

A Novel Approach in Drug Discovery: Synthesis of Estrone – Talaromycin Natural Product Hybrids

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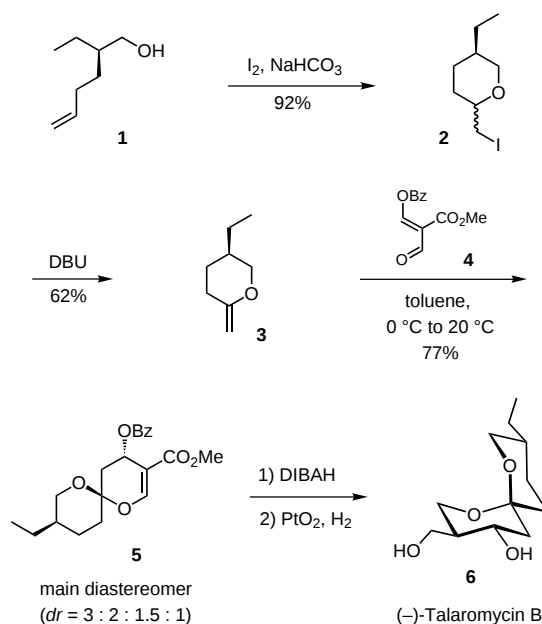
Dedicated to Professor Henning Hopf on the occasion of his 60th birthday

Abstract: Hetero-Diels–Alder reaction of the steroidal exocyclic enol ethers **14** and **15**, obtained from the secoestrones **8** and **9** by reduction, iodoetherification, and elimination, with ethyl *O*-benzoyldiformylacetate (**16**) leads to the spiroacetals **17** and **18** as a mixture of four diastereomers. Reduction of the major diastereomers **17a** and **18a** with DIBAH and subsequent hydrogenation yields the novel natural product hybrids **21**, **23**, **24**, and **25**, which possess the structural features of the steroid estrone (**7**) and the mycotoxin talaromycin **6**.

Keywords: anticancer agents • combinatorial chemistry • cycloadditions • spiro compounds • steroids • talaromycin

Introduction

The synthesis of hybrid natural products by combining structurally different naturally occurring compounds with high biological activities appears to be a promising approach to increase the number and, especially, the diversity of substances for pharmacological testing. By this means, it may be possible to improve the probability of finding new lead structures. Owing to their ability to penetrate cell membranes and bind to specific receptors, steroids represent a valuable class of natural products in this context. It has already been shown that the chemotherapeutic activity of cytostatics against estrone hormone-receptive tumors can be increased by linking them to estrone.^[1,2] Our aim was to combine estrone with mycotoxins to design a new class of cytotoxic compounds. Recently, we reported the enantioselective total synthesis of the biologically highly active spirocyclic mycotoxin (–)-talaromycin B (**6**).^[3] Our strategy was based on an intermolecular hetero-Diels–Alder reaction^[4] of methyl *O*-benzoyldiformylacetate (**4**)^[5] as a 1-oxa-1,3-butadiene with the exocyclic enol ether **3** obtained from **1** by iodoetherification followed by elimination (Scheme 1).^[3d]

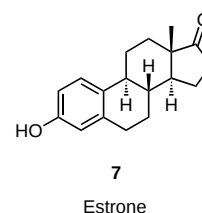


Scheme 1. Enantioselective total synthesis of (–)-talaromycin B (**6**) employing a hetero-Diels–Alder reaction.

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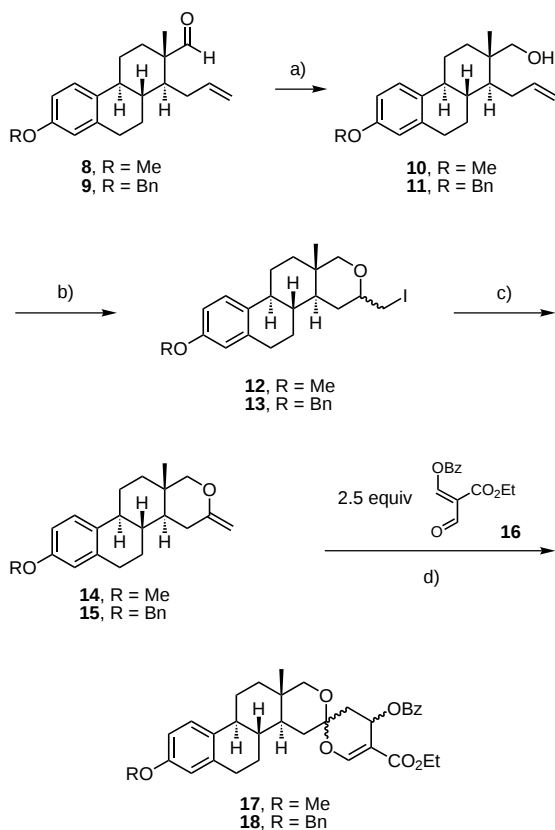
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We present here the synthesis of hybrid natural products consisting of estrone (**7**) and the mycotoxin talaromycin **6** using this method, starting from the D-secoestrones **8** and **9**.^[6]



Results and Discussion

The D-secoestrone **8** and **9**, which are easily accessible in five steps from estrone (**7**) by employing a Grob fragmentation as the key step,^[7] were reduced to the alcohols **10** and **11** by using sodium or potassium borohydride (Scheme 2). Subsequent iodoetherification afforded the iodoethers **12** and **13** as 2:1 and 2.5:1 mixtures, respectively, of both possible epimers in

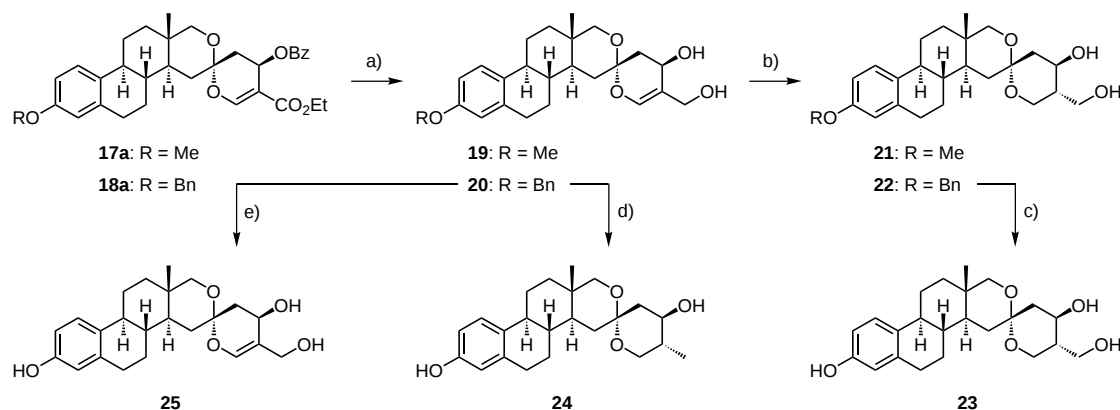


Scheme 2. Synthesis of the spiroacetals **17** and **18**; a) **8**: 10 equiv NaBH₄, MeOH, RT, 30 min; **9**: 10 equiv KBH₄, MeOH, RT, 30 min, 99 % of **11**; b) I₂, NaHCO₃, Et₂O/H₂O, RT, 4 h; **12**: 99 % from **8** (*ds* = 2:1); **13**: 96 % (*ds* = 2.5:1); c) DBU (neat), 90–100 °C, 30 min; d) toluene/CH₂Cl₂, RT, 14 h; **17**: 76 % from **12** (*dr* = **a:b:c:d** = 3.9:3.2:1.0:1.0); **18**: 72 % from **13** (*dr* = **a:b:c:d** = 4.5:4.0:1.5:1.0); Bn = benzyl, Bz = benzoyl.

