very pronounced, since publications on that topic are missing. In contrast, the related dimeric secalonic acids such as **2**, also containing a functionalized tetrahydroxanthenone skeleton,[2a] are of high pharmacological interest due to their antibacterial, cytostatic, and anti-HIV properties.[3]

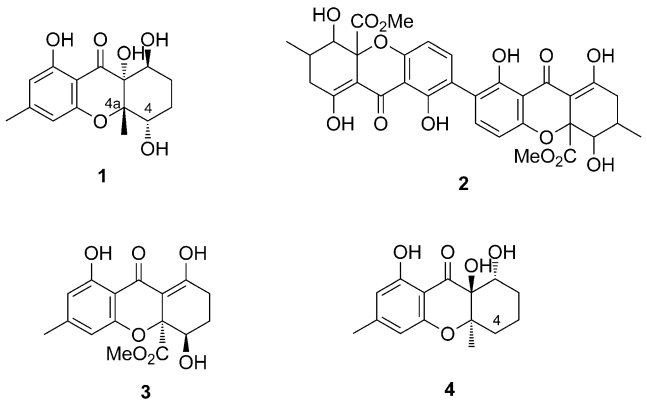

Figure 1. Diversonol (**1**), secalonic acid (**2**), blennolide C (**3**), and 4-dehydroxydiversonol (**4**).

These compounds were originally isolated from *Claviceps purpurea*[4] and their structure was determined by Franck et al.[5] In the corresponding monomeric unit called blennolide C (**3**), which was isolated from *Blennoria sp.*,[6] a methoxycarbonyl moiety at C-4a exists instead of a methyl group as in **1**. However, dimeric compounds as the dicerandrols[7] and phomoxanthones[8] containing a hydroxymethyl or acetoxymethyl group at C-4a are also known.

We have recently published a synthesis of enantiopure 4-dehydroxydiversonol[9] (**4**) by using an enantioselective domino-Wacker/carbonylation/methoxylation reaction. This domino process[10] has also been used for the synthesis of chromans, dioxins and oxazins.[11] Here we describe the total synthesis of enantiopure (−)-diversonol (*ent*-**1**) based on this procedure, which was followed by the introduction of the hydroxyl group at C-4 (numbering as in **1**) employing a Sharpless dihydroxylation. Moreover, also the synthesis of diastereomeric *rac*-1,9a-epidiversonol *rac*-**41** is presented.

Results and Discussion

The retrosynthetic analysis of *ent*-**1** (Scheme 1) leads to the chroman **7** by using the tetrahydroxanthenone **5** and the chromanone **6**. It was assumed by our group that chromanone **6** might be accessible from **7** by hydroxylation at C-2, chain elongation, hydrogenation, and benzylic oxidation. For the synthesis of **7**, we wanted to use the enantioselective domino-Wacker/carbonylation/methoxylation reaction of **8** developed by our group.[9]

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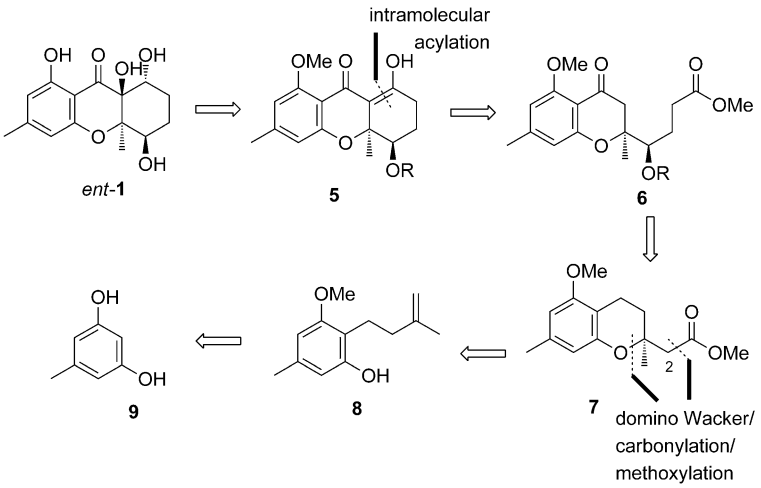
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204037.

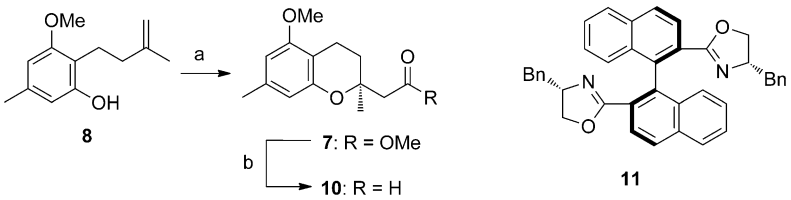


Scheme 1. Retrosynthetic analysis of (−)-diversonol (*ent*-**1**).

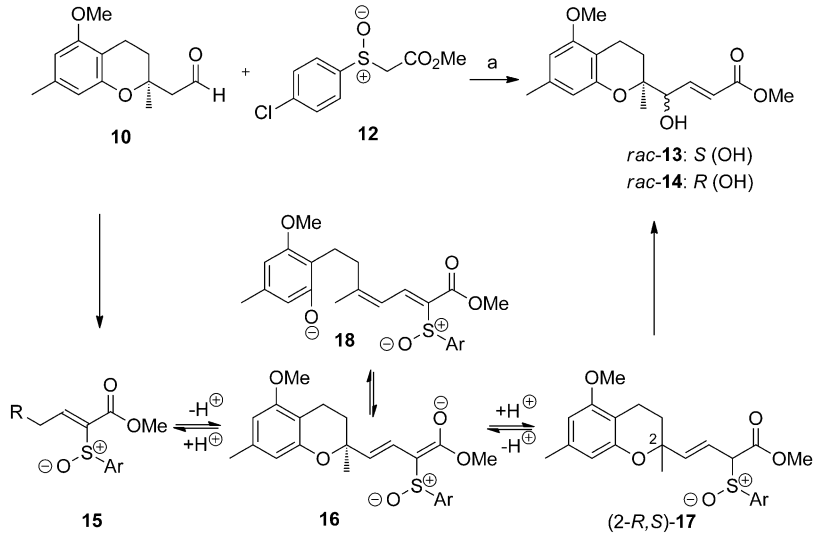
Thus, reaction of **8**, which is easily accessible from orcinol (**9**), with catalytic amounts of palladium(II) trifluoroacetate [$Pd(tfa)_2$] and the Bn-BOXAX ligand[12] (**11**) under a carbon monoxide atmosphere and methanol as solvent gave **7** in 80% yield and with an enantiomeric excess (*ee*) of 96% (Scheme 2). In this process, *p*-benzoquinone was used to oxidize the formed Pd^0 into Pd^{II} needed for the Wacker oxidation.

