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Syntheses of retipolide E and ornatipolide, 14-membered biaryl-ether macrolactones from mushrooms

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Abstract—Two approaches for the total synthesis of the spiromacrolide retipolide E (**5**) are described, the first using a modified Mitsunobu reaction as key step for the formation of the strained 14-membered macrolactone, the second a nucleophilic aromatic substitution (S_NAr). In the first approach an α-oxomacrolactone **15** was obtained, which could either be converted into ornatipolide (**6**) or further transformed into racemic retipolide E [(*R*,*S*)-**5**] by directed aldol condensation with a methyl arylpyruvate. The second approach allowed the synthesis of either racemic or enantiomerically pure retipolide E (**5**). In the latter case Evans' methodology was used for the introduction of stereogenic center via stereoselective alkylation. The oxazolidinone auxiliary was removed under mild conditions by exchange for 2-arylethanol **22** with Otera's distannoxane catalyst. Synthetic retipolide E allowed the identification of this biosynthetic intermediate in the fruit bodies of the North American mushroom *Retiboletus retipes*.

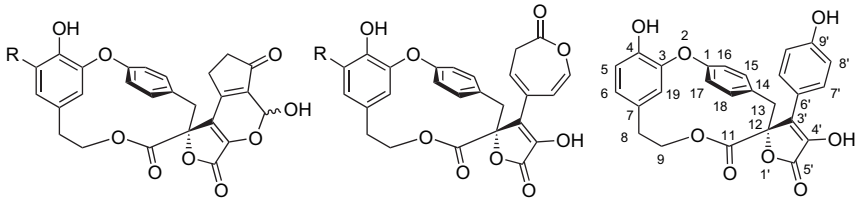
1. Introduction

Fruit bodies of the North American mushrooms *Retiboletus retipes* (Berk. & Curtis) Binder and Bresinsky and *Retiboletus ornatipes* (Peck) Binder and Bresinsky[1] contain several closely related macrolactones, named retipolides A–D (**1**–**4**).[2,3] The major compound, retipolide A, is responsible for the yellow color and bitter taste of these mushrooms. Its absolute (*R*)-configuration has been unambiguously assigned by X-ray analysis of a suitable derivative.[2] The structures of the retipolides suggest a common origin from a hitherto hypothetical 4-hydroxyphenyl analog, retipolide E (**5**), which could undergo oxidative ring enlargement to retipolide C (**3**), followed by rearrangement into retipolide A (**1**).[3] For the identification of the proposed precursor **5** in the fungal extract, we decided to synthesize racemic retipolide E as a reference compound for chromatographic comparison.

2. Results and discussion

2.1. Retrosynthetic considerations

Our first synthetic approach is based on the idea that the spiro system of retipolide E (**5**) could be obtained by aldol condensation of a suitably protected 14-membered α-oxomacrolide **A** with an *O*-protected methyl 3-(4-hydroxyphenyl)pyruvate **B** (Scheme 1). A possible pathway for the synthesis of oxomacrolide **A** is the cyclization of a suitable hydroxy acid **C**.[4] Alternatively, the macrocyclic ring could be closed at the diaryl ether linkage by intramolecular nucleophilic aromatic substitution of an adequate precursor **D**, which is accessible by transesterification of methyl ester **E** with a suitable 2-arylethanol derivative. This approach could be adapted for the synthesis of (*R*)-retipolide E (**5**), if enantiomerically pure butenolide **E** is used as starting material.



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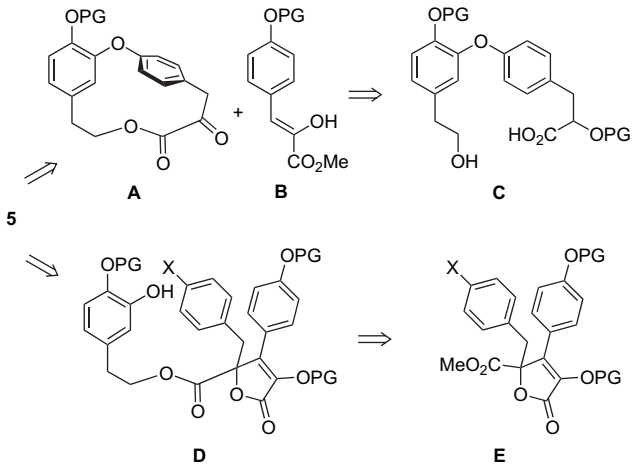
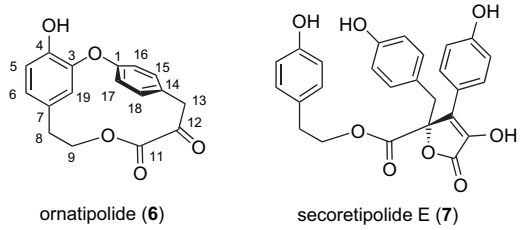


Scheme 1. Retrosynthesis of retipolide E (**5**).

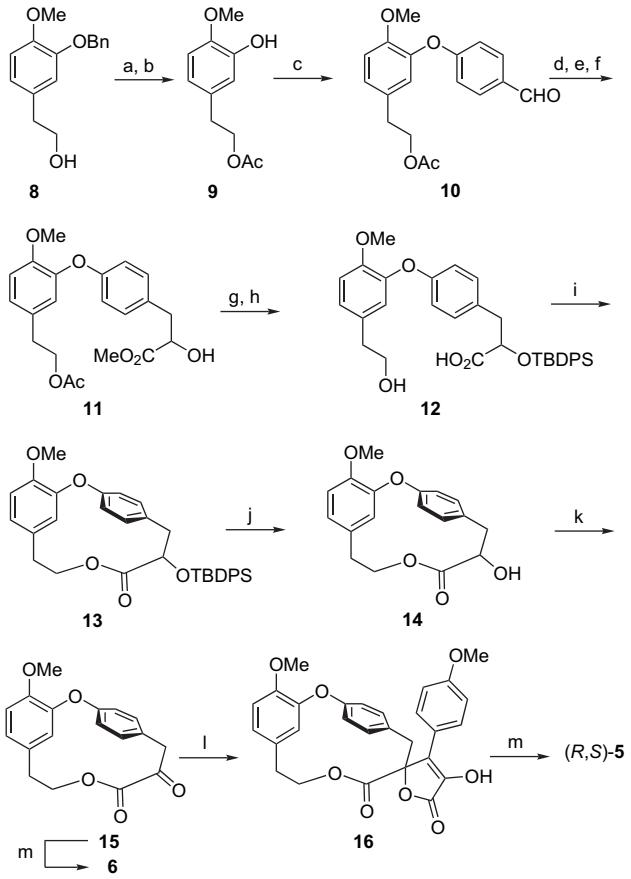
Interestingly, the free phenol corresponding to macrolide **A**, named ornatipolide (**6**), has been isolated from a Japanese collection of *R. ornatipes*,[5] and secoretipolide E (**7**), a compound resembling ester **D**, has been detected in the methanol extract of *R. retipes*.[2] The biosynthetic relevance of these findings remains to be investigated.



2.2. Synthesis of ornatipolide (6) and (*R*,*S*)-retipolide E [(*R*,*S*)-5] via macrolactonization

Our first approach started from the known 2-(3-benzyloxy-4-methoxyphenyl)ethanol (**8**),[6] which was converted in two steps into acetate **9** (Scheme 2). Copper-catalyzed coupling of the latter with 4-bromobenzaldehyde yielded the biphenyl ether aldehyde **10**, which was used for the introduction of the hydroxy acid side chain by Darzens' methodology. Reaction of aldehyde **10** with methyl chloroacetate under basic conditions gave the corresponding glycidic ester, which was acetylated to reintroduce the O-protecting group and subsequently hydrogenolyzed at the benzylic position to afford hydroxy ester **11** in 41% yield without isolation of the intermediates. After protection of the hydroxy group with *tert*-butyldiphenylchlorosilane (TBDPS-Cl) and hydrolysis of the ester groups, the resulting hydroxy acid **12** was obtained ready for macrocyclization.

As has already been observed with a simpler analog,[4] most of the popular methods for the macrocyclization to the 14-membered lactone failed and delivered only the corresponding diolide. In contrast, our modified Mitsunobu procedure[4] afforded the desired macrolide **13** in 55% yield. This could be further improved to 73% by simultaneously adding all the constituents (DEAD, PPh_3, and hydroxy acid **12**) as toluene solutions within 6 h to a toluene solution of DEAD in PPh_3. In this case the reaction was performed on a 2.14 mmol scale reaching a 0.0015 M end concentration. On scaling up to 10 mmol



Scheme 2. Synthesis of (*R*,*S*)-retipolide E [(*R*,*S*)-**5**] by macrolactonization. Reagents and conditions: (a) Ac_2O, pyridine; (b) H_2, Pd/C, 77% (2 steps); (c) 4-bromobenzaldehyde, CuO, 82%; (d) $ClCH_2CO_2Me$, NaOMe, MeOH; (e) Ac_2O, pyridine; (f) H_2, Pd/C, 41% (3 steps); (g) TBDPS-Cl, imidazole, DMAP; (h) LiOH, THF, H_2O, 85% (2 steps); (i) DEAD, PPh_3, 73%; (j) *n*-Bu_4NF (97%); (k) PCC (94%); (l) methyl 3-(4-methoxyphenyl)pyruvate, NEt_3, EtOAc, 90%; (m) BI_3, CH_2Cl_2, 0 °C (47%). Bn=benzyl, TBDPS-Cl=*tert*-butyldiphenylchlorosilane, DMAP=4-(dimethylamino)pyridine, DEAD=diethyl azodicarboxylate, PCC=pyridinium chlorochromate.

and an end concentration of 0.0079 M, a decrease in the yield of lactone **13** to 53% was observed.