excellent yields. The low diastereoselectivity was of no concern as the new stereogenic center was destroyed in the next step. The subsequent elimination to give the exocyclic enol ethers **14** and **15** as single double-bond isomers was achieved under solvent-free conditions with DBU as the base at 90 °C. The methylene-tetrahydropyrans **14** and **15** thus obtained had to be used directly in the next step without further purification, since they are rather sensitive and prone to isomerization. Hetero-Diels–Alder reactions of **14** and **15** with ethyl *O*-benzoyldiformylacetate (**16**) gave the spiroacetals^[8] **17** and **18** in overall yields of 76 % and 72 %, respectively, as mixtures of four diastereomers. The diastereomer ratios were determined as 3.9:3.2:1.0:1.0 for **17** and 4.5:4.0:1.5:1.0 for **18** by HPLC analysis. The separation of the major diastereomers **17a** and **18a** was achieved by column chromatography and subsequent crystallization. The relative configurations of the two compounds were determined by X-ray analysis.^[9] It can be assumed that the formation of the major diastereomers **17a** and **18a** results from an *exo* attack of the heterodiene *anti* to the angular methyl group at C-5 in **14** and **15**, respectively.

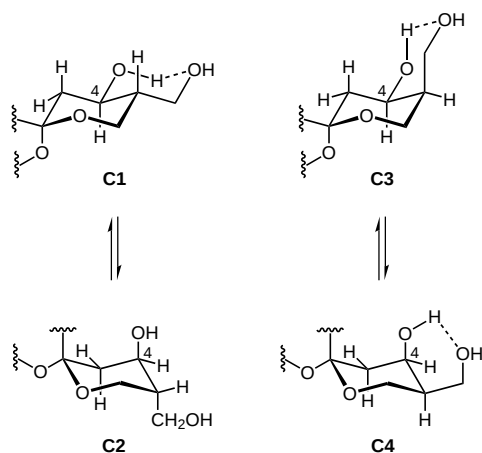
The two ester moieties in **17a** and **18a** were reduced with DIBAH to afford the diols **19** and **20** in yields of 70 % and 76 %, respectively (Scheme 3). The double bonds in **19** and **20** were then hydrogenated in a highly stereoselective manner, by employing 50 bar of hydrogen pressure and 10 mol % PtO₂ as catalyst, to give the protected estrone–talaromycin hybrids **21** and **22** in quantitative yield. The selective generation of the newly formed stereogenic centers in **21** and **22** resulted from a β -addition of hydrogen to the olefinic double bond. The benzyl group in **22** could be removed by catalytic hydrogenolysis in the presence of Pd/C under 65 bar to give the estrone–talaromycin hybrid **23** in 99 % yield. Hydrogenation of **20** with Pd/C as catalyst led to both cleavage of the benzyl ether moiety and reduction of the allylic alcohol. This furnished the diol **24** as a single diastereomer in quantitative yield.^[10] The hybrid **25** was obtained in 90 % yield by a Birch reduction of **20** with lithium in liquid ammonia at –78 °C. In this reaction only the benzyl ether is cleaved, while the allylic alcohol is left mainly untouched.

The configuration at C-4 of the new compounds **21** and **22** was determined by NMR analysis. The ¹H NMR coupling



Scheme 3. Synthesis of the estrone–talaromycin hybrids **23**, **24**, and **25**; a) 12 equiv DIBAH, THF/CH₂Cl₂, –78 °C, 21 h; **19**: 70 %; **20**: 76 %; b) 10 mol % PtO₂, H₂ (50 bar), MeOH/ethyl acetate, RT, 12 h, 99 %; c) 10 mol % Pd/C, H₂ (65 bar), MeOH/ethyl acetate, RT, 20 h, 99 %; d) 10 mol % Pd/C, H₂ (65 bar), MeOH/ethyl acetate, RT, 24 h, 99 %; e) Li, NH₃ (l), MeOH, –78 °C, 3 h, 90 %.

constants of the 4-H signal at $\delta = 3.81$ for **21** ($J_1 = J_2 = 10.9$ Hz, $J_3 = 4.9$ Hz) and at $\delta = 3.80$ for **22** ($J_1 = J_2 = 10.6$ Hz, $J_3 = 4.8$ Hz) result from two axial–axial couplings and one axial–equatorial coupling. This coupling pattern is only possible in conformation **C1** of the given diastereomers **21** and **22** (Scheme 4). Owing to the anomeric effect and the



Scheme 4. Conformation of the spiroacetal moiety in **21** and **22**.

H-bonding interaction, conformation **C1** should be more stable than conformation **C2**; therefore, it is not surprising that **21** and **22** mainly exist in the former conformation.

The toxicities of the new hybrid compounds were determined by performing HTCFA tests (Human tumor colony forming ability). For this purpose, 10^2 to 10^5 human lung cancer cells of the line A 549 were placed in six-well multiplates and cultivated in a culture medium that contained 90% DMEM (Dulbecco's modified Eagle's medium) and 10% FCS (fetal calf serum). After 24 h of cultivation, the medium was removed, and the cells were incubated with different concentrations of the synthesized estrone–talaromycin hybrids dissolved in DMSO/culture medium for 24 h. The remaining cells were cultivated for a further 8–9 days at 37 °C in air with a CO₂ content of 7.5% and dyed with Löffler's methylene blue; finally the relative colony-forming rate was determined.^[11] Effective dosage values (ED₅₀) of 23 μM for **19**, 30 μM for **21**, 73 μM for **23**, and 95 μM for **24** were determined. The measured cytotoxicities of the new compounds are comparable with that of the well-known anticancer agent cyclophosphamide. The obtained values represent the lower limits of the cytotoxicities, since the tested compounds caused some problems with regard to solubility in the culture medium. We had expected compound **23** to show at least the same cytotoxicity as **21**; however, the slightly lower cytotoxicity of the former may be explained in terms of a reduced ability to penetrate the cell membrane due to its higher polarity.

Conclusion

The combination of different natural products showing pronounced biological activities seems to be a promising new approach for the generation of pharmacologically

interesting compounds in combinatorial chemistry. The described linkage of estrone to the mycotoxin talaromycin has led to a new class of natural product hybrids that exhibits anticancer activity.