For the installation of the hydroxy group at C-4 (numbering as in **1**), we first investigated a direct transformation employing a hydroxylating Knoevenagel condensation (Scheme 3).[13] For this purpose, ester **7** was reduced by using diisobutylaluminum hydride (DIBAL) in toluene at −78°C to yield aldehyde **10** in 86% yield, which was then treated with racemic as well as enantiopure sulfinyl acetate **12** and piperidine as base in acetonitrile at room temperature. The reaction proceeded very well to give the two diastereomeric hydroxyl compounds **13** and **14** in a ratio of almost 1:1, in nearly quantitative yield, which could easily be separated by chromatography. Unfortunately, the steric integrity of the stereogenic center in **10** is lost in this process leading to the racemic products *rac*-**13** and *rac*-**14**. We explain this result by assuming an opening of the chroman ring-system to give the intermediate **18**. Thus, condensation of aldehyde **10** with the sulfinyl acetate **12** and piperidine as base probably gives **15**, which stays in an equilibrium with **16** and **18** leading to (2-*R*,*S*)-**17**; 2,3-sigmatropic rearrangement of (2-*R*,*S*)-**17** then affords *rac*-**13** and *rac*-**14**.[14] All attempts to avoid the ring-opening by using different bases and solvents were not successful.

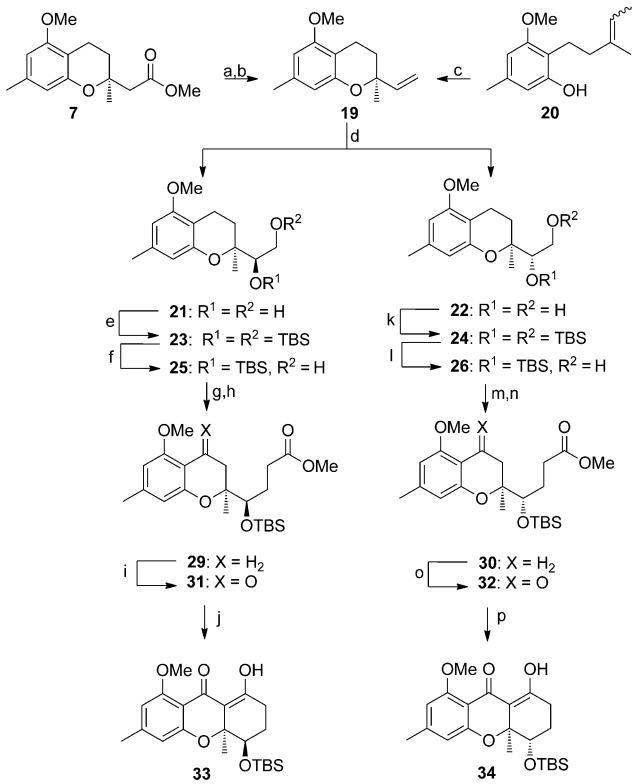
Due to these unexpected difficulties, we revised our synthetic strategy and introduced the necessary hydroxyl group by a Sharpless dihydroxylation[15] of the vinyl chroman **19**[16] (Scheme 4). Compound **19** is accessible from **7** by $LiAlH_4$ reduction of the ester moiety to give the corresponding alcohol with ≥99% *ee* after purification on a chiral IA phase. It followed an elimination using *o*-NO_2-C_6H_4SeCN/*meta*-chloroperbenzoic acid (*m*CPBA).[17] Compound **19** can also be prepared directly by an enantioselective Wacker oxidation of **20** in the presence of the BOXAX



Scheme 2. Synthesis of **10**: a) $[Pd(tfa)_2]$ (3 mol%), (*S*,*S*)-Bn-BOXAX (**11**) (12 mol%), *p*-benzoquinone, CO (1 atm), MeOH, RT, 15 h, 80%, 96% *ee*; b) DIBAL, toluene, −78°C, 45 min, 86%.



Scheme 3. Synthesis of *rac*-**13** and *rac*-**14** and proposed pathway for the racemization by a retro 1,6-Michael addition. a) piperidine, acetonitrile, RT, 7 h, 91%.