Treatment of macrolide **13** with tetra-*n*-butylammonium fluoride furnished the free hydroxylactone **14**, which could be oxidized to the desired oxolactone **15** in excellent yield. According to the NMR spectra, compound **15** in $CDCl_3$ is completely present in the keto form, which is unusual for phenylpyruvate moieties.[7] Removal of the *O*-methyl group with boron triiodide yielded phenol **6**, in all respects identical with ornatipolide from *R. ornatipes*.[5]

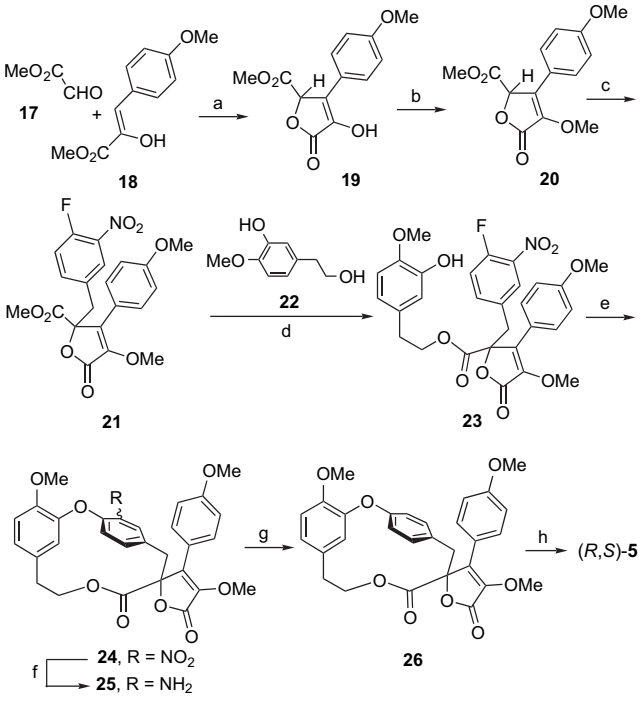
Condensation of ketone **15** with methyl 3-(4-methoxyphenyl)pyruvate in the presence of triethylamine afforded (*R*,*S*)-retipolide E dimethyl ether (**16**) in nearly quantitative yield. The exclusive formation of the desired condensation product can be explained by the absence of the enol form of the oxomacrolide and the high reactivity due to ring strain. Treatment of **16** with BI_3 yielded (*R*,*S*)-retipolide E [(*R*,*S*)-**5**]. The compound was obtained from **8** in 13 steps with 6.2% overall yield.

The synthetic sample enabled us to detect retipolide E in the crude extract of *R. retipes* by chromatographic comparison.

Optically active retipolide E (**5**) was subsequently isolated in larger quantity and its spectroscopic data matched those of the synthetic racemate.[2]

2.3. Synthesis of (*R*,*S*)-retipolide E by intramolecular aromatic nucleophilic substitution

Our second synthesis started from methyl glyoxylate (**17**), which was obtained by ozonolysis of dimethyl fumarate and reductive workup with dimethyl sulfide. Treatment of the crude solution with methyl 3-(4-methoxyphenyl)pyruvate (**18**) and triethylamine yielded hydroxylactone **19**,[8] which afforded enol methyl ether **20** on treatment with diazomethane (Scheme 3). Alkylation of ester **20** with 4-fluoro-3-nitrobenzyl bromide[9] was carried out with 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at room temperature to yield the substitution product **21**. The transesterification of methyl ester **21** with 2-(3-hydroxy-4-methoxyphenyl)ethanol (**22**)[10,11] to ester **23** was easily achieved with Otera's catalyst 1,3-dichlorotetrabutyldistannoxane.[12] Due to the steric hindrance of the ester group in **23**, alternative procedures based on base or acid catalysis were unsuccessful.

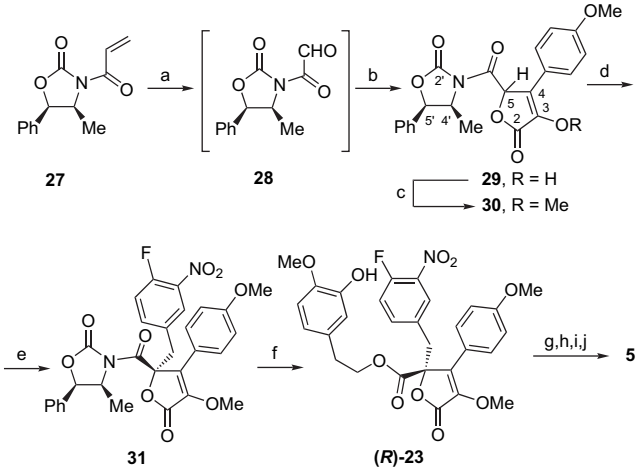


Scheme 3. Synthesis of (*R*,*S*)-retipolide E [(*R*,*S*)-**5**] via intramolecular aromatic nucleophilic substitution. Reagents and conditions: (a) NEt_3, EtOAc, RT, 72%; (b) CH_2N_2, Et_2O, 80%; (c) 4-fluoro-3-nitrobenzyl bromide, DBU, MeCN, rt, 83%; (d) **22**, 1,3-dichlorotetrabutyldistannoxane (cat.), toluene, reflux, 90%; (e) K_2CO_3, MeCN, 61% (1:1 mixture of atropdiastereomers); (f) H_2, Pd/C, 86% (1:1 mixture of atropdiastereomers); (g) *tert*-butyl nitrite, DMF, 62%; (h) BI_3, CH_2Cl_2, 41%. DBU=1,8-diazabicyclo[5.4.0]undec-7-ene.

The 14-membered lactone **24** was produced from the activated fluoride **23** by treatment with K_2CO_3 in DMF.[9,13] The intramolecular S_NAr reaction afforded **24** in 61% yield as a 1:1 mixture of the two atropdiastereomers.[13c] The ring closure is indicated by the strong up-field NMR shift of the 19-H proton from δ ~6.6 in **23** to δ ~4.8 in **24**. The orthogonal 1,4-disubstituted benzene ring shields this proton, an effect typically observed for all retipolides.[2] Reduction of the nitro group by catalytic hydrogenation yielded amino compound **25**, which could be deaminated to (*R*,*S*)-retipolide E trimethyl ether (**26**) by treatment with *tert*-butyl nitrite.[14] Removal of the *O*-methyl groups with BI_3 at −78 °C[15] afforded racemic retipolide E [(*R*,*S*)-**5**], identical with the compound obtained with our first synthesis. The S_NAr strategy yielded retipolide E in eight steps from methyl glyoxylate (**17**) with 5.7% overall yield.

2.4. Stereoselective synthesis of (*R*)-retipolide E (5) via intramolecular aromatic nucleophilic substitution

The second approach to retipolide E could be easily adapted for the synthesis of the optically active compound. For this purpose, the enantiomerically pure 4-fluoro-3-nitrobenzyl compound **31** was prepared using Evans' methodology[16] (Scheme 4). The (−)-norephedrine-derived auxiliary was introduced by condensation of *N*-glyoxyloyloxazolidinone **28**, prepared in situ by ozonolysis of the corresponding propenoyl compound **27**,[17] with methyl 3-(4-methoxyphenyl)pyruvate (**18**). The resulting hydroxybutenolide **29** was obtained as a mixture of two diastereomers, which was transformed into enol ether **30** by treatment with diazomethane. Alkylation of **30** with 4-fluoro-3-nitrobenzyl bromide in acetonitrile in the presence of DBU yielded a 4:1 mixture of the 4*R* and 4*S* diastereomers, from which the pure 4*R* compound **31** could be separated by fractional crystallization in 44% yield. Interestingly, treatment of the imide **31** with 2-arylethanol **22** in the presence of distannoxane as catalyst yielded the desired ester (*R*)-**23** in 66% yield. To our knowledge this is the first example for the direct conversion of an Evans imide into a carboxylic ester under exceptionally mild conditions. Ester (*R*)-**23** could be transformed into (*R*)-retipolide (**5**) by the same sequence of reactions that were applied to the racemic compound. The CD spectrum of the synthetic material was also in agreement with that of the natural sample,[2] thus proving the (*R*)-configuration of retipolide E.



Scheme 4. Synthesis of (*R*)-retipolide E (**5**) via intramolecular aromatic nucleophilic substitution. Reagents and conditions: (a) O_3, EtOAc, −78 °C, then Me_2S, 59%; (b) **18**, NEt_3, EtOAc, rt, 59%; (c) CH_2N_2, Et_2O, 73%; (d) 4-fluoro-3-nitrobenzyl bromide, DBU, MeCN, rt, *R*/*S*=4:1; (e) separation of (*R*)-diastereomer by crystallization, 44% (two steps); (f) 2-(3-hydroxy-4-methoxyphenyl)ethanol (**22**), 1,3-dichlorotetrabutyldistannoxane (cat.), toluene, reflux, 66%; the experimental conditions for steps (g)–(j) correspond to those given for steps (e)–(h) in Scheme 3.