Experimental Section

General methods: All solvents were distilled and dried prior to use. Reagents and materials were obtained from commercial suppliers and were used without further purification. Analytical thin-layer chromatography was performed on precoated silica gel SIL G/UV₂₅₄ plates (Macherey, Nagel). Silica gel 32–63 (0.032–0.063 mm) (Macherey, Nagel) was used for column chromatography. HPLC was carried out on a Kontron HPLC instrument with a Merck Lichrospher 100 RP-18 (5 μm) column and HPLC-grade solvents (80% CH₃CN/20% H₂O) for elution at a flow rate of 0.5 mL min^{−1}. Melting points were determined on a Mettler FP61 apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were recorded from samples in KBr pellets on Bruker IFS 25 or Vector 22 spectrometers. UV/Vis spectra were recorded on a Perkin–Elmer Lambda 9 spectrophotometer with sample solutions in 1 cm quartz cuvettes. NMR spectra were recorded on Varian VXR200 [50 MHz (¹³C)], Bruker AMX300 [300 MHz (¹H), 75 MHz (¹³C)], Varian VXR500 [500 MHz (¹H), 125 MHz (¹³C)], or Bruker AM400 spectrometers [400 MHz (¹H), 100 MHz, (¹³C)] at room temperature unless otherwise noted. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS, $\delta = 0$). Alternatively, spectra were referenced to the resonances of residual solvent protons. Multiplicities of ¹³C NMR peaks were determined by using the APT pulse sequence. EI mass spectra were measured on a Varian MAT 311A with an ionization energy of 70 eV. High-resolution mass spectra (HRMS) were measured on a Varian MAT 731 (EI) or on a Bruker Bioapex Fourier transform ion cyclotron resonance mass spectrometer equipped with an external electrospray ionization source. Elemental analyses were performed in the Microanalytical Laboratory of the Georg-August University Göttingen. Crystal data were collected on a Stoe-Siemens AED diffractometer. Programs used: Bruker AXS SAINT (data reduction), SHELXS-97 (solution), and SHELXL-97 (refinement).^[9]

Reduction of the aldehydes **8** and **9**

Alcohol 11: KBH₄ (2.85 g, 52.9 mmol) was added to a solution of the aldehyde **9** (1.98 g, 5.29 mmol) in methanol (80 mL) at 0 °C. The mixture was stirred for 30 min at room temperature, then diluted with water (150 mL), acidified with 10% H₂SO₄ (20 mL), saturated with NH₄Cl, and extracted with CH₂Cl₂ (3 × 60 mL). The combined organic extracts were dried with Na₂SO₄ and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether/*tert*-butyl methyl ether, 5:1) furnished 1.97 g (5.23 mmol, 99%) of **11**. $R_f = 0.16$ (PE/MTBE, 5:1); $[\alpha]_D^{20} = +72.0$ ($c = 0.5$ in CHCl₃); UV/Vis (CH₃CN): $\lambda_{\max}$ (lg ϵ) = 200.5 (4.729), 278.5 (3.300), 286.0 nm (3.259); IR (KBr): $\tilde{\nu} = 3408$ (OH), 3111, 3032 (Ar-H), 2922 (CH₃), 2862 (CH), 1608, 1576, 1499 (C=C), 841 cm^{−1} (Ar-H); ¹H NMR (500 MHz, CDCl₃): $\delta = 0.78$ (s, 3H, 2-CH₃), 1.21–1.54 (m, 6H, 10-H₂, 4-H_a, 3-H_a, OH, 1-H), 1.74 (m_c, 1H, 10a-H), 2.05 (m_c, 1H, 3-H_b), 2.13–2.18 (m, 1H, 4-H_b), 2.19–2.34 (m, 3H, 4a-H, 1'-H₂), 2.80–2.85 (m, 2H, 9-H₂), 3.28 (d, $J = 10.1$ Hz, 1H, CH₂OH), 3.60 (d, $J = 10.1$ Hz, 1H, CH₂OH), 4.95 (dd, $J = 10.0$, 3.0 Hz, 1H, 3'-H₂), 5.02 (s, 2H, CH₂Ph), 5.05 (dd, $J = 17.2$, 3.0 Hz, 1H, 3'-H_E), 5.91 (dddd, $J = 17.2$, 10.0, 7.0, 6.0 Hz, 1H, 2'-H), 6.70 (d, $J = 2.5$ Hz, 1H, 8-H), 6.77 (dd, $J = 8.5$, 2.5 Hz, 1H, 6-H), 7.21 (d, $J = 8.5$ Hz, 1H, 5-H), 7.28–7.42 (m, 5H, Ph-H); ¹³C NMR (50 MHz, CDCl₃): $\delta = 16.25$, 26.18, 27.58, 30.44, 32.40, 35.82, 38.89, 41.18, 43.44, 44.24, 69.90, 70.97, 112.3, 114.3, 114.4, 126.4, 127.4 (2C), 127.8, 128.5 (2C), 133.1, 137.3, 137.9, 140.4, 156.7; MS (EI, 70 eV): m/z (%): 376.4 (96) [M]⁺, 91.1 (100) [C_7H_7]⁺, 57.1 (40) [C_4H_9]⁺, 43.1 (26) [C_3H_7]⁺, 41.1 (24) [C_3H_5]⁺; elemental analysis calcd (%) for C₂₆H₃₂O₂ (376.2): C 82.94, H 8.57; found C 82.73, H 8.49.

Alcohol 10: Aldehyde **8** (2.68 g, 9.0 mmol) was reduced with NaBH₄ (3.38 g, 90 mmol) in methanol (120 mL) as described for **11** to give alcohol **10**. The product was used without purification for the next step.

Iodoetherification of **10** and **11**

Tetrahydropyran 12: Water (7.5 mL), NaHCO₃ (1.13 g, 13.5 mmol), and iodine (3.43 g, 13.5 mmol) were added to a solution of crude alcohol **10**

(2.70 g, 9.0 mmol) in diethyl ether (25 mL) at 0 °C. The resulting mixture was stirred at room temperature for 4 h, and then the reaction was quenched by the addition of saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (25 mL). The mixture was extracted with diethyl ether (3 × 30 mL), and the combined extracts were dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by column filtration gave 3.84 g (99 % yield) of a mixture of the two diastereomeric tetrahydropyrans **12**. Separation of the diastereomers could be achieved by column chromatography (petroleum ether/*tert*-butyl methyl ether 20:1). The major diastereomer was obtained as white crystals. Analytical data for the major isomer: m.p. 126.4 °C; $[\alpha]_{\text{D}}^{20} = +54.0$ ($c = 0.5$ in CHCl_3); IR (KBr): $\tilde{\nu} = 2936$ (CH_3), 2866 (Ar-H), 2846 cm^{-1} (Ar-H); UV/Vis (CH_3CN): λ_{max} ($\lg \epsilon$) = 200.0 (4.654), 278.5 (3.299), 286.0 nm (3.255); ^1H NMR (400 MHz, CDCl_3): $\delta = 1.00$ (s, 3H, 5- CH_3), 1.10–1.38 (m, 5H, 1'-c-H, 1'- H_2 , 3- H_2), 1.40–1.65 (m, 2H, 8'- H_2), 1.82 (br d, $J = 12.0$ Hz, 1H, 4-H), 1.93–2.02 (m, 1H, 2'- H_a), 2.25–2.37 (m, 2H, 2'- H_b , 7b-H), 2.78–2.90 (m, 2H, 3'- H_2), 3.17 (d, $J = 10.8$ Hz, 1H, 6- H_a), 3.19–3.35 (m, 3H, 2- CH_2 I, 2-H), 3.57 (d, $J = 10.8$ Hz, 1H, 6- H_b), 3.78 (s, 3H, 5'- OCH_3), 6.63 (d, $J = 2.7$ Hz, 1H, 4'-H), 6.72 (dd, $J = 8.6$, 2.7 Hz, 1H, 6'-H), 7.20 (d, $J = 8.6$ Hz, 1H, 7'-H); ^{13}C NMR (50 MHz, CDCl_3): $\delta = 10.62$, 16.62, 25.39, 25.61, 29.85, 30.42, 33.86, 34.96, 38.40, 43.61, 47.09, 55.12, 76.38, 79.84, 111.5, 113.4, 126.0, 132.3, 137.6, 157.4; MS (EI, 70 eV): m/z (%): 426.4 (100) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{20}\text{H}_{27}\text{IO}_2$ (426.3): C 56.35, H 6.38; found C 56.10, H 6.10.