Scheme 4. Synthesis of **33** and **34**: a) $LiAlH_4$, Et_2O, 0 °C→RT, 2 h, 98 %; b) 1) nBu_3P, *o*-NO_2-C_6H_4SeCN, THF, RT, 1 h; 2) *m*CPBA, CH_2Cl_2, −40 °C, 1 h, iPr_2NH, −40 °C→RT, 12 h, 98 % (2 steps); c) $[Pd(tfa)_2]$ (10 mol %), (*S*,*S*)-Bn-BOXAX (**11**) (20 mol %), *p*-benzoquinone, MeOH, RT, 22 h, for (*E*)-**20**: 75 %, 93 % *ee*; for (*Z*)-**20**: 79 %, 83 % *ee*; for the *E*/*Z*-mixture (*E*/*Z* = 1:2.4): 78 %, 87 % *ee*; d) AD-mix α, $MeSO_2NH_2$, *t*BuOH/H_2O, RT, 5 d, 93 %, d.r. = 3.8:1; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 2.5 h, 99 %; f) HF·py, RT, 60 h, 70 % (93 % brsm); g) DMP, CH_2Cl_2, 0 °C→RT, 2 h, 95 %; h) 1) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C, 1.5 h; 2) H_2 (4 bar), 10 mol % Pd/C, EtOAc, RT, 15 h, 95 % (2 steps); i) method A: *t*BuOOH, $[Mn(OAc)_3]\cdot 2H_2O$ (40 mol %), EtOAc, MS 3 Å, RT, 4 d, 51 %; method B: 1) DDQ, benzene, heat at reflux, 2 h; 2) $[Mn(dpm)_3]$ (10 mol %), $PhSiH_3$, O_2 (1 atm), EtOH, RT, 4.5 h; 3) MnO_2, CH_2Cl_2, reflux, 4 d, 84 % (3 steps); j) Ti(*i*OPr)Cl_3, NEt_3, CH_2Cl_2, 0 °C, 1 h, 84 %; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 2.5 h, quant.; l) HF·pyridine, THF/pyridine, RT, 52 h, 73 % (98 % brsm); m) DMP, CH_2Cl_2, 0 °C→RT, 2.5 h, 89 %; n) 1) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C, 1.5 h; 2) H_2 (4 bar), 10 mol % Pd/C, EtOAc, RT, 15 h, 98 % (2 steps); o) *t*BuOOH, $[Mn(OAc)_3]\cdot 2H_2O$ (40 mol %), EtOAc, MS 3 Å, RT, 4 d, 42 %; p) Ti(*i*OPr)Cl_3, NEt_3, CH_2Cl_2, 0 °C, 2.5 h, 69 %.

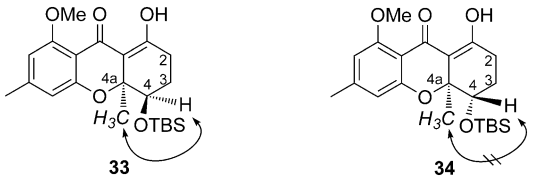
ligand[12] (**11**), but with an *ee* value of only 87 % by using the *E*/*Z* mixture of **20** (*E*/*Z* = 1:2.4) as a substrate, the procedure was less suitable. The enantioselectivity of the Wacker oxidation could be improved to 93 % by employing the pure *E* compound, whereas the *Z* compound gave an *ee* value of 83 %. However, the separation of the *E*/*Z*-mixture of **20** by chromatography is rather tedious and not practicable for larger amounts.

The Sharpless dihydroxylation of vinyl chroman **19** using AD-mix α and methane sulfonamide as additive furnished the diols **21** and **22** as a 3.8:1 mixture of separable diastereomers in 93 % yield. Silylation of **21** with (*tert*-butyldimethylsilyl)methanesulfonate (TBSOTf) to give **23**, which was followed by selective removal of the primary TBS group with HF·pyridine, afforded alcohol **25** in 70 % yield (2 steps, 93 % based on recovered starting material (brsm)). The requisite side-chain was introduced through the corresponding aldehyde by oxidation of **25** with DMP followed by a Wittig–Horner reaction with $(MeO)_2P(O)CH_2CO_2Me$ to provide a 5:1 mixture of the α,β-unsaturated esters (determined by ^1H NMR spectroscopy), which was hydrogenated in the presence of Pd/C to yield chroman **29** in 90 % yield over three steps.

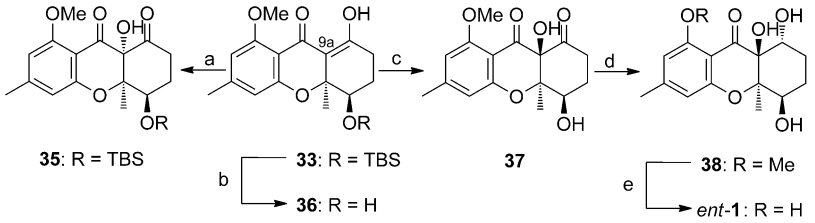
Chroman **29** was then oxidized at the benzylic position upon treatment with excess *tert*-butylhydroperoxide and catalytic amounts of $[Mn(OAc)_3]$ to give the corresponding chromanone **31** in 51 % yield.[18] A similar method employing dirhodium-tetrakiscaprolactamate as the catalyst was less suitable.[19] The preparation of the chromanone **31** could also be performed in a three-step procedure. Starting from **29**, dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) led to the corresponding chromene, which was hydroxylated in the presence of $PhSiH_3$, O_2 and catalytic amounts of $[Mn(dpm)_3]$,[20] and further oxidized with MnO_2 to give **31** in 84 % overall yield. For the intramolecular acylation to provide the desired tetrahydroxanthenone **33**, the chromanone **31** was treated with $TiCl_4$ and NEt_3 in dichloromethane at 0 °C; however, a modest yield of 65 % was obtained. Fortunately, the use of Ti(*i*PrO)Cl_3 increased the yield to 84 %; this could be explained by the formation of a more nucleophilic Ti-enolate.[21] Comparison of **33** with racemic *rac*-**33** by chromatography on a chiral phase gave an *ee* value of ≥ 99 %.

For an entry to the C-4-epimer of (−)-diversonol (*ent-4-epi*-**1**), we transformed **22**, obtained as the minor diastereomer in the Sharpless dihydroxylation of **19**, into the tetrahydroxanthenone **34** through the intermediates **22**, **24**, **26**, **30**, and **32** by using the procedures as described in the synthesis of **33** (Scheme 4).

The relative configuration of the stereogenic centers in **33** and **34** was determined by comparison of the coupling constants. For the *trans*-compound **33**, the coupling constants $J = 1.8$ and 3.9 Hz of the signal at $\delta = 4.02$ ppm for 4-H show that 4-H has an almost synclinal orientation to both hydrogen atoms at C-3; this requires an axial orientation of the OTBS-group. Similar spectroscopic investigations were performed with **34**. From the coupling constants $J = 12.1$ and 4.6 Hz of the signal for 4-H at $\delta = 4.11$ ppm, it can be deduced that the OTBS group in the *cis*-epimer **34** has an equatorial orientation. These results were confirmed by NOE experiments (Scheme 5).