In conclusion, we have synthesized the highly strained 14-membered lactone system of the fungal metabolite retipolide E by two different strategies. In the course of these investigations, the Mitsunobu technique for the formation of such macrolactones from the corresponding hydroxy acids was further improved and a mild method for the direct exchange of Evans oxazolidinone auxiliaries against alcohols was developed. The synthesis of retipolide E allowed us the detection and isolation of this elusive biosynthetic precursor from the fungal extract.

3. Experimental

3.1. General

UV–vis: Varian Cary 17; NMR: Bruker AC 200, Bruker ARX 300, Bruker WM 400, Varian EM 390, Varian VXR 400S, Bruker WH 90, and Bruker AMX 600 instruments with chemical shifts in parts per million δ units relative to TMS as internal standard. For retipolide E (**5**) and its derivatives **16** and **24**–**26**, the assignments of the H-atoms are given in Figure 1; MS (EI) and HRMS (EI) were recorded on a Finnigan MAT 90, MAT 95, or A.M.E. Kratos MS 50 mass spectrometer, equipped with an EI ion source operated at 70 eV; TLC: silica gel 60 F TLC plates 0.2 mm (Merck); flash column chromatography (FC): silica gel 60 (40–63 μm, 230–400 mash, Merck); hexanes refers to the fraction of petroleum ether with bp 40–60 °C; C, H, N analyses were performed by the Microanalytical Laboratory of the Chemistry Department, LMU, München or of the Institute for Organic Chemistry and Biochemistry, University of Bonn.

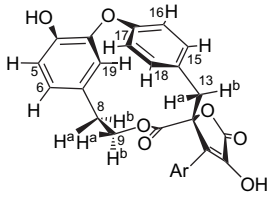


Figure 1. Conformation of retipolide E (**5**) with numbering of the H atoms used in the ^{1}H NMR spectra of compounds **5**, **16**, and **24**–**26** (Ar=C_6H_4OH or C_6H_4OMe).

3.2. Synthesis of ornatipolide and (*R*,*S*)-retipolide A via macrolactonization

3.2.1. 2-(3-Hydroxy-4-methoxyphenyl)ethyl acetate (9). A mixture of 2-(3-benzyloxy-4-methoxyphenyl)ethanol (**8**)[6] (80.0 g, 310 mmol), Ac_2O (59.0 mL, 620 mmol), and pyridine (50.0 mL, 620 mmol) was refluxed under an argon atmosphere for 1.5 h. After cooling to rt, the solution was poured into ice-cold aq HCl (5%, 720 mL) and extracted with Et_2O (2×500 mL). The combined organic phases were washed with water (500 mL), satd aq $NaHCO_3$ (3×500 mL), and brine (500 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield a yellowish solid (89 g), which was dissolved in EtOAc (200 mL). After addition of 10% Pd on charcoal (5.0 g), the mixture was shaken at rt for 3 h under H_2 (3 atm). The catalyst was removed by filtration over Celite and the solution concentrated under reduced pressure. Recrystallization of the residue from Et_2O/hexanes yielded **9** (49.0 g, 77%) as colorless crystals. Mp 40 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.76 (t, J=7 Hz, 2H), 3.78 (s, 3H), 4.16 (t, J=7 Hz, 2H), 5.77 (s, 1H), 6.50–6.83 (m, 3H); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ 21.1, 34.5, 56.0, 65.2, 110.8, 115.2, 120.3, 131.2, 145.4, 145.7, 171.2; MS (EI) *m*/*z* (rel int.): 210 (8, M^+), 151 (12), 150 (100), 137 (43), 135 (49), 122 (10), 107 (6), 94 (6), 91 (10), 43 (28). Anal. Calcd for $C_{11}H_{14}O_4$: C 62.85; H 6.71; found: C 62.98; H 6.60.

3.2.2. 2-[3-(4-Formylphenoxy)-4-methoxyphenyl]ethyl acetate (10). A mixture of **9** (49.0 g, 233 mmol), 4-bromobenzaldehyde (47.4 g, 256 mmol), anhydrous K_2CO_3 (64.4 g, 466 mmol), and dry pyridine (250 mL) was stirred under an argon atmosphere at 90 °C (bath temperature). After addition of CuO (46.3 g, 582 mmol), the bath temperature was raised to 135 °C and the stirring continued for 18 h. The suspension was cooled to rt, diluted with EtOAc (2 L), and filtered over Celite. The filtrate was washed with 1 M aq $NaHSO_4$ (1.5 L, 3×), water (500 mL), 0.1 M aq NaOH (500 mL), water (500 mL), and brine (500 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 3:1, R_f=0.34) afforded **10** (60 g, 82%) as a colorless, highly viscous oil. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.00 (s, 3H), 2.85 (t, J=7 Hz, 2H), 3.70 (s, 3H), 4.22 (t, J=7 Hz, 2H), 6.80–7.17 (m, 5H), 7.67–7.90 (m, 2H), 9.89 (s, 1H); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ 20.9, 34.2, 56.0, 64.8, 113.2, 116.3 (2C), 123.1, 126.6, 131.0, 131.3, 131.9 (2C), 142.8, 150.4, 163.6, 171.0, 190.8; MS (EI) *m*/*z* (rel int.): 314.1 (6, M^+), 255 (20), 254 (100), 242 (7), 241 (13), 211 (16), 77 (9), 43 (29). Anal. Calcd for $C_{18}H_{18}O_5$: C 68.78; H 5.77; found: C 68.86; H 5.81.

3.2.3. Methyl 3-{4-[5-(2-acetoxyethyl)-2-methoxyphenoxy]phenyl}-2-hydroxypropionate (11). A solution of **10** (56.2 g, 179 mmol) in methyl chloroacetate (26.5 mL, 268 mmol) was added under an argon atmosphere to a stirred solution of NaOMe (14.5 g, 268 mmol) in dry MeOH (250 mL), maintained at −10 °C. The mixture was warmed to rt and stirred for 18 h. After addition of acetic acid (5.1 mL, 89.0 mmol), the solution was poured into ice water (900 mL) and extracted with EtOAc (2×300 mL). The combined organic phases were washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting orange oil (68.1 g) was purified by flash chromatography (hexanes/EtOAc, 1:1), whereby all fractions with R_f=0.39 (hexanes/EtOAc, 1:1) were combined to afford a colorless oil (49.7 g), which was dissolved in dry pyridine (70 mL) and treated with Ac_2O (54.4 mL, 576 mmol) at 0 °C under an argon atmosphere. The solution was stirred for 18 h at rt, then poured into ice water (500 mL), and extracted with EtOAc (2×200 mL). The combined organic phases were washed with 20% aq citric acid (1 L, then 500 mL), satd aq $NaHCO_3$ (2×500 mL), and brine (500 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield a brown oil (51.8 g), which was dissolved in a mixture of EtOAc (15 mL) and MeOH (150 mL). The solution was transferred to a shaking apparatus and hydrogenated with 10% Pd on charcoal (5.00 g) and Na_2CO_3 (1.00 g) at 3 atmH_2 pressure. After removal of the catalyst by filtration over a Celite pad and evaporation of the solvent under reduced pressure, the oily residue was diluted with Et_2O (500 mL), filtered, and concentrated again. The resulting yellowish oil (51.6 g)

was purified by flash chromatography, first on a column with hexanes/EtOAc (3:2, R_f=0.31), then on a second column with $CHCl_3$/acetone (20:1, R_f=0.41) to yield **11** (28.7 g, 41%) as a colorless solid. Mp 63–64 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.92 (s, 3H), 2.76 (t, J=7 Hz, 2H), 2.81–3.16 (m, 3H), 3.64 (s, 3H), 3.74 (s, 3H), 4.17 (t, J=7 Hz, 2H), 4.27–4.50 (m, 1H), 6.49–7.47 (m, 7H); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ 20.9, 34.2, 39.8, 52.4, 56.1, 64.9, 71.3, 112.9, 117.1 (2C), 121.6, 124.9, 130.4, 130.6 (2C), 130.9, 144.9, 150.1, 156.9, 171.0, 174.6; MS (EI) *m/z* (rel int.): 389 (6), 388 (29, M^+), 329 (12), 328 (53), 310 (6), 300 (33), 299 (98), 259 (15), 240 (35), 239 (100), 224 (10), 211 (16), 120 (10), 91 (10), 90 (13), 43 (23). Anal. Calcd for $C_{21}H_{24}O_7$: C 64.94; H 6.23; found: C 64.90; H 6.40.