Tetrahydropyran 13: Alcohol **11** (1.97 g, 5.23 mmol) was transformed as described above in the preparation of **12** to yield the two diastereomeric tetrahydropyrans **13** (2.52 g, 5.02 mmol, 96 %) as a 2.5:1 mixture. Separation of the diastereomers could be achieved by column chromatography (petroleum ether/*tert*-butyl methyl ether, 20:1). Analytical data for the major isomer: $R_f = 0.41$ (PE/MTBE, 20:1); m.p. 108.8 °C; $[\alpha]_{\text{D}}^{20} = +46.2$ ($c = 1.0$ in CHCl_3); IR (KBr): $\tilde{\nu} = 2935$ (CH_3), 2860 (Ar-H), 2843 cm^{-1} (Ar-H); UV/Vis (CH_3CN): λ_{max} ($\lg \epsilon$) = 200.5 (3.993), 278.0 (2.638), 286.0 nm (2.586); ^1H NMR (500 MHz, CDCl_3): $\delta = 0.99$ (s, 3H, 5- CH_3), 1.14–1.36 (m, 5H, 1'-c-H, 1'- H_2 , 3- H_2), 1.41–1.57 (m, 2H, 8'- H_2), 1.79 (br d, $J = 12.4$ Hz, 1H, 4-H), 1.93–2.01 (m, 1H, 2'- H_a), 2.24–2.32 (m, 2H, 2'- H_b , 7b-H), 2.79–2.85 (m, 2H, 3'- H_2), 3.16 (d, $J = 10.8$ Hz, 1H, 6- H_a), 3.21–3.32 (m, 3H, 2- CH_2 I, 2-H), 3.55 (d, $J = 10.8$ Hz, 1H, 6- H_b), 5.02 (s, 2H, CH_2Ph), 6.70 (d, $J = 2.8$ Hz, 1H, 4'-H), 6.77 (dd, $J = 8.6$, 2.8 Hz, 1H, 6'-H), 7.19 (d, $J = 8.6$ Hz, 1H, 7'-H), 7.28–7.44 (m, 5H, Ph-H); ^{13}C NMR (50 MHz, CDCl_3): $\delta = 10.63$, 16.64, 25.41, 25.63, 29.88, 30.45, 33.90, 35.00, 38.41, 43.69, 47.14, 69.88, 77.36, 79.90, 112.4, 114.5, 126.1, 127.4 (2C), 127.8, 128.5 (2C), 132.7, 137.2, 137.7, 156.7; MS (EI, 70 eV): m/z (%): 502.3 (36) $[M]^+$, 91.1 (100) $[\text{C}_7\text{H}_7]^+$; elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{31}\text{IO}_2$ (502.4): C 62.15, H 6.22; found C 62.45, H 6.16.

Elimination of the iodides **12** and **13**

Enol ether 14: All glassware used for this preparation was first washed with a concentrated solution of potassium hydroxide in water/ethanol (1:1) and dried in vacuo. The tetrahydropyran **12** (426 mg, 1.0 mmol) and DBU (244 mg, 1.6 mmol, 240 μL) were heated at 90–100 °C for 30 min. The mixture was then cooled to room temperature and diluted with diethyl ether (13 mL), CH_2Cl_2 (13 mL), and water (8 mL). The organic layer was separated, washed with water (10 mL), dried with Na_2SO_4 , and concentrated in vacuo. Crude **14** was used for the next step without further purification. $\text{C}_{20}\text{H}_{26}\text{O}_2$ (298.4).

Enol ether 15: Treatment of iodide **13** (1.45 g, 2.88 mmol) as described in the preparation of **14** gave the enol ether **15**, which was used for the next step without further purification. $\text{C}_{26}\text{H}_{30}\text{O}_2$ (374.5).

Hetero-Diels–Alder reaction of **14** and **15** with ethyl *O*-benzoyldiformylacetate (**16**)

Spiroacetal 17: The anhydrous sodium salt of ethyl diformylacetate (380 mg, 2.50 mmol), which was obtained by titration of the free acid with aqueous sodium hydroxide solution and drying in vacuo, was suspended in toluene (4.0 mL) and treated with benzoyl chloride (351 mg, 2.50 mmol, 290 μL). The resulting suspension was stirred for 1 h at room temperature and then cooled to 0 °C. A solution of the crude enol ether **14** (298 mg, 1.00 mmol) in toluene/ CH_2Cl_2 (0.7 mL, 1:1) was added and stirring was continued for 3 h at 0 °C and for a further 11 h at room temperature. The reaction was then quenched by the addition of saturated aqueous sodium bicarbonate solution (4.0 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 3.0 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Column