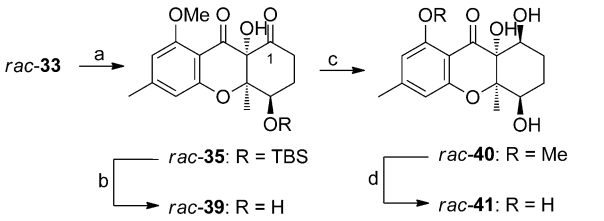
Scheme 5. NOE experiments of **33** and **34**. The excited methyl group is depicted in italic.



Scheme 6. Synthesis of (−)-diversonol (*ent*-**1**): a) IBX, DMSO/H_2O, 60 °C, 12 h, 32 %; b) HF·pyridine, THF, 30 °C, 5 d, 72 % (94 % brsm); c) MMPP, EtOH, 0 °C, 2 h, d.r. = 5:1, 46 %; d) $NaBH_4$, MeOH/CH_2Cl_2, −78 °C, 2 h, 62 %; e) BBr_3, CH_2Cl_2, −78 °C→RT, 5.5 h, 75 %.

Having the enantiopure tetrahydroxanthenone **33** in hand, the stage was set for the introduction of the quaternary hydroxyl group at C-9a to give (−)-diversonol (*ent*-**1**) (Scheme 6). However, hydroxylation of **33** employing magnesium monoperoxyphthalate (MMPP), dimethyldioxirane (DMDO) or *meta*-chloroperbenzoic acid (*m*CPBA) were not successful, whereas the oxidation of **33** with *o*-iodoxybenzoic acid (IBX) in DMSO/water[22] at 60 °C furnished 32 % of the undesired compound **35**. The stereochemical outcome of the transformation seems to be due to the steric bulk of the OTBS group, which forces the oxidation to take place *anti* to the OTBS-group. Therefore, we removed the TBS group in **33** by desilylation using HF·pyridine in THF at 30 °C for 5 d to give **36** in 72 % yield (94 % brsm). Under these conditions, a structural isomerization[2d] of the skeleton was not observed. The obtained compound **36** with a free hydroxyl group at C-4 was then oxidized by using magnesium monoperoxyphthalate (MMPP) in EtOH at 0 °C for 2 h to give the desired dihydroxy compound **37** along with its C-9a epimer in a 5:1 ratio. The reduction of the C-1 carbonyl moiety with $NaBH_4$ in a mixture of MeOH/CH_2Cl_2 to give **38** and cleavage of the aryl methyl ether using BBr_3 at 0 °C in CH_2Cl_2 for 5.5 h afforded the desired enantiopure (−)-diversonol (*ent*-**1**) in 21 % yield over three steps.[2b] The spectroscopic data (^{1}H NMR, ^{13}C NMR and MS) match with those published for the natural diversonol (**1**). Moreover, the structure of the final product has been confirmed by a crystal structure analysis. However, the measured optical rotation with $[\alpha]_D^{22} = -62$ ($c = 0.16$, MeOH) is slightly lower than the published value of $[\alpha]_D^{29} = +70$ ($c = 0.33$, MeOH). Since the BOXAX ligand **11** used in the enantioselective domino Wacker/carbonylation/methoxylation reaction of **8** and in the Wacker oxidation of **20** is easily accessible also in the other enantiomeric form, the described procedure also allows the synthesis of (+)-diversonol (**1**).

Following up our initial observations on the hydroxylation step of **33** and having substantial amounts of the racemic compound *rac*-**33** in hand, we also performed the synthesis of *rac*-**41**, a diastereomer of diversonol (**1**) (Scheme 7). For this purpose, *rac*-**33** was subjected to an IBX oxidation in DMSO/water at 60 °C for 4 h to yield the α-configured hydroxyl compound *rac*-**35** in 49 % yield.[22,23] Since the necessary reduction of the carbonyl group at C-1 in *rac*-**35** was not possible, probably due to a steric shielding of both of its faces, we removed the TBS group by using HF·pyridine, which was followed by the reduction of the carbonyl moiety with $NaBH_4$ in a mixture of MeOH/CH_2Cl_2; by this method *rac*-**40** was obtained in 31 % yield over two steps. The final cleavage of the aryl methyl ether using BBr_3 in dichloromethane at 0 °C for 48 h afforded *rac*-1,9a-*epi*-diversonol (*rac*-**41**) in 47 % yield (Scheme 7).



Scheme 7. Synthesis of *rac-epi*-1,9a-diversonol *rac*-**41**: a) IBX, DMSO/H_2O, 60 °C, 4 h, 49 %; b) HF·pyridine, THF/pyridine, 50 °C, 60 h, 43 %; c) $NaBH_4$, MeOH/CH_2Cl_2, −78 °C, 2 h, 71 %; d) BBr_3, CH_2Cl_2, −78 °C→0 °C, 48 h, 47 %.

Conclusion

We have developed a new enantioselective procedure for the total synthesis of (−)-diversonol (*ent*-**1**) and its diastereomer *rac*-**41**. Key steps are an enantioselective Pd-catalyzed domino Wacker/cabonylation/methoxylation reaction of **8** and an enantioselective Wacker oxidation of **20**, respectively.

Experimental Section

Synthesis of 19, 31, 33, 35, 41 and (−)-1: The syntheses of all other new compounds including spectroscopic data can be found in the Supporting Information.