3.2.4. 2-*tert*-Butyldiphenylsilanyloxy-3-{4-[5-(2-hydroxyethyl)-2-methoxyphenoxy]phenyl}propionic acid (12). Imidazole (3.21 g, 47.2 mmol), *tert*-butyldiphenylchlorosilane (11.0 mL, 42.8 mmol), and DMAP (0.22 g, 1.8 mmol) were added under an argon atmosphere to a stirred solution of **11** (14.1 g, 36.3 mmol) in dry CH_2Cl_2 (150 mL) and the stirring was continued for 20 h at rt. The mixture was diluted with Et_2O (1 L) and washed with 0.5 M aq $NaHSO_4$ (400 mL), satd aq $NaHCO_3$ (300 mL), and water (300 mL). Concentration under reduced pressure yielded the silyl derivative as a colorless oil, which was dissolved in THF/water (1 L, 2:1) and treated dropwise with stirring over 2 h with a solution of $LiOH\cdot H_2O$ (4.57 g, 109 mmol) in THF/water (550 mL, 1:1). The stirring was continued for 3 d at rt. After reduction of the volume under vacuum to 500 mL, the solution was acidified with 1 N aq $NaHSO_4$ to pH 1–2, saturated with NaCl, and extracted with EtOAc (2×600 mL). The organic phases were washed with water (3×400 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc/AcOH, 60:40:1, R_f=0.28) yielded **12** (17.5 g, 85%) as a colorless oil. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.03 (s, 9H), 2.63 (t, J=7 Hz, 2H), 2.86 (d, J=6 Hz, 2H), 3.64 (t, J=7 Hz, 2H), 3.68 (s, 3H), 4.39 (t, J=6 Hz, 1H), 6.12 (br s, 2H), 6.60–7.70 (m, 17H); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ 19.1, 26.7 (3C), 37.7, 40.4, 55.7, 63.1, 73.5, 112.7, 116.8 (2C), 121.3, 124.9, 127.4 (4C), 129.6, 129.7, 130.5, 130.9 (2C), 131.3, 132.6, 132.7, 135.6 (2C), 135.8 (2C), 144.7, 149.7, 156.7, 176.6; MS (EI) *m/z* (rel int.): 570 (1.3, M^+), 347 (13), 329 (14), 269 (22), 258 (14), 257 (100), 239 (10), 199 (67), 135 (24), 78 (18). Anal. Calcd for $C_{34}H_{38}O_6Si$: C 71.55; H 6.71; found: C 71.61; H 6.87.

3.2.5. 12-(*tert*-Butyldiphenylsilanyloxy)-4-methoxy-2,10-dioxatricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-11-one (13). Three precision dropping funnels were charged with a solution of **12** (1.22 g, 2.14 mmol) in dry toluene/THF (100 mL, 9:1), a solution of diethyl azodicarboxylate (1.18 mL, 7.48 mmol) in dry toluene (100 mL), and a solution of PPh_3 (1.68 g, 6.41 mmol) in dry toluene (100 mL), respectively. Then, the three solutions were added simultaneously over 6 h at rt under an argon atmosphere to a vigorously stirred solution of diethyl azodicarboxylate (1.18 mL, 7.48 mmol) and PPh_3 (1.68 g, 6.41 mmol) in dry toluene (1.1 L). The reaction mixture was concentrated under reduced pressure and purified by flash chromatography, first with hexanes/EtOAc (5:1), then with hexanes/EtOAc (7:1, R_f=0.29), to afford **13** (866 mg, 73%) as a colorless oil. UV–vis (acetonitrile): λ_{max} (log ε) 218 (4.36), 272 nm (3.36); ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.14 (s, 9H), 2.37 (t, J=5 Hz, 2H), 3.18 (d, J=6 Hz, 2H), 3.44, 3.61 (each dt, J=11, 5 Hz, 1H), 3.88 (s, 3H), 4.43 (t, J=6 Hz, 1H), 4.80 (d, J=2 Hz, 1H), 6.49 (dd, J=8, 2 Hz, 1H), 6.68 (d, J=8 Hz, 1 H), 6.85–7.81 (m, 14 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.0, 26.6 (3C), 31.0, 40.0, 55.7, 66.5, 75.0, 110.8, 115.5, 120.4, 124.0, 124.4, 127.2 (2C), 127.6 (2C), 129.5, 129.8, 131.0, 132.0, 132.4, 132.6, 132.7, 133.2, 135.4 (2C), 135.5 (2C), 145.9, 152.4, 157.7, 171.9; MS (EI) *m/z* (rel int.): 552 (1.8, M^+), 496 (5), 495 (15), 468 (7), 467 (20), 389 (8), 371 (7), 329 (19), 240 (12), 239 (55), 225 (12), 200 (14), 199 (100), 197 (19), 195 (34), 183 (6), 135 (52), 134 (6), 104 (12), 91 (7); HRMS (EI) calcd for $C_{34}H_{36}O_5Si$ [M^+]: 552.2332, found: 552.2341.

3.2.6. 12-Hydroxy-4-methoxy-2,10-dioxatricyclo-[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-11-one (14). A 1.1 M solution of Et_4NF in THF (17.2 mL, 18.9 mmol) was added at 0 °C over 2 min to a stirred solution of **13** (9.51 g, 17.2 mmol) in THF (150 mL) and the stirring was continued for a further 20 min. After treatment with acetic acid (1.20 g, 20.0 mmol), the solution was concentrated under reduced pressure. The residue was purified twice by flash chromatography ($CHCl_3$/acetone, 20:1, R_f=0.50) to yield **14** (5.22 g, 97%) as a colorless solid. Mp 218–220 °C; UV–vis (acetonitrile): λ_{max} (log ε) 216 (4.23), 276 nm (3.33); IR (KBr, cm^{-1}): 3520s, 1740s, 1715m; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.61 (d, J=9.3 Hz, 1H), 2.75 (t, J=4.6 Hz, 2H), 3.00 (dd, J=13.0, 7.6 Hz, 1H), 3.31 (dd, J=13.0, 4.4 Hz, 1H), 3.93 (s, 3H), 3.96, 4.13 (each dt, J=11.5, 4.6 Hz, 1H), 4.41 (ddd, J=9.3, 7.6, 4.4 Hz, 1H), 4.79 (d, J=2.2 Hz, 1H), 6.57 (dd, J=8.1, 2.2 Hz, 1H), 6.73 (d, J=8.1 Hz, 1H), 7.06, 7.10 (each dd, J=6.8, 2.0 Hz, 1H), 7.26, 7.30 (each dd, J=6.8, 2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.5, 41.4, 56.0, 67.8, 74.0, 111.2, 115.5, 120.8, 124.7, 125.4, 131.1, 131.2, 132.1, 133.1, 146.3, 152.6, 158.0, 173.2; MS (EI) *m/z* (rel int.): 315 (6), 314 (48, M^+), 257 (11), 240 (28), 239 (100), 225 (13), 104 (16), 91 (22); HRMS (EI) calcd for $C_{18}H_{18}O_5$ [M^+]: 314.1154, found: 314.1155. Anal. Calcd for $C_{18}H_{18}O_5$: C 68.78; H 5.77; found: C 68.68; H 5.86.

3.2.7. 4-Methoxy-2,10-dioxatricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-11,12-dione (15). Pyridinium chlorochromate (10.5 g, 48.6 mmol) was added to a stirred solution of **14** (5.10 g, 16.2 mmol) in dry CH_2Cl_2 at rt under an argon atmosphere and the stirring was continued for 48 h. The reaction mixture was filtered over a Celite pad, rinsed with $CHCl_3$ (300 mL), and concentrated under reduced pressure to a volume of 20 mL. Flash chromatography of the dark-brown solution ($CHCl_3$/acetone, 50:1) yielded a brown oil that was flash chromatographed again to yield **15** (4.77 g, 94%) as a colorless solid. Mp 123 °C; R_f=0.23 ($CHCl_3$/acetone, 50:1); UV–vis (acetonitrile): λ_{max} (log ε) 214 (4.28), 276 nm (3.48); IR (KBr, cm^{-1}): 1730s (sh), 1720s; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.83 (m, 2H), 3.94 (s, 3H), 4.04 (s, 2H), 4.19 (m, 2H), 4.92 (d, J=2.1 Hz, 1H), 6.61 (dd, J=8.2, 2.1 Hz, 1H), 6.77 (d, J=8.2 Hz, 1H), 7.11–7.21 (m, 2H), 7.33–7.43 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.4,

47.3, 56.1, 67.9, 111.4, 115.2, 121.3, 126.0 (2C), 127.3, 132.0, 132.9 (2C), 146.6, 152.1, 158.6, 164.3, 191.7; MS (EI) *m/z* (rel int.): 313 (20), 312 (100, M^+), 259 (7), 240 (40), 239 (62), 226 (7), 225 (32), 211 (10), 105 (16), 104 (37), 103 (7), 91 (16), 90 (11); HRMS (EI) calcd for $C_{18}H_{16}O_5$: [M^+] 312.0998, found: 312.0999.

3.2.8. Ornatipolide, 4-hydroxy-2,10-dioxatricyclo-[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-11,12-dione (6). A solution of BI_3 (540 mg, 1.4 mmol) in dry CH_2Cl_2 (9 mL) was slowly added to a solution of **15** (87 mg, 0.28 mmol) in dry CH_2Cl_2 (10 mL), maintained under an argon atmosphere in the dark at −78 °C. The solution was stirred for 10 min at −78 °C, then warmed to rt, treated with 1 N aq $NaHSO_3$ (20 mL), and extracted with CH_2Cl_2 (3×). The combined extracts were washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by TLC on silica gel (toluene/EtOAc/HCO_2H, 10:5:3, R_f=0.62) yielded **6** (20 mg, 25%) as a colorless oil. UV–vis (acetonitrile): λ_{max} (log ε) 276 nm (4.46); ^{1}H NMR (300 MHz, acetone-d_6): δ 2.68 (obscured by H_2O signal, 2H, 8-H), 4.07 (s, 2H, 13-H), 4.14 (dd, *J*=4.7, 4.7 Hz, 2H, 9-H), 4.93 (d, *J*=2.0 Hz, 1H, 19-H), 6.55 (dd, *J*=8.1, 2.0 Hz, 1H, 6-H), 6.73 (d, *J*=8.1 Hz, 1H, 5-H), 7.16 (d, *J*=8.5 Hz, 2H, 16-H, 17-H), 7.44 (d, *J*=8.5 Hz, 2H, 15-H, 18-H), 8.04 (s, 1H, 4-OH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.79 (m, 2H, 8-H), 4.03 (s, 2H, 13-H), 4.17 (m, 2H, 9-H), 4.89 (br s, 1H, 19-H), 5.49 (br s, 1H, 4-OH), 6.53 (d, *J*=7.5 Hz, 1H, 6-H), 6.77 (d, *J*=7.5 Hz, 1H, 5-H), 7.12 (d, *J*=7.5 Hz, 2H, 16-H, 17-H), 7.36 (d, *J*=7.5 Hz, 2H, 15-H, 18-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 31.5 (C-8), 47.3 (C-13), 67.9 (C-9), 114.8 (C-19), 115.0 (C-5), 122.0 (C-6), 125.9 (C-16, C-17), 127.7 (C-14), 131.6 (C-7), 133.0 (C-15, C-18), 143.0 (C-4), 150.2 (C-3), 158.3 (C-1), 164.2 (C-11), 191.6 (C-12); MS (EI) *m/z* (rel int.): 299 (17, M^++H), 298 (100, M^+), 226 (32), 225 (42), 211 (6), 197 (4), 120 (34), 107 (23), 77 (6).