filtration through deactivated silica gel (1 % NaHCO_3) gave 405 mg (76 % based on **12**) of **17** as a mixture of four diastereomers in a 3.9:3.2:1.0:1.0 ratio, with **17a** as the major isomer (HPLC). Compound **17a** was isolated by crystallization after column chromatography on deactivated silica gel (1 % NaHCO_3 , gradient: petroleum ether/ethyl acetate 10:1 to 5:1). Data for the pure diastereomer **17a**: m.p. 167.2 °C; $[\alpha]_{\text{D}}^{20} = +104.0$ ($c = 0.5$ in CHCl_3); IR (KBr): $\tilde{\nu} = 2944$ (CH_3), 1716 ($-\text{CO}_2-$), 1634, 1502 ($\text{C}=\text{C}$), 714 cm^{-1} (Ar-H); UV/Vis (CH_3CN): λ_{max} ($\lg \epsilon$) = 196.0 (4.902), 229.5 (4.499), 279.0 nm (3.435); ^1H NMR (500 MHz, CDCl_3): $\delta = 0.97$ (s, 3H, 9- CH_3), 1.13 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.20–1.36 (m, 4H, 2'- H_a , 1'- H_a , 10-H, 11- H_a), 1.45–1.54 (m, 2H, 1'- H_b , 8'- H_a), 1.63 (ddd, $J = 13.5$, 10.5, 2.7 Hz, 1H, 1'-c-H), 1.93–1.97 (m, 1H, 2'- H_b), 2.18 (dd, $J = 14.5$, 5.1 Hz, 1H, 5- H_a), 2.28–2.38 (m, 4H, 5- H_b , 7b-H, 8'- H_b , 11- H_b), 2.74–2.92 (m, 2H, 3'- H_2), 3.33 (d, $J = 10.8$ Hz, 1H, 8- H_a), 3.67 (d, $J = 10.8$ Hz, 1H, 8- H_b), 3.78 (s, 3H, 5'- OCH_3), 4.10 (dq, $J = 10.8$, 7.1 Hz, 1H, CH_aCH_3), 4.17 (dq, $J = 10.8$, 7.1 Hz, 1H, CH_bCH_3), 6.13 (t, $J = 5.3$ Hz, 1H, 4-H), 6.64 (d, $J = 2.8$ Hz, 1H, 4'-H), 6.73 (dd, $J = 8.4$, 2.8 Hz, 1H, 6'-H), 7.20 (d, $J = 8.4$ Hz, 1H, 7'-H), 7.44 (t, $J = 6.1$ Hz, 2H, Bz- H_m), 7.56 (tt, $J = 6.1$, 1.2 Hz, 1H, Bz- H_l), 7.57 (s, 1H, 2-H), 8.04 (dd, $J = 8.4$, 1.2 Hz, 2H, Bz- H_o); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 14.22$, 15.88, 25.33, 25.65, 29.83, 33.25, 33.28, 35.09, 37.74, 38.29, 41.42, 43.53, 55.18, 60.09, 61.00, 73.97, 99.11, 106.1, 111.7, 113.6, 126.1, 128.2 (2C), 129.8 (2C), 131.0, 132.4, 132.6, 137.7, 155.7, 157.6, 166.3, 166.4; MS (EI, 70 eV): m/z (%): 546.7 (9) $[M]^+$, 441.6 (12) $[M - \text{C}_7\text{H}_5\text{O}]^+$, 424.6 (38) $[M - \text{PhCO}_2\text{H}]^+$, 298.4 (34) $[M - \text{PhCO}_2\text{H} - \text{C}_7\text{H}_5\text{O}_2]^+$, 122.2 (86) $[\text{PhCO}_2\text{H}]^+$; elemental analysis calcd (%) for $\text{C}_{33}\text{H}_{38}\text{O}_7$ (546.7): C 72.51, H 7.01; found C 72.38, H 6.84.

Spiroacetal 18: Reaction of **16** and the crude enol ether **15** as described above in the preparation of **17** gave 1.29 g (2.07 mmol, 72 % based on **13**) of the spiroacetal **18** as a mixture of four diastereomers in a 4.5:4.0:1.5:1.0 ratio, with **18a** as the major isomer (HPLC). Compound **18a** was isolated by crystallization after column chromatography on deactivated silica gel (1 % NaHCO_3 , gradient: petroleum ether/ethyl acetate, 10:1 to 5:1). $R_f = 0.32$ (PE/EtOAc, 5:1); m.p. 159.9 °C; $[\alpha]_{\text{D}}^{20} = +88.8$ ($c = 1.0$ in CHCl_3); IR (KBr): $\tilde{\nu} = 2941$ (CH_3), 1718 ($-\text{CO}_2-$), 1633 ($\text{C}=\text{C}$), 1503 ($\text{C}=\text{C}$), 712 cm^{-1} (Ar-H); UV/Vis (CH_3CN): λ_{max} ($\lg \epsilon$) = 229.5 (3.574), 278.5 nm (2.460); ^1H NMR (500 MHz, CDCl_3): $\delta = 0.97$ (s, 3H, 9- CH_3), 1.12 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.18–1.35 (m, 4H, 1'- H_a , 2'- H_a , 10-H, 11- H_a), 1.42–1.56 (m, 2H, 1'- H_b , 8'- H_a), 1.61 (ddd, $J = 13.3$, 10.8, 3.9 Hz, 1H, 1'-c-H), 1.89–1.97 (m, 1H, 2'- H_b), 2.16 (dd, $J = 14.4$, 5.3 Hz, 1H, 5- H_a), 2.26–2.37 (m, 4H, 5- H_b , 7b-H, 8'- H_b , 11- H_b), 2.72–2.81 (m, 1H, 3'- H_a), 2.86 (m, 1H, 3'- H_b), 3.31 (d, $J = 10.7$ Hz, 1H, 8- H_a), 3.65 (d, $J = 10.7$ Hz, 1H, 8- H_b), 4.08 (dq, $J = 10.8$, 7.1 Hz, 1H, CH_aCH_3), 4.16 (dq, $J = 10.8$, 7.1 Hz, 1H, CH_bCH_3), 5.02 (s, 2H, CH_2Ph), 6.11 (t, $J = 5.4$ Hz, 1H, 4-H), 6.71 (d, $J = 2.6$ Hz, 1H, 4'-H), 6.78 (dd, $J = 8.5$, 2.6 Hz, 1H, 6'-H), 7.19 (d, $J = 8.5$ Hz, 1H, 7'-H), 7.28–7.45 (m, 7H, 5 × Bn-H, 2 × Bz- H_m), 7.55 (m, 1H, Bz- H_l), 7.65 (s, 1H, 2-H), 8.02 (dd, $J = 8.4$, 1.1 Hz, 2H, Bz- H_o); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 14.13$, 15.78, 25.28, 25.75, 29.74, 31.89, 33.17, 34.96, 38.25, 38.28, 41.42, 43.46, 60.10, 62.80, 69.90, 73.92, 101.5, 105.8, 112.4, 114.5, 126.1, 127.4 (2C), 127.8, 128.3 (2C), 128.5 (2C), 129.6 (2C), 130.3, 132.7, 133.0, 137.2, 137.6, 155.5, 156.8, 165.5, 166.1; MS (EI, 70 eV): m/z (%): 622.4 (4) $[M]^+$, 546.5 (25) $[M - \text{C}_6\text{H}_5]^+$, 500.4 (19) $[M - \text{PhCO}_2\text{H}]^+$, 374.4 (14) $[M - \text{PhCO}_2\text{H} - \text{C}_7\text{H}_{10}\text{O}_2]^+$, 91.1 (100) $[\text{C}_7\text{H}_7]^+$; elemental analysis calcd (%) for $\text{C}_{39}\text{H}_{42}\text{O}_7$ (622.8): C 75.22, H 6.80; found C 75.20, H 6.66.

DIBAH reduction of the diesters **17a** and **18a**

Diol 19: A solution of the diester **17a** (111 mg, 0.20 mmol) in THF/ CH_2Cl_2 (30 mL, 1:1) was treated with DIBAH solution in toluene (1M, 2.40 mmol, 2.40 mL) at –78 °C. The resulting mixture was stirred for 21 h at –78 °C, allowed to warm to room temperature, and quenched with saturated sodium bicarbonate solution (0.1 mL) and 10 % aqueous sodium hydroxide solution (0.2 mL). The resulting mixture was filtered, diluted with CH_2Cl_2 (100 mL), washed with water (30 mL) and brine (30 mL), and dried with MgSO_4 . After evaporation of the solvents, chromatographic purification (SiO_2 , petroleum ether/ethyl acetate, 1:1) of the residue gave 57 mg of the diol **19** (70 %) as a white solid. M.p. 146.9 °C; $[\alpha]_{\text{D}}^{20} = +114.7$ ($c = 0.17$ in MeOH); IR (KBr): $\tilde{\nu} = 3426$ (OH), 2930 (CH_3), 1666 ($\text{C}=\text{C}$), 840 cm^{-1} (Ar-H); UV/Vis (CH_3CN): λ_{max} ($\lg \epsilon$) = 200.5 (4.694), 278.5 (3.292), 286.0 nm (3.259); ^1H NMR (500 MHz, CDCl_3): $\delta = 0.99$ (s, 3H, 9- CH_3), 1.20–1.50 (m, 7H, 2'- H_a , 8'- H_2 , 1'- H_2 , 10-H, OH), 1.65 (m, 1H, 2'- H_b), 1.85 (dd, $J = 13.0$, 9.3 Hz, 1H, 5- H_a), 1.94–1.98 (m, 1H, 3'- H_a), 1.96 (dd, $J = 13.5$, 3.7 Hz, 1H, 11- H_a), 2.24 (dd, $J = 13.0$, 6.4 Hz, 1H, 5- H_b), 2.30–2.36 (m, 2H, 11- H_b , 1'-c-H), 2.78–2.90 (m, 2H, 3'- H_b , 7b-H), 3.18 (d, $J = 10.7$ Hz, 1H, 8- H_a),