(*S*)-5-Methoxy-2,7-dimethyl-2-vinylchroman (19): A solution of $[Pd(tfa)_2]$ (7.8 mg, 23.6 μmol, 10 mol %) and (*S*,*S*)-Bn-BOXAX (**11**) (27.0 mg, 47.2 μmol, 20 mol %) in MeOH (0.5 mL) was stirred at room temperature for 15 min. After addition of a solution of phenol (*E*)-**20** (52.0 mg, 0.236 mmol, 1.00 equiv) in MeOH (1 mL) and *p*-benzoquinone (102 mg, 0.944 mmol, 4.00 equiv) stirring was continued at room temperature for 22 h. The mixture was poured into 1 N HCl (20 mL) and extracted with methyl *tert*-butyl ether (MTBE) (4 × 10 mL). The combined extracts were washed with 1N NaOH (3 × 10 mL) and dried over Na_2SO_4. After evaporation of the solvent in vacuo and column chromatography on silica gel (petroleum ether/EtOAc = 100:1→70:1) vinylchroman **19** was obtained as a yellowish oil (38.4 mg, 0.176 mmol, 75 %, 93 % *ee*). Analytical HPLC (column: Daicel Chiralcel OD): 250 × 4.6 mm, 5 μm, $\lambda = 275$ nm, flow: 0.8 mL min^{-1}, eluent: *n*-hexane/isopropanol 99.5:0.5, $t_R = 10.1$ ((−)-**19**), 11.9 min ((+)-**19**). *Z*-**20** and the *E*/*Z*-mixture of **20** (*E*/*Z* = 1:2.4) were also converted to **19** using the described procedure. For *Z*-**20**: (79 %, 83 % *ee*) and for the *E*/*Z*-mixture of **20**: (78 %, 87 % *ee*). $[\alpha]_D^{23} = -55.7$ ($c = 0.50$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 3H, 2′-CH_3), 1.76 (ddd, $J = 13.5$, 9.8, 5.9 Hz, 1H, 3′-H_a), 1.90 (ddd, $J = 13.5$, 6.1, 5.0 Hz,

1H, 3′-H_b), 2.28 (s, 3H, 7′-CH_3), 2.44 (ddd, J=16.7, 9.8, 6.0 Hz, 1H, 4′-H_a), 2.65 (dt, J=17.0, 5.4 Hz, 1H, 4′-H_b), 3.78 (s, 3H, 5′-OCH_3), 5.05 (dd, J=10.8, 1.3 Hz, 1H, 2-H_{cis}), 5.17 (dd, J=17.3, 1.3 Hz, 1H, 2-H_{trans}), 5.85 (dd, J=17.3, 10.8 Hz, 1H, 1-H), 6.22 (s, 1H, 6′-H), 6.36 (s, 1H, 8′-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.7 (C-4′), 21.6 (7′-CH_3), 26.8 (2′-CH_3), 31.3 (C-3′), 55.3 (5′-OCH_3), 76.2 (C-2′), 102.7 (C-8′), 107.3 (C-4a′), 110.1 (C-6′), 113.6 (C-2), 136.9 (C-7′), 141.4 (C-1), 154.4, 157.5 (C-5′, C-8a′) ppm. IR (film): $\tilde{\nu}$=3082, 2952, 2927, 1615, 1583, 1459, 1409, 1350, 1261, 1229, 1209, 1126, 1091, 1023, 1013, 923, 814, 583 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lg ε)=208 (4.6293), 273 (2.9367), 280 (2.9163), 333 nm (2.247); MS (ESI): m/z (%): 241.1 (33) $[M+Na]^+$, 219.1 (100) $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{14}H_{18}O_2$ (218.29): 219.1380 $[M+H]^+$; found: 219.1378 (ESI-HRMS).

Methyl (*R*)-4-(*tert*-butyldimethylsilyloxy)-4-[(*S*)-5-methoxy-2,7-dimethyl-4-oxochroman-2-yl]butanoate (31): *Method A*: A mixture of chroman **29** (1.32 g, 3.12 mmol, 1.00 equiv), *tert*-butyl hydroperoxide (2.95 mL of a 5.5 M solution in decane, 16.2 mmol, 5.20 equiv) and powdered molecular sieves 3 Å (1.2 g) in EtOAc (20 mL) was stirred at room temperature for 30 min. Then $[Mn(OAc)_3]\cdot 2H_2O$ (86 mg, 0.312 mmol, 10 mol%) was added and stirring continued for four days; additional $Mn(OAc)_3\cdot 2H_2O$ (86 mg, 0.312 mmol, 10 mol%) and *tert*-butyl hydroperoxide (0.57 mL, 3.12 mol, 1.00 equiv) were added after 24, 48, and 72 h. Thereafter, the mixture was filtered over silica gel (eluting with EtOAc). Concentration in vacuo and column chromatography on silica gel (petroleum ether/EtOAc 30:1→1:1) furnished chromanone **31** as a yellow oil (701 mg, 1.60 mmol, 51%).