3.2.9. (*R*,*S*)-Retipolide E dimethyl ether (16). A solution of **15** (1.00 g, 3.20 mmol), methyl 3-(4-methoxyphenyl)pyruvate (1.67 g, 8.00 mmol), and NEt_3 (2.23 mL, 16.0 mmol) in dry EtOAc (25 mL) was stirred for 5 h under an argon atmosphere at rt. The solution was diluted with EtOAc (200 mL), washed with 1 N aq $NaHCO_3$ (100 mL), water (2×100 mL), and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography ($CHCl_3$/acetone, gradient 50:1–10:1) yielded a yellowish solid, which on crystallization from acetone afforded **16** (1.57 g, 90%) as colorless crystals, containing 1 mol of acetone per mol. Mp 252–254 °C; R_f=0.25 ($CHCl_3$/acetone, 50:1), 0.45 ($CHCl_3$/acetone, 20:1); UV–vis (acetonitrile): λ_{max} (log ε) 214 (4.29), 2.26 (sh, 4.21), 290 (sh, 3.92), 304 nm (3.94); IR (KBr, cm^{-1}): 3360s (br), 1755s, 1720s, 1600m, 1255s; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.54 (dd, *J*=17.3, 5.3 Hz, 1H, 8-H^a), 3.00 (dddd, *J*=17.3, 11.0, 1.8, 0.5 Hz, 1H, 8-H^b), 3.03 (d, *J*=13.8 Hz, 1H, 13-H^b), 3.50 (br s, 1H, OH), 3.86 (ddd, *J*=11.1, 5.3, 1.8 Hz, 1H, 9-H^b), 3.87, 3.94 (each s, 3H, OMe), 3.98 (d, *J*=13.8 Hz, 1H, 13-H^a), 4.28 (dd, *J*=11.1, 11.0 Hz, 1H, 9-H^a), 4.76 (dd, *J*=2.2, 0.5 Hz, 1H, 19-H), 6.55 (dd, *J*=8.2, 2.2 Hz, 1H, 6-H), 6.73 (d, *J*=8.2 Hz, 1H, 5-H), 6.97–7.06 (m, 2H), 7.01 (dd, *J*=8.4, 2.4 Hz, 1H, 17-H), 7.25 (dd, *J*=8.4, 2.4 Hz, 1H, 16-H), 7.32 (dd, *J*=8.4, 2.2 Hz, 1H, 18-H), 7.62 (dd, *J*=8.4, 2.2 Hz, 1H, 15-H), 8.10–8.19 (m, 2H); ^{13}C NMR (100.6 MHz, acetone-d_6/$CDCl_3$, 1:1): δ 31.1, 43.7, 54.7, 55.5, 67.7, 88.0, 110.8, 113.4 (2C), 114.7, 120.6, 121.7, 123.6, 123.8, 128.5, 130.6 (2C), 131.1, 132.3, 132.4, 133.3, 138.5, 146.0, 152.2, 157.9, 159.5, 167.1, 167.5; MS (EI) *m/z* (rel int.): 488 (0.6), 445 (26), 444 (100, M^+), 414 (13), 354 (6), 240 (25), 226 (12), 221 (11), 135 (84), 121 (12), 91 (14), 90 (11), 57 (12), 44 (44); HRMS (EI) calcd for $C_{28}H_{24}O_8$ [M^+]: 488.1471, found: 488.1458. Anal. Calcd for $C_{28}H_{24}O_8 \cdot CH_3COCH_3$: C 68.12; H 5.53; found: C 68.08; H 5.58.

3.2.10. (*R*,*S*)-Retipolide E, 4,4′-dihydroxy-3′-(4-hydroxyphenyl)spiro{2.10-dioxatricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12,2′(5′*H*)-furan}-11,5′-dione [(*R*,*S*)-5]. A 0.23 M solution of BI_3 in CH_2Cl_2 (7.2 mL, 1.65 mmol) was added to a stirred solution of **16**·acetone (90 mg) in dry CH_2Cl_2 (5 mL), maintained under an argon atmosphere at 0 °C. The mixture was stirred for 10 min at 0 °C and then concentrated under reduced pressure. The solid residue was triturated with ice water (10 mL), filtered off, and rinsed with water (50 mL). Purification by flash chromatography ($CHCl_3$/acetone, 4:1, R_f=0.33) afforded (*R*,*S*)-**5** (36 mg, 47%) as a colorless solid. Mp 245–247 °C; UV–vis (acetonitrile): λ_{max} (log ε) 212 (4.02), 2.24 (sh, 3.90), 290 (sh, 3.58), 304 (3.59), 350 nm (2.84); IR (KBr, cm^{-1}): 3410s, 3300s, 1730s, 1715s, 1585m, 1510m, 1495m, 1430m, 1260s, 1110m, 970m, 915m, 870m, 840m; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.59 (dd, *J*=17.1, 5.2 Hz, 1H, 8-H^a), 2.84 (dddd, *J*=17.1, 11.2, 1.2, 0.9 Hz, 1H, 8-H^b), 3.17 (d, *J*=13.8 Hz, 13-H^b), 3.90 (ddd, *J*=11.3, 5.2, 1.2 Hz, 1H, 9-H^b), 3.95 (d, *J*=13.8 Hz, 1H, 13-H^a), 4.21 (dd, *J*=11.3, 11.2 Hz, 1H, 9-H^a), 4.79 (dd, *J*=2.1, 0.9 Hz, 1H, 19-H), 6.50 (dd, *J*=8.0, 2.1 Hz, 1H, 6-H), 6.70 (d, *J*=8.0 Hz, 1H, 5-H), 6.95 (AA′BB′-d, *J*=8.9 Hz, 2H, 8′-H), 6.96 (dd, *J*=8.5, 2.5 Hz, 1H, 17-H), 7.20 (dd, *J*=8.5, 2.5 Hz, 1H, 16-H), 7.35 (dd, *J*=8.5, 2.5 Hz, 1H, 18-H), 7.65 (dd, *J*=8.5, 2.5 Hz, 1H, 15-H), 7.90 (s, 1H, OH), 8.00 (AA′BB′-d, *J*=8.9 Hz, 2H, 7′-H), 8.72 (s, 1H, OH), 9.24 (br s, 1H, OH); ^{13}C NMR (100.6 MHz, acetone-d_6): δ 32.2 (C8), 44.3 (C13), 68.8 (C9), 89.1 (C12), 115.9 (C19), 115.9 (2×C8′), 116.3 (C5), 122.2 (C6′), 122.3 (C6), 124.65 (C16), 124.72 (C17), 129.9 (C3′), 132.1 (2×C7′), 132.5 (C7), 133.1 (C14), 133.9 (C18), 134.6 (C15), 139.8 (C4′), 144.6 (C4), 152.4 (C3), 158.8 (C-9′), 159.3 (C1), 167.8 (C5′), 168.7 (C11); MS (EI) *m/z* (rel int.): 460 (1.5, M^+), 417 (15), 416 (84), 226 (29), 225 (16), 207 (14), 198 (14), 188 (17), 121 (8), 120 (11), 91 (30), 44 (100); HRMS (EI) calcd for $C_{26}H_{20}O_8$ [M^+]: 460.1158, found: 460.1152.

3.3. Synthesis of (*R*,*S*)-retipolide E via intramolecular nucleophilic aromatic substitution

3.3.1. Methyl 4-hydroxy-3-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (19). A solution of dimethyl fumarate (4.32 g, 30.0 mmol) in EtOAc (200 mL) was cooled to −78 °C and treated with ozone until the solution remained light blue. The excess of ozone was then removed by bubbling argon through the solution. Dimethyl sulfide (6.60 mL, 90.0 mmol) was added and the solution warmed to rt. The mixture was treated with methyl 3-(4-methoxyphenyl)pyruvate (**18**) (13.5 g, 65.0 mmol) and NEt_3 (9.10 mL,

65.0 mmol) and stirred for 4 h. After dilution with EtOAc (150 mL), the solution was washed with 1 M aq $NaHSO_4$ (3×), water, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by recrystallization from EtOAc/hexanes to yield **19** (11.4 g, 72%) as colorless needles. Mp 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75, 3.85 (each s, 3H, OMe), 5.73 (s, 1H, 5-H), 6.12 (s, 1H, OH), 6.97 (m, 2H, Ar═H), 7.73 (m, 2H, Ar═H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.2, 55.5, 76.8, 115.0 (2C), 123.0, 126.2, 129.5 (2C), 137.7, 161.0, 169.0, 169.5; MS (EI) *m/z* (rel int.): 265 (6), 264 (44, M^+), 220 (19), 193 (10), 192 (100), 191 (77), 162 (7), 161 (65), 149 (14), 135 (13), 134 (12), 133 (22), 132 (17), 117 (69), 91 (8), 89 (10). Anal. Calcd for $C_{13}H_{12}O_6$: C 59.09; H 4.58; found: C 59.21; H 4.55.