3.48 (d, $J = 10.7$ Hz, 1H, 8-H_b), 3.78 (s, 3H, 5'-OCH₃), 4.15 (d, $J = 12.0$ Hz, 1H, 3-CH₂OH), 4.27 (d, $J = 12.0$ Hz, 1H, 3-CH₂OH), 4.70 (m, 1H, 4-H), 6.30 (s, 1H, 2-H), 6.63 (d, $J = 2.8$ Hz, 1H, 4'-H), 6.72 (dd, $J = 8.5$, 2.8 Hz, 1H, 6'-H), 7.20 (d, $J = 8.5$ Hz, 1H, 7'-H); ¹³C NMR (75 MHz, CD₃OD): $\delta = 16.35$, 26.66, 26.89, 30.84, 34.35, 34.57, 36.36, 39.97, 42.81, 42.85, 45.07, 55.64, 61.17, 62.43, 74.45, 101.1, 112.7, 114.6, 117.5, 126.9, 133.9, 138.9, 140.4, 159.1; MS (EI, 70 eV): m/z (%): 400.3 (3) [M]⁺, 298.3 (100) [$M - C_4H_6O_3$]⁺; elemental analysis calcd (%) for C₂₄H₃₂O₅ (400.5): C 71.97, H 8.05; found C 71.72, H 8.14.

Diol 20: Reduction of **18a** (278 mg, 0.45 mmol) as described above in the preparation of **19** gave the diol **20** (163 mg, 0.34 mmol, 76%) as a white solid. $R_f = 0.17$ (PE/EtOAc, 1:1); m.p. 157.2 °C; [α]_D²⁰ = +146.0 ($c = 0.3$ in CHCl₃); IR (KBr): $\tilde{\nu} = 3376$ (OH), 2929 (CH₃), 1664 (C=C), 841 cm⁻¹ (Ar-H); UV/Vis (CH₃CN): λ_{max} (lg ϵ) = 201.5 (4.031), 278.5 (2.536), 286.0 nm (2.480); ¹H NMR (500 MHz, CDCl₃): $\delta = 0.97$ (s, 3H, 9-CH₃), 1.19–1.55 (m, 7H, 2'-H_a, 8'-H₂, 1'-H₂, 10-H, OH), 1.63 (m, 2H, 2'-H_b, OH), 1.82 (dd, $J = 12.9$, 9.5 Hz, 1H, 5-H_a), 1.87–1.97 (m, 2H, 3'-H_a, 11-H₂), 2.22 (dd, $J = 12.9$, 6.6 Hz, 1H, 5-H_b), 2.26–2.36 (m, 2H, 11-H_b, 1'-c-H), 2.74–2.86 (m, 2H, 3'-H_b, 7b-H), 3.16 (d, $J = 10.7$ Hz, 1H, 8-H_a), 3.46 (d, $J = 10.7$ Hz, 1H, 8-H_b), 4.14 (d, $J = 11.9$ Hz, 1H, 3-CH₂OH), 4.23 (d, $J = 11.9$ Hz, 1H, 3-CH₂OH), 4.67 (brdd, $J = 9.5$, 6.6 Hz, 1H, 4-H), 5.01 (s, 2H, CH₂Ph), 6.28 (s, 1H, 2-H), 6.70 (d, $J = 2.6$ Hz, 1H, 4'-H), 6.77 (dd, $J = 8.5$, 2.6 Hz, 1H, 6'-H), 7.18 (d, $J = 8.5$ Hz, 1H, 7'-H), 7.27–7.44 (m, 5H, Ph-H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 15.85$, 25.32, 25.58, 29.84, 33.15, 33.44, 35.06, 38.26, 41.22, 41.61, 43.52, 62.59, 63.38, 69.94, 73.33, 99.88, 112.4, 114.6, 114.8, 126.1, 127.4 (2C), 127.8, 128.5 (2C), 132.9, 137.2, 137.8, 140.0, 156.8; MS (EI, 70 eV): m/z (%): 476.5 (2) [M]⁺, 458.4 (46) [$M - H_2O$]⁺, 374.4 (100) [$M - C_4H_6O_3$]⁺, 91.1 (60) [C_7H_7]⁺; HRMS: calcd for C₃₀H₃₆O₅ 476.2563; found 476.2562.

Selective hydrogenation of **19** and **20**

Hybrid compound 21: A suspension of diol **19** (40 mg, 100 μ mol) and PtO₂ (2.3 mg, 10 μ mol, 10 mol %) in methanol/ethyl acetate (10 mL, 1:1) was subjected to 50 bar of hydrogen pressure at room temperature for 12 h. The catalyst was then removed by filtration through a short pad of silica gel. Evaporation of the solvent from the filtrate gave 40 mg (99 μ mol, 99%) of **21** as a white solid. M.p. 150 °C (dec.); [α]_D²⁰ = +109.7 ($c = 0.3$ in MeOH); IR (KBr): $\tilde{\nu} = 3420$ (OH), 2926 (CH₃), 2872 (Ar-O-CH₃), 1608 (C=C), 844 cm⁻¹ (Ar-H); UV/Vis (CH₃CN): λ_{max} (lg ϵ) = 200.0 (4.606), 278.5 (3.276), 286.0 nm (3.242); ¹H NMR (500 MHz, CD₃OD): $\delta = 0.98$ (s, 3H, 9-CH₃), 1.15–1.35 (m, 6H, 1'-H₂, 8'-H₂, 10-H, OH), 1.38–1.50 (m, 3H, 1'-c-H, 3-H, OH), 1.55–1.70 (m, 2H, 5-H_a, 7b-H), 1.73 (dd, $J = 13.1$, 3.8 Hz, 1H, 2'-H_a), 1.92–1.96 (m, 1H, 2'-H_b), 2.00 (dd, $J = 12.6$, 5.0 Hz, 1H, 5-H_b), 2.23–2.33 (m, 2H, 11-H₂), 2.71–2.80 (m, 2H, 3'-H₂), 3.08 (d, $J = 10.6$ Hz, 1H, 8-H_a), 3.33 (d, $J = 10.6$ Hz, 1H, 8-H_b), 3.46 (t, $J = 11.3$ Hz, 1H, 2-H_a), 3.49 (dd, $J = 11.3$, 7.5 Hz, 1H, 2-H_b), 3.72 (s, 3H, 5'-OCH₃), 3.76 (dd, $J = 11.2$, 4.8 Hz, 1H, 3-CH₂OH), 3.81 (td, $J = 10.9$, 4.9 Hz, 1H, 4-H), 3.83 (dd, $J = 11.2$, 3.8 Hz, 1H, 3-CH₂OH), 6.58 (d, $J = 2.6$ Hz, 1H, 4'-H), 6.66 (dd, $J = 8.5$, 2.6 Hz, 1H, 6'-H), 7.14 (d, $J = 8.5$ Hz, 1H, 7'-H); ¹³C NMR (125 MHz, CD₃OD): $\delta = 16.34$, 26.71, 26.85, 30.91, 34.51, 35.36, 36.37, 39.93, 42.95, 45.07, 45.73, 47.51, 55.54, 61.73, 62.61, 66.29, 73.16, 99.84, 112.6, 114.4, 127.0, 133.8, 138.8, 159.0; MS (EI, 70 eV): m/z (%): 402.5 (100) [M]⁺; HRMS: calcd for C₂₄H₃₄O₅ 402.2406; found 402.2406; elemental analysis calcd (%) for C₂₄H₃₄O₅ (402.5): C 71.61, H 8.51; found C 71.53, H 8.65.