Method B: A solution of **29** (107 mg, 0.253 mmol, 1.00 equiv) in benzene (10 mL) was treated with DDQ (115 mg, 0.507 mmol, 2.00 equiv) and heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature and filtrated over silica gel (eluting with EtOAc). Evaporation of the solvent in vacuo and column chromatography on silica gel (petroleum ether/EtOAc=30:1→10:1) furnished the corresponding chromene as a colorless oil (101 mg, 0.240 mmol, 95%). A solution of the chromene (103 mg, 0.245 mmol, 1.00 equiv) in CH_2Cl_2 (6.1 mL) was treated with $[Mn(dpm)_3]$ (15 mg, 24.8 μmol, 10 mol%) and $PhSiH_3$ (125 μL, 106 mg, 0.98 mmol, 4.00 equiv). Oxygen was passed through the resulting mixture for 5 min before being stirred under an O_2 atmosphere at room temperature for further 4.5 h. Addition of silica gel, evaporation of the solvent and column chromatography on silica gel (*n*-hexane/EtOAc=9:1→1:1) provided chromanone **31** and the corresponding diastereomeric alcohols, which were oxidized by adding MnO_2 (48 mg, 0.49 mmol, 2.00 equiv) to the alcohol mixture in CH_2Cl_2 (12 mL). The resulting mixture was heated at reflux for four days (not at night). Additional MnO_2 (48 mg, 0.49 mmol, 2.00 equiv) was added every 3 h (4 additions per day) with a total amount of 1.92 g (19.6 mmol, 80 equiv) of MnO_2. After filtration over silica gel (eluting with EtOAc), evaporation of the solvent and column chromatography on silica gel (*n*-hexane/EtOAc=9:1→1:1), (94.7 mg, 0.217 mmol, 88%) of the combined chromanone **31** were obtained as a colourless oil. $[\alpha]_D^{25}=-19.4$ (c=0.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.04 (s, 3H, $Si(CH_3)_a$), 0.10 (s, 3H, $Si(CH_3)_b$), 0.84 (s, 9H, $SiC(CH_3)_3$), 1.27 (s, 3H, 2′-CH_3), 1.50–1.63 (m, 1H, 3-H_a), 1.82–1.93 (m, 1H, 3-H_b), 2.28 (s, 3H, 7′-CH_3), 2.31 (d, J=16.1 Hz, 1H, 3′-H_a), 2.29–2.57 (m, 2H, 2-H_a, 2-H_b), 3.11 (d, J=16.0 Hz, 1H, 3′-H_b), 3.66 (s, 3H, 1-OCH_3), 3.82 (dd, J=9.3, 3.0 Hz, 1H, 4-H), 3.86 (s, 3H, 5′-OCH_3), 6.25 (s, 1H, Ar-H), 6.27 (s, 1H, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=−4.5, −3.6 ($Si(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), 19.9 (2′-CH_3), 22.5 (7′-CH_3), 26.1 ($SiC(CH_3)_3$), 27.4 (C-3), 30.8 (C-2), 43.1 (C-3′), 51.6 (1-OCH_3), 56.0 (5′-OCH_3), 76.5 (C-4), 83.7 (C-2′), 104.4, 110.8 (C-6′, C-8′), 108.3 (C-4a′), 147.3 (C-7′), 160.0, 160.7 (C-5′, C-8a′), 173.6 (C-1), 190.9 (C-4′) ppm; IR (film): $\tilde{\nu}$=2953, 2930, 2855, 1737, 1682, 1613, 1568, 1463, 1416, 1351, 1250, 1221, 1169, 1142, 1104, 1081, 996, 833, 776 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lg ε)=194 (4.3426), 221 (4.2539), 269 (3.9905), 325 nm (3.5392); MS (ESI): m/z (%)=895.4 (100) $[2M+Na]^+$, 459.2 (17) $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{23}H_{36}O_6Si$ (436.61): 459.2173 $[M+Na]^+$; found: 459.2168.

(4*R*,4a*S*)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-8-methoxy-4a,6-dimethyl-2,3,4,4a-tetrahydroxanthen-9-one (33): $TiCl_4$ (2.86 mL of a 1.0 M solution in CH_2Cl_2, 2.86 mmol, 2.60 equiv) was added slowly to $Ti(OiPr)_4$ (286 μL, 272 mg, 0.95 mmol, 0.87 equiv) in CH_2Cl_2 (5 mL) at 0 °C and the resulting mixture stirred for 15 min at 0 °C; on the other hand, NEt_3 (426 μL, 311 mg, 3.08 mmol, 2.8 equiv) was added to a solution of chromanone **31** (480 mg, 1.10 mmol) in CH_2Cl_2 (22 mL) at 0 °C. Subsequently, the solution of $Ti(OiPr)Cl_3$ was transferred slowly through a transfer cannula to the solution of **31**, and the resulting solution was stirred at 0 °C for further 60 min (TLC monitoring) before being quenched with water (100 mL). The aqueous layer was extracted with EtOAc (6×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography on silica gel (*n*-hexane/EtOAc 9:1 → 5:1) yielded tetrahydroxanthenone **33** as a pale yellow solid (373 mg, 0.92 mmol, 84%). Optical rotation: $[\alpha]_D^{25}=-78.8$ (c=0.50, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.00 (s, 3H, $Si(CH_3)_a$), 0.13 (s, 3H, $Si(CH_3)_b$), 0.83 (s, 9H, $SiC(CH_3)_3$), 1.37 (s, 3H, 4a-CH_3), 1.87–1.96 (m, 2H, 3-H_a, 3-H_b), 2.24 (ddd, J=18.7, 5.8, 1.9 Hz, 1H, 2-H_a), 2.30 (s, 3H, 6-CH_3), 2.74 (ddd, J=18.9, 11.0, 8.0 Hz, 1H, 2-H_b), 3.91 (s, 3H, 8-OCH_3), 4.03 (dd, J=3.8, 1.9 Hz, 1H, 4-H), 6.28 (s, 1H, Ar-H), 6.30 (s, 1H, Ar-H), 16.22 (s, 1H, 1-OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.0, −4.2 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 22.4 (6-CH_3), 25.7 (4a-CH_3), 25.8 (C-3, $SiC(CH_3)_3$), 26.4 (C-2), 56.1 (8-OCH_3), 71.3 (C-4), 80.1 (C-4a), 105.1, 111.0 (C-5, C-7), 105.6 (C-9a), 107.0 (C-8a), 146.8 (C-6), 159.8, 160.4 (C-8, C-10a), 180.6 (C-9), 182.2 (C-1) ppm; IR (film) $\tilde{\nu}$=2953, 2926, 2851, 1604, 1460, 1406, 1356, 1245, 1225, 1199, 1110, 1085, 995, 877, 834, 818, 772, 723, 683, 638 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lg ε)=198 nm (4.2799), 281 (3.4838), 332 (4.0611); MS (ESI): m/z (%): 1235.6 (46) $[3M+Na]^+$, 831.4 (100) $[2M+Na]^+$, 427.2 (36) $[M+Na]^+$, 405.2 (14) $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{22}H_{32}O_5Si$ (404.57): 427.1911 $[M+Na]^+$; found: 427.1911.