3.3.2. Methyl 4-methoxy-3-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (20). A freshly prepared solution of diazomethane in Et_2O (250 mL) was added to a solution of **19** (6.61 g, 25 mmol) in acetone (40 mL). The mixture was stirred for 1 h, then treated with acetic acid (1 mL), and concentrated. Purification by flash chromatography (hexanes/Et_2O, 2:1, R_f=0.53) afforded **20** (5.54 g, 80%) as a colorless powder. Mp 96 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 3.71, 3.83, 4.13 (each s, 3H, OMe), 5.68 (s, 1H, 5-H), 6.94 (m, 2H, Ar═H), 7.71 (m, 2H, Ar═H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.4, 55.7, 58.8, 76.7, 115.0 (2C), 122.3, 130.1 (2C), 134.6, 140.0, 161.9, 167.5, 168.4; MS (EI) *m/z* (rel int.): 279 (15), 278 (100, M^+), 220 (6), 219 (47), 191 (33), 176 (31), 148 (10), 135 (6), 120 (7). Anal. Calcd for $C_{14}H_{14}O_6$: C 60.43; H 5.07; found: C 60.56; H 5.12.

3.3.3. Methyl 2-(4-fluoro-3-nitrobenzyl)-4-methoxy-3-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (21). DBU (1.10 g, 7.20 mmol) was slowly added to a solution of **20** (2.00 g, 7.19 mmol) and 4-fluoro-3-nitrobenzyl bromide[9] (1.99 g, 8.50 mmol) in dry acetonitrile (150 mL). The solution was stirred for 1 h, diluted with Et_2O, and washed with 2 M HCl, satd aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 3:2, R_f=0.53) and recrystallized from CH_2Cl_2/*n*-hexane (3:2) to give **21** (2.59 g, 83%) as colorless needles, Mp 104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47, 3.66 (each d, *J*=14.7 Hz, 1H, benz. CH_2), 3.83, 3.88, 3.92 (each s, 3H, OMe), 7.00 (m, 2H, Ar═H), 7.12 (dd, *J*=10.5, 8.6 Hz, 1H, Ar═H), 7.25–7.29 (m, 1H, Ar═H), 7.44–7.48 (m, 1H, Ar═H), 7.54 (m, 2H, Ar═H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.4, 53.9, 55.5, 58.6, 84.0, 114.8 (2C), 118.1, 121.2, 127.7, 129.4 (2C), 130.3, 134.7, 136.7, 137.6, 141.1, 154.8, 160.9, 166.2, 169.1; MS (EI) *m/z* (rel int.): 432 (23), 431 (100, M^+), 373 (5), 372 (24), 344 (7), 284 (14), 277 (16), 249 (39), 221 (21), 206 (10), 154 (13), 148 (12), 147 (11), 135 (10), 119 (16), 108 (17). Anal. Calcd for $C_{21}H_{18}FNO_8$: C 58.47; H 4.21; N 3.25; found: C 58.72; H 4.29; N 3.35.

3.3.4. 2-(3-Hydroxy-4-methoxyphenyl)ethanol (22). A solution of TMEDA (9.06 g, 78 mmol) in dry THF (150 mL), maintained at −78 °C under an argon atmosphere, was treated dropwise with 60 mL (78.0 mmol) of a 1.3 M solution of *s*-BuLi in cyclohexane/*n*-heptane (1:1). After 10 min, a solution of 2-(4-methoxyphenyl)ethanol (2.97 g, 19.5 mmol) in dry THF (50 mL) was added dropwise over a period of 1 h. The mixture was stirred for 10 min and then treated dropwise with trimethyl borate (21.7 mL, 195 mmol). After 15 min, the mixture was allowed to warm to 0 °C and the stirring continued for 1 h at this temperature. Acetic acid (15 mL) was then added in one portion, followed by dropwise addition of hydrogen peroxide (30%, 10 mL). The mixture was slowly warmed to rt and diluted with Et_2O (200 mL) and water (150 mL). The two phases were separated and the aqueous layer extracted with Et_2O (2×). The combined organic layers were washed with 10% aq ammonium ferrous(II) sulfate and saturated with $(NH_4)_2SO_4$ (4×). After washing with diluted aq $NaHSO_3$, water, and brine, the organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 3:2, R_f=0.21) yielded **22** (2.04 g, 62%) as a colorless oil, which was crystallized from *t*-BuOMe/*n*-hexane. Mp 77 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (s, 1H, OH), 2.76 (t, *J*=6.5 Hz, 2H), 3.80 (t, *J*=6.5 Hz, 2H), 3.85 (s, 3H), 5.62 (s, 1H, OH), 6.63 (dd, *J*=8.2, 2.0 Hz, 1H), 6.72 (d, *J*=8.2 Hz, 1H), 6.73 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.5, 56.0, 63.7, 110.8, 115.1, 120.5, 131.6, 145.2, 145.7; MS (EI) *m/z* (rel int.): 168 (28, M^+), 138 (9), 137 (100), 122 (11). Anal. Calcd for $C_9H_{12}O_3$: C 64.27; H 7.19; found: C 64.76; H 7.19.

3.3.5. 2-(3-Hydroxy-4-methoxyphenyl)ethyl 2-(4-fluoro-3-nitrobenzyl)-4-methoxy-3-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (23). 1,3-Dichlorotetrabutyldistannoxane[12] (552 mg, 1.00 mmol) was added to a solution of **21** (863 mg, 2.0 mmol) and **22** (1.01 g, 6.01 mmol) in dry toluene (80 mL). The mixture was refluxed for 20 h and then concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/acetone, 70:1, R_f=0.40) to yield **23** (1.05 g, 90%) as a light yellow oil in addition to recovered **21** (44 mg) and **22** (650 mg, R_f=0.25).

Ester **23**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (t, *J*=6.6 Hz, 2H, CH_2CH_2OH), 3.40, 3.61 (each d, *J*=14.6 Hz, 1H, benz. CH_2), 3.82, 3.86, 3.90 (each s, 3H, OMe), 4.37–4.41 (m, 2H, CH_2OH), 5.56 (s, 1H, OH), 6.54 (dd, *J*=8.2, 2.0 Hz, 1H, Ar═H), 6.64 (d, *J*=8.2 Hz, 1H, Ar═H), 6.67 (d, *J*=2.0 Hz, 1H, Ar═H), 6.94 (m, 2H, Ar═H), 7.10 (dd, *J*=10.3, 8.5 Hz, 1H, Ar═H), 7.21–7.25 (m, 1H, Ar═H), 7.38–7.41 (m, 3H, Ar═H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.2, 38.2, 55.4, 55.9, 58.7, 67.5, 84.1, 110.7, 114.6 (2C) 115.0, 118.0, 120.4, 121.2, 127.7, 129.4 (2C), 130.0, 130.3, 135.0, 137.2, 137.5, 141.1, 145.5, 145.6, 154.7, 160.8, 166.4, 168.3; MS (EI) *m/z* (rel int.): 569 (7), 568 (35), 567 (100, M^+), 537 (7), 417 (7), 372 (5), 284 (6), 154 (9), 150 (72), 137 (10), 136 (5), 135 (10), 119 (15), 108 (7), 107 (5), 91 (18). Anal. Calcd for $C_{29}H_{26}FNO_{10}$: C 61.37; H 4.62; N 2.47; found: C 61.44; H 4.83; N 2.20.