Hybrid compound 22: The diol **20** (70 mg, 147 μ mol) was hydrogenated as described for **19** to give 70 mg (146 μ mol, 99%) of **22** as a white solid. $R_f = 0.12$ (PE/EtOAc, 1:2); [α]_D²⁰ = +98.0 ($c = 0.2$ in DMF); IR (KBr): $\tilde{\nu} = 3385$ (OH), 3063, 3032 (Ar-H), 2926 (CH₃), 1608, 1577 cm⁻¹ (C=C); UV/Vis (CH₃CN): λ_{max} (lg ϵ) = 200.5 (4.045), 249.5 (3.317), 278.5 (2.627), 286.0 nm (2.581); ¹H NMR (500 MHz, CD₃OD): $\delta = 0.98$ (s, 3H, 9-CH₃), 1.15–1.35 (m, 6H, 1'-H₂, 8'-H₂, 10-H, OH), 1.38–1.52 (m, 3H, 3-H, OH, 1'-c-H), 1.58–1.70 (m, 2H, 5-H_a, 7b-H), 1.74 (dd, $J = 13.1$, 3.4 Hz, 1H, 2'-H_a), 1.92–1.97 (m, 1H, 2'-H_b), 2.01 (dd, $J = 12.4$, 5.0 Hz, 1H, 5-H_b), 2.22–2.35 (m, 2H, 11-H₂), 2.73–2.84 (m, 2H, 3'-H₂), 3.09 (d, $J = 10.6$ Hz, 1H, 8-H_a), 3.34 (d, $J = 10.6$ Hz, 1H, 8-H_b), 3.46 (t, $J = 11.3$ Hz, 1H, 2-H_a), 3.49 (dd, $J = 11.3$, 7.5 Hz, 1H, 2-H_b), 3.76 (dd, $J = 11.2$, 4.8 Hz, 1H, 3-CH₂OH), 3.80 (td, $J = 10.6$, 4.8 Hz, 1H, 4-H), 3.84 (dd, $J = 11.2$, 3.9 Hz, 1H, 3-CH₂OH), 5.01 (s, 2H, CH₂Ph), 6.67 (d, $J = 2.7$ Hz, 1H, 4'-H), 6.73 (dd, $J = 8.7$, 2.7 Hz, 1H, 6'-H), 7.16 (d, $J = 8.7$ Hz, 1H, 7'-H), 7.26–7.42 (m, 5H, Ph-H); ¹³C NMR (75 MHz, [D₆]DMSO): $\delta = 15.61$, 25.00, 29.30, 32.94 (2C), 33.80, 34.55, 37.86, 41.06, 42.99, 44.71, 46.22, 59.52, 61.16, 63.62, 68.94, 71.02, 97.77, 112.2, 114.2, 125.8,

127.3 (2C), 127.5, 128.2 (2C), 132.5, 137.3 (2C), 156.1; MS (EI, 70 eV): m/z (%): 478.1 (100) [M]⁺, 91.0 (75) [C_7H_7]⁺; HRMS: calcd for C₃₀H₃₈O₅ 478.2719; found 478.2719.

Hybrid compound 23: A suspension of diol **22** (70 mg, 146 μ mol) and Pd/C (16 mg, 10% Pd on charcoal, 15 μ mol, 10 mol %) in methanol/ethyl acetate (15 mL, 1:1) was subjected to 65 bar of hydrogen pressure at room temperature for 20 h. The catalyst was removed by filtration through a short pad of silica gel. Evaporation of the solvent from the filtrate gave 56 mg (145 μ mol, 99%) of **23** as a white solid. $R_f = 0.11$ (PE/EtOAc, 1:2); [α]_D²⁰ = +108.4 ($c = 0.25$ in DMF); IR (KBr): $\tilde{\nu} = 3433$ (OH), 3020 (Ar-H), 2924 (CH₃), 1616, 1582, 1499 (C=C), 827 cm⁻¹ (Ar-H); UV/Vis (CH₃CN): λ_{max} (lg ϵ) = 199.0 (3.948), 280.0 (2.704), 287.0 nm (2.666); ¹H NMR (500 MHz, [D₇]DMF, 45 °C): $\delta = 0.98$ (s, 3H, 9-CH₃), 1.10–1.45 (m, 9H, 1'-H₂, 11-H₂, 10-H, 2 × OH, 2'-H_a, 5-H_a), 1.54–1.67 (m, 2H, 3-H, 1'-c-H), 1.71 (dd, $J = 13.1$, 3.8 Hz, 1H, 2'-H_b), 1.88–2.03 (m, 2H, 8'-H_a, OH), 1.99 (dd, $J = 12.1$, 5.0 Hz, 1H, 5-H_b), 2.19–2.32 (m, 2H, 7b-H, 8'-H_b), 2.68–2.80 (m, 2H, 3'-H₂), 3.06 (d, $J = 10.6$ Hz, 1H, 8-H_a), 3.29 (d, $J = 10.6$ Hz, 1H, 8-H_b), 3.43 (t, $J = 11.3$ Hz, 1H, 2-H_a), 3.49 (dd, $J = 10.6$, 7.2 Hz, 1H, 3-CH₂OH), 3.75 (dd, $J = 11.3$, 4.8 Hz, 1H, 2-H_b), 3.81 (td, $J = 10.8$, 5.0 Hz, 1H, 4-H), 3.82 (dd, $J = 10.6$, 4.0 Hz, 1H, 3-CH₂OH), 6.54 (d, $J = 2.6$ Hz, 1H, 4'-H), 6.62 (dd, $J = 8.5$, 2.6 Hz, 1H, 6'-H), 7.09 (d, $J = 8.5$ Hz, 1H, 7'-H); ¹³C NMR (125 MHz, [D₇]DMF, 45 °C): $\delta = 16.10$, 26.10, 26.23, 30.15, 33.91, 34.92, 35.69, 39.24, 42.35, 44.26, 45.74, 47.48, 61.28, 62.12, 65.49, 72.25, 98.86, 113.5, 115.5, 126.4, 131.6, 138.1, 156.2; MS (EI, 70 eV): m/z (%): 388.1 (81) [M]⁺, 186.0 (100) [$C_{13}H_{14}O$]⁺; HRMS: calcd for C₂₃H₃₂O₅ 388.2250; found 388.2249.