(−)-Diversonol (*ent*-**1**): A solution of enantiopure **36** (33.0 mg, 0.114 mmol, 1.00 equiv) in EtOH (6.5 mL) was treated with MMPP (80%, 39.0 mg, 63.1 μmol, 0.55 equiv) at 0 °C and stirred for 2 h at 0 °C. The reaction was quenched by addition of silica gel (1.5 g) at 0 °C before being concentrated in vacuo at 0 °C. Filtration over silica gel (eluting with petroleum ether/EtOAc=1:4) and purification by RP-HPLC with water (A), MeOH (B) as the eluent (Jasco Kromasil 100 C18, 250×20 mm, 7 μm, gradient: 0–30 min: 70A/30B→50A/50B, 30–40 min: 50A/50B→ 0 A/B100, 40–50 min: 0A/100B→70 A/30B, flow: 18 mL min^{-1}, λ=284 nm, t_R=20.4 min) yielded diketone **37** as a white solid (16.0 mg, 52.2 μmol, 46%, diastereomeric ratio (d.r.)=5:1). A solution of **37** (15.3 mg, 49.9 μmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) and MeOH (0.5 mL) was treated with powdered $NaBH_4$ (1.9 mg, 49.9 μmol, 1.00 equiv) at −78 °C for 1.5 h. Additional $NaBH_4$ (0.6 mg, 15.9 μmol, 0.32 equiv) was added at −78 °C and stirring continued for 30 min at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) at −78 °C and the mixture poured into EtOAc (10 mL). The aq. layer was extracted with EtOAc (5×4 mL) and the combined organic layers were dried over Na_2SO_4. Purification by RP-HPLC with water (A), MeOH (B) as the eluent (Jasco Kromasil 100 C18, 250×20 mm, 7 μm, gradient: 0–30 min: 70A/30B→50A/50B, 30–40 min: 50A/50B→0 A/B100, 40–50 min: 0A/100B→70 A/30B, flow: 18 mL min^{-1}, λ=284 nm, t_R=23.1 min) yielded **38** as a white solid (9.5 mg, 30.8 μmol, 62%). BBr_3 (0.31 mL of a 1 M solution in CH_2Cl_2, 0.31 mmol, 10.1 equiv) was added slowly to a solution of **38** (9.5 mg, 30.8 μmol, 1.00 equiv) in CH_2Cl_2 (2 mL) at −78 °C. The resulting red solution was stirred for 30 min at −78 °C, 1.5 h at 0 °C and 3.5 h at room temperature before being quenched with water (10 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. Purification by RP-HPLC with water (A), MeOH (B) as the eluent (Jasco Kromasil 100 C18, 250×20 mm, 7 μm, gradient: 0–30 min: 70 A/30B→50A/50B, 30–40 min: 50A/50B→0A/B100, 40–50 min: 0A/100B→70A/30B, flow: 18 mL min^{-1}, λ=284 nm, t_R=29.9 min) furnished (−)-diversonol (*ent*-**1**) as a white solid (6.8 mg, 23.1 μmol, 75%). $[\alpha]_D^{22}=-62.0$ (c=0.16, $CHCl_3$); ^{1}H NMR (600 MHz, $[D_6]$DMSO): δ=1.40 (s, 3H, 4a-CH_3), 1.46 (d, J=14.2 Hz, 1H, 2-H_a), 1.69 (d, J=14.2 Hz, 1H, 3-H_a), 1.97 (tdd, J=14.2, 4.4, 2.4 Hz, 1H, 3-H_b), 2.17 (ddd, J=17.2, 8.7, 3.4 Hz, 1H, 2-H_b), 2.25 (s, 3H, 6-CH_3), 3.99 (brs, 1H, 1-H), 4.29 (brs, 1H, 4-H), 4.95 (brs, 1H, OH), 6.29 (s, 1H, 5-H), 6.31 (s, 1H, 7-H), 6.59 (brs, 1H, OH), 11.29 (brs, 1H, OH) ppm; ^{13}C NMR (125 MHz, $[D_6]$DMSO): δ=19.4 (4a-CH_3), 21.9 (6-CH_3), 22.6 (C-2), 24.8 (C-3), 66.2 (C-4), 73.3 (C-1), 75.5 (C-4a), 81.0 (C-9a), 104.4 (C-8a), 108.5 (C-5),

108.8 (C-7), 149.1 (C-6), 158.3 (C-10a), 161.5 (C-8), 194.0 (C-9) ppm; IR (film): $\tilde{\nu}$ = 3554, 3358, 2978, 2942, 2879, 1655, 1630, 1570, 1439, 1387, 1352, 1327, 1252, 1197, 1093, 1056, 1022, 998, 883, 850, 829, 722, 675, 606, 575, 529 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lg ε) = 196 (4.2362), 210 (4.1737), 282 (3.9576), 379 nm (4.3401); MS (ESI): *m/z* (%) = 611.2 (100) $[2M+Na]^+$, 317.1 (100) $[M+Na]^+$, 295.1 (13) $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{15}H_{18}O_6$ (294.30): 317.0995 $[M+Na]^+$; found: 317.0996.

(4*R*,4a*R*,9a*S*)-4-(*tert*-Butyldimethylsilyloxy)-9a-hydroxy-8-methoxy-4a,6-dimethyl-2,3,4,4a-tetrahydro-1*H*-xanthene-1,9(9a*H*)-dione (35) and (*rac*-35): *Synthesis of* **35**: Water (1.2 mL) and tetrahydroxanthenone 33 (325 mg, 0.803 mmol, 1.00 equiv) was added to a solution of IBX (536 mg, 2.01 mmol, 2.50 equiv) in DMSO (3.8 mL) and the resulting mixture heated at 60 °C for 9 h. Additional IBX (112 mg, 0.402 mmol, 0.50 equiv) was added at room temperature and stirring was continued for 3 h at 60 °C. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL) and stirred vigorously for 30 min. The precipitate was removed by filtration, washed with CH_2Cl_2 (4 × 50 mL) and the combined organic phases were treated with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were washed with brine (1 × 100 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo and column chromatography on silica gel (petroleum ether/EtOAc = 4:1) furnished **35** as a white solid (109 mg, 0.259 mmol, 32 %).