3.3.6. (*R*,*S*)-Nitroretipolide (24, 1:1 mixture of atropdiastereomers). A solution of **23** (289 mg, 0.51 mmol) in dry DMF (4 mL) was added dropwise to a vigorously stirred suspension of anhydrous K_2CO_3 (280 mg, 2.00 mmol) in dry DMF (130 mL) under an argon atmosphere over a period of 1 h. The stirring was continued for 3 h at rt. The mixture

was then diluted with CH_2Cl_2 (150 mL), washed with 2 M HCl (3×), water, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography ($CHCl_3$/acetone, 100:1, R_f=0.41 and 0.35) afforded **24** (170 mg, 61%) as a yellow oil, which was crystallized from CH_2Cl_2/*n*-hexane as a yellow powder. Mp 208 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54/2.55* (each dd, *J*=17.3, 5.2 Hz, together 1H, 8-H^a), 3.01 (dd, *J*=17.3, 10.4 Hz, 1H, 8-H^b), 3.05/3.06* (each d, *J*=13.5 Hz, together 1H, 13-H^b), 3.76*/3.77 (each d, *J*=13.5 Hz, together 1H, 13-H^a), 3.85, 3.86 (each s, 3H, OMe), 3.86–3.92 (m, 1H, 9-H^b), 3.93 (s, 3H, OMe), 4.23/4.24* (each dd, *J*=11.1, 10.4 Hz, together 1H, 9-H^a), 4.82*/4.86 (each d, *J*=1.5 Hz, together 1H, 19-H), 6.59 (dd, *J*=8.2, 1.5 Hz, 1H, 6-H), 6.76 (d, *J*=8.2 Hz, 1H, 5-H), 6.99 (m, 2H, 8′-H), 7.44 (d, *J*=8.4 Hz, 1H, 17-H), 7.61 (m, 2H, 7′-H), 7.82 (dd, *J*=8.4, 2.2 Hz, 1H, 18-H), 7.89/8.25* (each d, *J*=2.2 Hz, together 1H, 15-H), * signals belong to the same atropdiastereomer; ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.0, 43.8, 55.7, 56.8, 59.6, 69.1, 87.8, 112.7, 114.4 (2C), 114.5, 121.5, 123.1, 128.0, 129.0, 131.6 (2C), 132.8, 133.1, 134.7, 138.8, 142.2, 144.2, 147.7, 151.5, 152.9, 161.0, 166.3, 167.5; MS (EI) *m*/*z* (rel int.): 549 (7), 548 (31), 547 (100, M^+), 487 (7), 285 (18), 284 (56), 235 (9), 207 (6), 151 (5), 150 (6), 149 (8), 147 (8), 135 (9), 134 (7), 121 (7), 119 (14), 105 (10), 104 (24), 103 (6), 91 (9). Anal. Calcd for $C_{29}H_{25}NO_{10}$: C 63.62; H 4.60; N 2.56; found: C 63.80; H 4.72; N 2.65.

3.3.7. (*R*,*S*)-Aminoretipolide (25, 1:1 mixture of atropdiastereomers). A mixture of **24** (295 mg, 0.54 mmol) and Pd on charcoal (10%, 30 mg) in $CHCl_3$/MeOH (4:1, 125 mL) was hydrogenated under vigorous stirring for 16 h at rt and then filtered through a pad of Celite. The catalyst was rinsed with $CHCl_3$ (150 mL) and the combined filtrates were concentrated under reduced pressure. Purification by flash chromatography ($CHCl_3$/acetone, 100:1, R_f= 0.25/0.22) afforded **25** (240 mg, 86%) as an oil, which was crystallized from CH_2Cl_2/*n*-hexane. Colorless powder; mp 227 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (br s, H, NH_2), 2.57/2.58* (each dd, *J*=17.4, 5.2 Hz, together 1H, 8-H^a), 2.90/2.92* (each d, *J*=13.5 Hz, together 1H, 13-H^b), 3.05/3.06* (each dd, *J*=17.4, 10.9 Hz, together 1H, 8-H^b), 3.55*/3.57 (each d, *J*=13.5 Hz, together 1H, 13-H^a), 3.80–3.88 (m, 1H, 9-H^b), 3.83, 3.85, 3.92 (each s, 3H, OMe), 4.23/4.27* (each dd, *J*=11.3, 10.9 Hz, together 1H, 9-H^a), 5.09/5.15* (each d, *J*=1.5 Hz, together 1H, 19-H), 6.52–6.77 (m, 3H, Ar═H), 6.94–7.00 (m, 4H, 8′-H, Ar═H), 7.55–7.60 (m, 2H, 7′-H), * signals belong the same atropdiastereomer; ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.6, 44.5, 55.7, 56.5, 59.5, 68.8, 88.4, 111.7, 114.2 (2C), 114.3, 119.7, 120.4. 121.8, 122.5, 123.6, 124.8, 129.9, 131.6 (2C), 132.5, 141.9, 144.5, 147.2, 150.5, 152.0, 160.7, 166.5, 167.9; MS (EI) *m*/*z* (rel int.): 519 (8), 518 (31), 517 (100, M^+), 342 (5), 295 (5), 254 (17), 225 (6), 184 (11), 151 (6), 149 (8), 147 (5), 124 (6), 119 (5), 104 (6).

3.3.8. (*R*,*S*)-Retipolide E trimethyl ether (26). A solution of **25** (259 mg, 0.50 mmol) in dry DMF (1 mL) was added dropwise at 65 °C over 10 min to a solution of freshly distilled *tert*-butyl nitrite (83.0 mg, 0.80 mmol) in dry DMF (33 mL). The mixture was stirred for 20 min, then cooled to rt, and diluted with CH_2Cl_2 (150 mL). The solution was washed with 2 M HCl (3×), water, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dried for 16 h in vacuo and then flash chromatographed ($CHCl_3$/acetone, 100:1) to afford a yellow oil, which was further purified by a second flash chromatography (hexanes/EtOAc, 2:1, R_f=0.35) to yield **26** (155 mg, 62%) as a colorless solid. Recrystallization from CH_2Cl_2/*n*-hexane gave colorless prisms. Mp 210 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (dd, *J*=17.3, 5.4 Hz, 1H, 8-H^a), 3.00 (ddd, *J*=17.3, 11.0, 1.1 Hz, 1H, 8-H^b), 3.02 (d, *J*=13.6 Hz, 1H, 13-H^b), 3.69 (d, *J*=13.6 Hz, 1H, 13-H^a), 3.84, 3.85 (each s, 3H, OMe), 3.89 (ddd, *J*=11.1, 5.4, 1.1 Hz, 1H, 9-H^b), 3.92 (s, 3H, OMe), 4.22 (dd, *J*=11.1, 11.0 Hz, 1H, 9-H^a), 4.73 (d, *J*=1.5 Hz, 1H, 19-H), 6.54 (dd, *J*=8.2. 1.5 Hz, 1H, 6-H), 6.72 (d, *J*=8.2 Hz, 1H, 5-H), 6.94 (dd, *J*=8.4, 2.4 Hz, 1H, 17-H), 6.98 (m, 2H, 8′-H), 7.16 (dd, *J*=8.4, 2.2 Hz, 1H, 18-H), 7.22 (dd, *J*=8.4, 2.4 Hz, 1H, 16-H), 7.61 (m, 2H, 7′-H), 7.62 (dd, *J*=8.4, 2.2 Hz, 1H, 15-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.6 (C8), 43.9 (C13), 55.3 (OMe), 56.1 (OMe), 59.1 (OMe), 68.4 (C9), 87.9 (C12), 111.2 (C5), 113.8 (2×C8′), 115.2 (C19), 120.9 (C6), 121.6 (C6′), 124.2 (C16), 124.6 (C17), 131.0 (C3′), 131.2 (2×C7′), 132.5 (C18), 132.6 (C7), 133.7 (C15), 134.9 (C14), 141.9 (C4′), 146.4 (C4), 152.7 (C3), 158.4 (C1), 160.4 (C9′), 166.2 (C5′), 167.4 (C11); MS (EI) *m*/*z* (rel int.): 504 (6), 503 (31), 502 (100, M^+), 359 (14), 276 (24), 255 (5), 253 (5), 251 (6), 240 (19), 239 (48), 226 (6), 225 (18), 211 (6), 206 (5), 205 (11), 147 (6), 134 (5), 120 (5), 119 (7), 105 (7), 104 (17). Anal. Calcd for $C_{29}H_{26}O_8 \cdot ½CH_2Cl_2$: C 65.02; H 4.99; found: C 65.42; H 4.98.

3.3.9. (*R*,*S*)-Retipolide E [(*R*,*S*)-5]. A solution of **26** (100 mg, 0.20 mmol) in dry CH_2Cl_2 (20 mL) was treated with a solution of boron triiodide (1.17 g, 3.00 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 30 min and then concentrated under reduced pressure. The residue was treated with water (50 mL) and extracted with CH_2Cl_2 (3×). The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography ($CHCl_3$/acetone, 4:1, R_f=0.21) afforded (*R*,*S*)-**5** (38.0 mg, 41%) as a colorless solid; mp 245 °C. The spectroscopic data were identical with those of Section 3.2.10.

3.4. Synthesis of (*R*)-retipolide E via intramolecular nucleophilic aromatic substitution

3.4.1. (4*S*,5*R*)-4-Methyl-5-phenyl-3-propenoyloxazolidin-2-one (27).[17] A mixture of (4*S*,5*R*)-4-methyl-5-phenyl-3-trimethylsilyl-2-oxazolidinone (12.0 g, 48.2 mmol),[17] $CuBr_2$ (15.1 g, 67.5 mmol), copper powder (217 mg, 3.4 mmol), and propenoyl chloride (21.7 mL, 265 mmol) in dry toluene (200 mL) was refluxed for 24 h. The suspension was then cooled to rt, filtered over Celite, and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 4:1, R_f=0.46) afforded **27** (8.02 g, 72%) as a yellow oil. The NMR data agreed with those given in Ref. 17.