Diol 24: A suspension of diol **20** (70 mg, 147 μ mol) and Pd/C (31 mg, 5% Pd on charcoal, 15 μ mol, 10 mol %) in methanol/ethyl acetate (15 mL, 1:1) was subjected to 65 bar of hydrogen pressure at room temperature for 24 h. The catalyst was then removed by filtration through a short pad of silica gel. Evaporation of the solvent from the filtrate gave 54 mg (146 μ mol, 99%) of compound **24** as a white solid. $R_f = 0.38$ (PE/EtOAc, 1:2); m.p. 227.9 °C; [α]_D²⁰ = +115.4 ($c = 0.5$ in DMF); IR (KBr): $\tilde{\nu} = 3455$ (OH), 2922 (CH₃), 1616, 1585, 1499 (C=C), 822 cm⁻¹ (Ar-H); UV/Vis (CH₃CN): λ_{max} (lg ϵ) = 199.0 (3.892), 280.0 (2.588), 287.0 nm (2.543); ¹H NMR (500 MHz, [D₇]DMF): $\delta = 0.90$ (d, $J = 6.7$ Hz, 3H, 3-CH₃), 0.96 (s, 3H, 9-CH₃), 1.10–1.29 (m, 4H, 1'-H_a, 11-H_a, 10-H, 2'-H_a), 1.34–1.52 (m, 4H, 3-H, 5-H_a, 1'-H_b, 2'-H_b), 1.56 (m, 1H, 1'-c-H), 1.70 (dd, $J = 13.2$, 3.6 Hz, 1H, 11-H_b), 1.89–1.95 (m, 1H, 8'-H_a), 1.98 (dd, $J = 12.6$, 4.6 Hz, 1H, 5-H_b), 2.19–2.26 (m, 1H, 7b-H), 2.26–2.33 (m, 1H, 8'-H_b), 2.72–2.76 (m, 2H, 3'-H₂), 3.07 (d, $J = 10.5$ Hz, 1H, 8-H_a), 3.23 (dd, $J = 11.3$, 11.3 Hz, 1H, 2-H_a), 3.29 (d, $J = 10.5$ Hz, 1H, 8-H_b), 3.50 (m, 2H, 2-H_b, 4-H), 4.68 (d, $J = 5.7$ Hz, 1H, 4-OH), 6.55 (d, $J = 2.5$ Hz, 1H, 4'-H), 6.63 (dd, $J = 8.4$, 2.5 Hz, 1H, 6'-H), 7.10 (d, $J = 8.4$ Hz, 1H, 7'-H), 9.23 (s, 1H, 5-OH); ¹³C NMR (125 MHz, [D₇]DMF): $\delta = 14.32$, 17.05, 27.03, 27.15, 31.00, 34.85, 35.80, 36.61, 40.11, 40.73, 43.81, 45.23, 46.80, 66.12, 70.39, 73.12, 100.2, 114.4, 116.4, 127.5, 132.4, 139.0, 157.2; MS (EI, 70 eV): m/z (%): 372.1 (100) [M]⁺, 287.1 (45) [$M - C_5H_9O$]⁺, 186.0 (92) [M]²⁺; HRMS (ESI): calcd for C₂₃H₃₃O₄ [$M+H$]⁺ m/z : 373.2379; found 373.2379.

Allylic alcohol 25: Lithium wire (5 mg, 0.72 mmol) was added to a solution of **20** (30 mg, 63 μ mol) in liquid ammonia (3 mL) and methanol (0.6 mL) at –78 °C, and the resulting mixture was stirred at this temperature for 3 h. Solid NH₄Cl was then added to remove the excess lithium; thereafter, *tert*-butyl methyl ether (10 mL) was added, and the mixture was allowed to warm to room temperature. After evaporation of the NH₃, the residue was partitioned between ethyl acetate (20 mL) and water (20 mL), the aqueous phase was extracted with ethyl acetate (3 × 40 mL), and the combined organic phases were washed with brine and dried with MgSO₄. Evaporation of the solvents and purification of the residue by column chromatography (petroleum ether/ethyl acetate, 1:1, with 1% MeOH) yielded 22 mg (57 μ mol, 90%) of **25** as a white solid. $R_f = 0.16$ (PE/EtOAc, 1:1); [α]_D²⁰ = +134.0 ($c = 0.2$ in DMF); IR (KBr): $\tilde{\nu} = 3397$, 3356 (OH), 2937 (CH₃), 1618, 1584, 1501 (C=C), 822 cm⁻¹ (Ar-H); UV/Vis (CH₃CN): λ_{max} (lg ϵ) = 199.5 nm (4.079), 280.0 (2.724), 286.5 (2.678); ¹H NMR (500 MHz, [D₇]DMF, 35 °C): $\delta = 0.98$ (s, 3H, 9-CH₃), 1.09–1.48 (m, 8H, 2'-H_a, 8'-H₂, 1'-H₂, 10-H, 2 × OH), 1.61 (m, 1H, 2'-H_b), 1.76 (dd, $J = 12.9$, 9.4 Hz, 1H, 5-H_a), 1.88–2.04 (m, 3H, 3'-H_a, 11-H_a, OH), 2.16 (dd, $J = 12.9$, 6.6 Hz, 1H, 5-H_b), 2.22–2.34 (m, 2H, 11-H_b, 1'-c-H), 2.70–2.80 (m, 2H, 3'-H_b, 7b-H), 3.13 (d, $J = 10.7$ Hz, 1H, 8-H_a), 3.48 (d, $J = 10.7$ Hz, 1H, 8-H_b), 3.93 (d, $J = 12.1$ Hz, 1H, 3-CH₂OH), 4.25 (d, $J = 12.1$ Hz, 1H, 3-CH₂OH), 4.55 (brdd, $J = 9.1$, 7.2 Hz, 1H, 4-H), 6.29 (s, 1H, 2-H), 6.47 (d, $J = 2.7$ Hz, 1H, 4'-H),

6.54 (dd, $J = 8.5, 2.7$ Hz, 1 H, 6'-H), 7.08 (d, $J = 8.5$ Hz, 1 H, 7'-H); ^{13}C NMR (125 MHz, $[\text{D}_7]\text{DMF}$): $\delta = 16.08, 26.04, 26.24, 30.17, 33.70, 33.95, 35.58, 39.15, 42.01, 42.62, 44.25, 60.34, 61.34, 73.49, 100.1, 113.5, 115.5, 118.2, 126.6, 131.4, 138.0, 138.1, 156.2$; MS (EI, 70 eV): m/z (%): 368.1 (17) $[\text{M} - \text{H}_2\text{O}]^+$, 284.1 (100) $[\text{M} - \text{C}_4\text{H}_6\text{O}_3]^+$, 43.1 (35) $[\text{C}_3\text{H}_7]^+$; HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{30}\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+ m/z$: 409.1991; found 409.1991.

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