Synthesis of ***rac*-35**: Compound *rac*-**35** was prepared according to the procedure described for enantiopure **35** by using freshly prepared IBX[23] with 49 % yield and a decreased reaction time of 4 h. Optical rotation of **35**: $[\alpha]_D^{23} = +5.9$ (c = 0.50, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = −0.07 (s, 3H, $Si(CH_3)_a$), 0.07 (s, 3H, $Si(CH_3)_b$), 0.80 (s, 9H, $SiC(CH_3)_3$), 1.26 (s, 3H, 4a-CH_3), 1.91–1.96 (m, 1H, 3-H_a), 2.12–2.20 (m, 1H, 3-H_b), 2.28 (s, 3H, 6-CH_3), 2.67 (m_c, 1H, 2-H_a), 2.74 (m_c, 1H, 2-H_b), 3.86 (s, 3H, 8-OCH_3), 4.18 (dd, J = 7.8, 3.6 Hz, 1H, 4-H), 4.65 (s, 1H, OH), 6.27 (s, 1H, Ar-H), 6.35 (s, 1H, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = −5.0, −4.6 ($Si(CH_3)_2$), 17.0 (6-CH_3), 18.1 ($SiC(CH_3)_3$), 22.5 (6-CH_3), 25.7 ($SiC(CH_3)_3$), 28.8 (C-2), 34.2 (C-2), 56.0 (8-OCH_3), 73.1 (C-4), 79.7 (C-4a), 86.6 (C-9a), 104.5, 110.6 (C-5, C-7), 107.1 (C-8a), 148.0 (C-6), 160.2, 161.0 (C-8, C-10a), 187.7 (C-9), 206.7 (C-1) ppm; IR (film): $\tilde{\nu}$ = 3432, 2928, 2852, 1718, 1683, 1618, 1575, 1466, 1414, 1387, 1360, 1248, 1224, 1128, 1088, 992, 892, 859, 834, 816, 783, 710, 595 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lg ε) = 195 (4.3334), 221 (4.1939), 276 (3.9978), 330 nm (3.4935); MS (ESI): *m/z* (%): 863.5 (100) $[2M+Na]^+$, 443.2 (74) $[M+Na]^+$, 421.3 (12) $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{32}O_6Si$ (420.57): 443.1860 $[M+Na]^+$; found: 443.1859.

(1*S*,4*R*,4a*R*,9a*R*)-1,4,8,9a-Tetrahydroxy-4a,6-dimethyl-2,3,4,4a-tetrahydro-1*H*-xanthen-9(9a*H*)-one (*rac*-41): BBr_3 (0.26 mL of a 1.0 M solution in CH_2Cl_2, 260 μmol, 10 equiv) was added slowly to a solution of methyl ether *rac*-**40** (8.0 mg, 26 μmol, 1.00 equiv) in CH_2Cl_2 (2 mL) at −78 °C. The resulting orange solution was stirred for 45 min at −78 °C and for 48 h at 0 °C before being quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. Column chromatography on silica gel (CH_2Cl_2/EtOAc 1:1) provided pure *rac*-**41** (3.6 mg, 47 %). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 1.46 (dq, J = 12.4, 3.7 Hz, 1H, 3-H_a), 1.54 (dq, J = 13.7, 2.8 Hz, 1H, 2-H_a), 1.87 (tt, J = 14.0, 3.3 Hz, 1H, 2-H_b), 2.11 (dq, J = 14.3, 3.1 Hz, 1H, 3-H_b), 2.22 (s, 3H, 6-CH_3), 3.56 (ddd, J = 11.7, 7.2, 4.1 Hz, 1H, 4-H), 3.61 (dt, J = 5.4, 2.8 Hz, 1H, 1-H), 4.64 (d, J = 5.2 Hz, 1H, 1-OH), 4.67 (d, J = 7.4 Hz, 1H, 4-OH), 5.67 (s, 1H, 9a-OH), 6.20 (s, 1H, 5-H), 6.22 (s, 1H, 7-H), 11.49 (s, 1H, 8-OH) ppm; ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 16.9 (4a-CH_3), 21.9 (6-CH_3), 24.4 (C-3), 27.9 (C-2), 70.6 (C-4), 71.4 (C-1), 76.4, 83.0 (C-4a, C-9a), 106.9 (C-8a), 107.7, 108.6 (C-5, C-7), 149.1 (C-6), 159.8, 160.2 (C-8, C-10a), 201.8 (C-9) ppm; IR (film): $\tilde{\nu}$ = 3311, 2945, 2921, 1643, 1569, 1449, 1358, 1193, 1141, 1104, 1068, 1014, 983, 939, 876, 837, 717, 661, 585 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lg ε) = 195 (4.2831), 210 (4.2455), 282 (4.0008), 348 nm (3.4131); MS (ESI): *m/z* (%): 611.2 (31) $[2M+Na]^+$, 317.1 (100) $[M+Na]^+$; HRMS (ESI): $C_{16}H_{20}O_6$ (294.30): calcd: 317.0996; found: 317.1001 $[M+Na]^+$.

Acknowledgements

The work was supported by Deutsche Forschungsgemeinschaft (DFG), Land Niedersachsen and Volkswagenstiftung. We thank Prof. A. M. Echavarren for valuable discussions. S.J. thanks the CaSuS Program for a Ph.D. scholarship. C.R. thanks the Stiftung Stipendienfonds des Verbandes der Chemischen Industrie (VCI) for a Ph.D. scholarship. J.R.R thanks the Konrad Adenauer Stiftung for a Ph.D. scholarship. Generous gifts of chemicals by Bayer AG, BASF SE, and Wacker Chemie AG are greatly appreciated.

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Received: November 11, 2012
Published online: February 18, 2013