3.4.2. (4*S*,5*R*)-3-[(*R*,*S*)-4-Hydroxy-3-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carbonyl]-4-methyl-5-phenyloxazolidin-2-one (29, 1:1 mixture of diastereomers). A solution of **27** (6.94 g, 30 mmol) in EtOAc (200 mL) was

cooled to −78 °C and treated with ozone until the color of the solution remained light blue. The excess of ozone was removed by bubbling argon through the solution. After addition of dimethyl sulfide (6.60 mL, 90.0 mmol), the solution was warmed to rt and reduced to half its volume in vacuo. Methyl 3-(4-methoxyphenyl)pyruvate (6.22 g, 30.0 mmol), NEt_3 (4.0 mL, 30.0 mmol), and EtOAc (100 mL) were added and the mixture was stirred for 2 h. The solution was then diluted with EtOAc (100 mL) and washed with 1 M aq $NaHSO_4$ (3×), water, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by recrystallization from EtOAc/hexanes to yield **29** (4.16 g) as colorless crystals. A second fraction of **29** (3.05 g) was isolated by flash chromatography of the residue (hexanes/EtOAc, 2:1, R_f=0.20 and 0.17). Total yield 7.21 g (59%); mp 84 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72/0.91* (d, *J*=6.5 Hz, 3H, Me), 3.79*/3.82 (s, 3H, OMe), 4.64*/4.79 (dq, *J*=7.3, 6.5 Hz, 1H, C*H*═Me), 5.62*/5.77 (d, *J*=7.3 Hz, 1H, C*H*═Ph), 6.31 (br s, 1H, OH), 6.95 (m, 2H, Ar═H), 7.25–7.37 (m, 3H, 2 Ar═H, CO═C*H*═O), 7.39–7.45 (m, 3H, Ar═H), * signals belong to the same diastereomer; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.2, 55.4, 55.7, 73.9, 79.7, 114.6 (2C), 121.8, 125.6, 126.5, 128.7 (2C), 128.9 (2C), 129.1 (2C), 132.4, 136.5, 152.7, 160.6, 166.1, 169.8; MS (EI) *m*/*z* (rel int.): 410 (7), 409 (35, M^+), 365 (18), 364 (17), 321 (16), 320 (27), 177 (12), 161 (15), 160 (9), 149 (16), 148 (12), 135 (9), 134 (15), 133 (21), 132 (17), 121 (9), 119 (10), 118 (100), 117 (32), 115 (11), 107 (15), 105 (6), 91 (19), 77 (11).

3.4.3. (4*S*,5*R*)-3-[(*R*,*S*)-4-Methoxy-3-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carbonyl]-4-methyl-5-phenyl-oxazolidin-2-one (30, 1:1 mixture of diastereoisomers). A freshly prepared solution of diazomethane in Et_2O (180 mL) was added to a solution of **29** (7.21 g, 17.6 mmol) in acetone (30 mL). The mixture was stirred for 1 h, then treated with acetic acid (1 mL), and concentrated. Purification by flash chromatography (hexanes/Et_2O, 3:1, R_f=0.32 and 0.30) afforded **30** (5.44 g, 73%) as a colorless powder. Mp 68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71/0.94* (d, *J*=6.6 Hz, 3H, Me), 3.86, 4.14 (each s, 3H, OMe), 4.70*/4.82 (dq, *J*=7.3, 6.6 Hz, 1H, C*H*═Me), 5.65*/5.79 (d, *J*=7.3 Hz, 1H, C*H*═Ph), 6.95–7.01 (m, 2H, Ar═H), 7.23–7.33 (m, 3H, 2 Ar═H, CO═C*H*═O), 7.43–7.46 (m, 3H, Ar═H), 7.63–7.67 (m, 2H, Ar═H), * signals belong to the same diastereomer; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 55.2, 55.4, 58.4/58.5, 72.9/73.2, 79.4/79.5, 114.1/114.2 (2C), 121.5, 125.5, 128.6/128.7 (2C), 128.8/128.9 (2C), 129.1 (2C), 132.5, 133.4, 139.9, 152.6, 160.7, 166.1, 167.6; MS (EI) *m*/*z* (rel int.): 424 (8), 423 (31, M^+), 365 (24), 321 (13), 189 (10), 177 (14), 162 (17), 161 (14), 135 (10), 134 (16), 133 (27), 132 (17), 118 (100), 117 (25), 107 (64), 91 (13).

3.4.4. (4*S*,5*R*)-3-[(*R*)-2-(4-Fluoro-3-nitrobenzyl)-4-methoxy-3-(4-methoxyphenyl)-5-oxotetrahydrofuran-2-carbonyl]-4-methyl-5-phenyl-2-oxazolidinone (31). DBU (457 mg, 3.00 mmol) was slowly added to a solution of **30** (1.27 g, 3.00 mmol) and 4-fluoro-3-nitrobenzyl bromide (702 mg, 3.00 mmol) in dry acetonitrile (75 mL). The solution was stirred for 3 h, diluted with Et_2O (250 mL), washed with 2 N aq HCl, satd aq $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 3:1, R_f=0.38) yielded **31** as a yellow oil (1.19 g, 69%). The major diastereomer (*S*,*R*,*R*)-**31** was separated by repeated fractional crystallization from EtOAc/hexanes (761 mg, 44%). Mp 244 °C; $[\alpha]_D^{25}$ +221.4 (*c* 0.50, acetonitrile); CD: λ_{max} (Δε) 200 (+11.0), 213 (−26.8), 238 (+3.3), 245 (+2.3), 257 (+3.8), 279 (+3.0), 290 (sh, +7.9), 314 (+12.4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, *J*=6.6 Hz, 3H, Me), 3.52, 3.75 (AB-qu, *J*=14.3 Hz, 2H, CH_2), 3.87, 4.94 (each s, 3H, OMe), 4.85 (dq, *J*=7.3, 6.6 Hz, 1H, C*H*═Me), 5.54 (d, *J*=7.3 Hz, 1H, C*H*═Ph), 7.00 (m, 2H, Ar═H), 7.11 (ddm, *J*=10.5, 8.6 Hz, 1H, Ar═H), 7.20–7.25 (m, 2H, Ar═H), 7.30 (ddd, *J*=8.6, 4.2, 2.2 Hz, Ar═H), 7.37–7.42 (m, 3H, Ar═H), 7.50 (dd, *J*=7.1, 2.2 Hz, 1H, Ar═H), 7.63 (m, 2H, Ar═H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 42.1, 55.8, 57.6, 59.0, 79.8, 85.5, 115.2 (2C), 118.5, 122.2, 126.1, 128.5, 129.2 (2C), 129.4 (2C), 129.5 (2C), 130.4, 131.5, 133.2, 136.7, 138.4, 144.2, 150.9, 153.8, 160.0, 167.2, 169.8; MS (EI) *m*/*z* (rel int.): 578 (7), 577 (35), 576 (100, M^+), 378 (13), 373 (28), 372 (98), 356 (12), 350 (11), 284 (24), 160 (23), 154 (15), 147 (17), 119 (12), 117 (18), 108 (10), 91 (11).

3.4.5. 2-(3-Hydroxy-4-methoxyphenyl)ethyl (*R*)-2-(4-fluoro-3-nitrobenzyl)-4-methoxy-3-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylate [(*R*)-23]. 1,3-Dichlorotetrabutyldistannoxane[12] (168 mg, 0.30 mmol) was added to a solution of **31** (250 mg, 0.43 mmol) and **22** (723 mg, 4.30 mmol) in dry toluene (30 mL). The mixture was refluxed for 20 h and then concentrated under reduced pressure. Purification by flash chromatography ($CHCl_3$/acetone, 70:1) yielded (*R*)-**23** (162 mg, 66%) as a light yellow oil. $[\alpha]_D^{25}$ +71.9 (*c* 0.99, acetonitrile); CD: λ_{max} (Δε) 210 (−4.8), 216 (−7.6), 288 (+4.4), 274 (−1.0), 297 (−2.4), 314 (−0.7). For spectroscopic data see Section 3.3.5.

3.4.6. (*R*)-Nitroretipolide [(*R*)-24, 1:1 mixture of atropdiastereomers]. Same experimental procedure as described under Section 3.3.6. (*R*)-**23** (108 mg, 0.19 mmol) afforded (*R*)-**24** (65 mg, 62%) as a yellow oil. CD: λ_{max} (Δε) 200 (+7.9), 212 (−18.8), 247 (+18.5), 278 (sh, +4.0), 322 (−0.5). For spectroscopic properties see Section 3.3.6.

3.4.7. (*R*)-Aminoretipolide [(*R*)-25, 1:1 mixture of atropdiastereomers]. Same experimental procedure as described under Section 3.3.7. (*R*)-**24** (46 mg, 0.08 mmol) afforded (*R*)-**25** (36 mg, 87%) as a colorless oil. CD: λ_{max} (Δε) 200 (+31.5), 213 (−30.5), 246 (+16.5), 281 (+0.6), 298 (+2.7). For spectroscopic properties see Section 3.3.7.

3.4.8. (*R*)-Retipolide E trimethyl ether (*R*-26). Same experimental procedure as described under Section 3.3.8. (*R*)-**25** (35 mg, 0.07 mmol) afforded (*R*)-**26** (20 mg, 58%) as a colorless oil. CD: λ_{max} (Δε) 200 (+3.0), 213 (−4.8), 224 (sh, −3.1), 246 (+3.6), 268 (sh, +1.8), 282 (+0.4). For spectroscopic properties see Section 3.3.8.

3.4.9. Retipolide E (5). Same experimental procedure as described under Section 3.3.9. (*R*)-**26** (16 mg, 0.03 mmol) afforded **5** (4 mg, 30%) as a colorless oil. CD: λ_{max} (Δε) 200 (+8.8), 213 (−13.2), 224 (sh, −9.5), 246 (+10.2), 270 (sh, +5.0), 288 (+1.2), 297 (+1.8). For spectroscopic data see

Section 3.2.10. The chromatographic, spectroscopic, and chiroptical properties were identical to those of natural retipolide E.

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References and notes

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