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A Versatile Synthesis of Cyclic Diphenyl Ether-Type Diarylheptanoids: Acerogenins, (±)-Galeon, and (±)-Pterocarine

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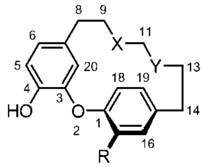
A versatile method for the total synthesis of cyclic diphenyl ether-type diarylheptanoids, acerogenin C, acerogenin L, (±)-galeon, and (±)-pterocarine was described. The Ullmann reaction of suitably substituted linear diphenylheptanoids was employed for the intramolecular formation of the key ether intermediates as the final step. The prerequisite diarylheptanoids were prepared by a series of cross-aldol condensation reactions from readily available starting benzaldehydes.

Introduction

Diarylheptanoids are a class of natural products containing the 1,7-diphenylheptane moiety, and they can be classified into three major groups: acyclics, cyclic biphenyls ([7.0]-metacyclophanes), and cyclic diphenyl ethers (14-oxa-[7.1]-metaparacyclophanes).[1] Although linear diarylheptanoids and cyclic biphenylheptanoids have been extensively studied because of their unique structures[2] and variety of biological properties,[3] studies on diphenyl ether-type cyclic diarylheptanoids such as acerogenins (**1a**–**d**),[4] galeon (**1e**),[5] and pterocarine (**1f**)[6] have been somewhat limited to their isolation from natural sources. Their intriguing structures have led to the establishment of a couple of strategic methods for the total synthesis of **1a**–**d** and their related acerosides.[7]



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No.	X	Y	R	name
1a	CH_2	CH(OH)	H	acerogenin A
1b	CH(OH)	CH_2	H	acerogenin B
1c	CH_2	C=O	H	acerogenin C
1d	C=O	CH_2	H	acerogenin L
1e	C=O	CH_2	OMe	galeon
1f	C=O	CH_2	OH	pterocarine

Recent findings on the potent cytotoxic activity of **1e** against selected cancer cell lines[8] and its inhibitory activity to the cell cycle at the G_0/G_1 phase, as well as the apoptosis inducing activity[6] of **1f**, prompted us to devise a general and versatile synthetic method of **1**.

The previous synthesis of acerogenin C and/or acerogenin L employed two different methodologies. Gonzalez and Zhu[7a,7b] used nucleophilic aromatic substitution (S_NAr) for the ether formation reaction and the acetoacetate ester synthesis for the construction of the diarylheptanoid skeleton, whereas Nógrádi et al.[7c] used the Ullmann reaction and the Wittig reaction, respectively. Attempts to synthesize acerogenin A by the Wittig reaction at the final stage of the synthetic sequence resulted in dimeric and polymeric products.[9]

As a part of our ongoing projects in the search and synthesis of biologically interesting molecules originating from natural sources, we herein describe a general synthetic method for the synthesis of **1** from readily available starting materials.[10] The present strategy employs the preparation of suitably substituted 1,7-diphenylheptanoids **2** by a series of cross-aldol condensation reactions and the formation of a diaryl ether bond by the Ullmann reaction at the late stage of the synthesis (Scheme 1). The advantage of this procedure is that all the cyclic diaryl ether-type diarylheptanoids can be prepared by inducing ether formation between either R^1 and R^4 or R^2 and R^3.

Results and Discussion

The prerequisite substituted cinnamaldehydes **5** were prepared from the suitably substituted benzaldehydes in good yields.[11] As shown in Scheme 2, the cross-aldol condensation (Claisen–Schmidt reaction) of cinnamaldehydes **5** with acetone (**4**) in the presence of 10% NaOH gave **6** in 91–93% yield, whereas condensation of unprotected 4-hydroxy-3-methoxycinnamaldehyde and 4-hydroxycinnamaldehyde

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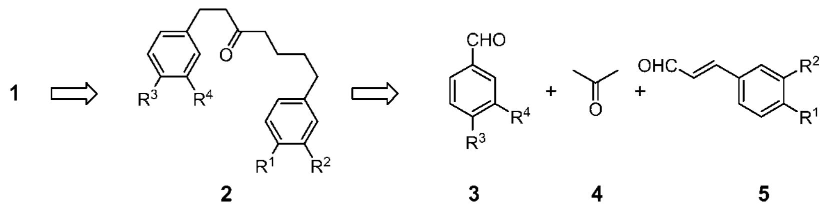
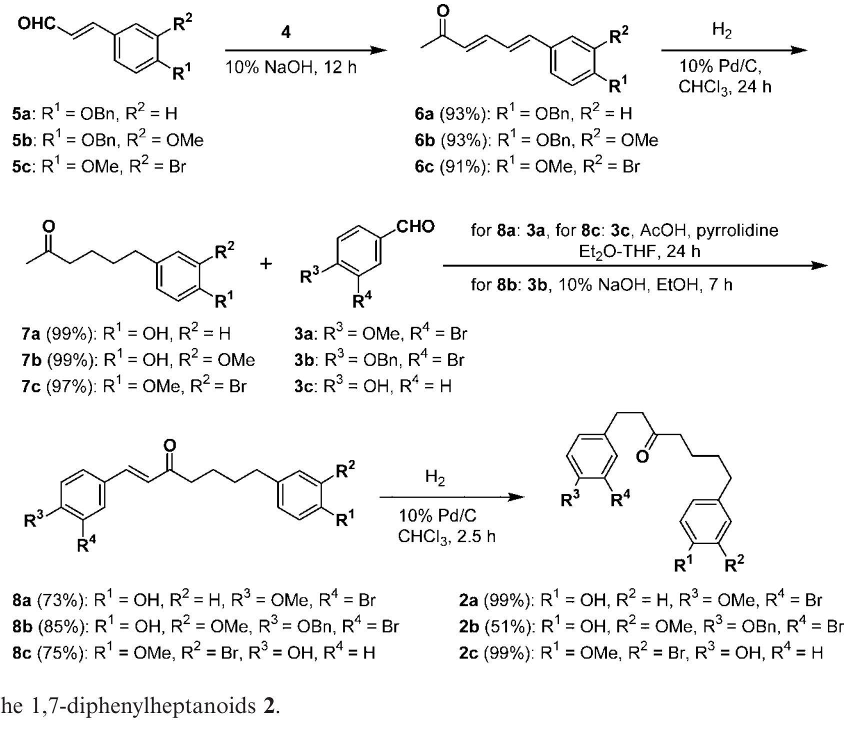


Scheme 1. Retrosynthesis.

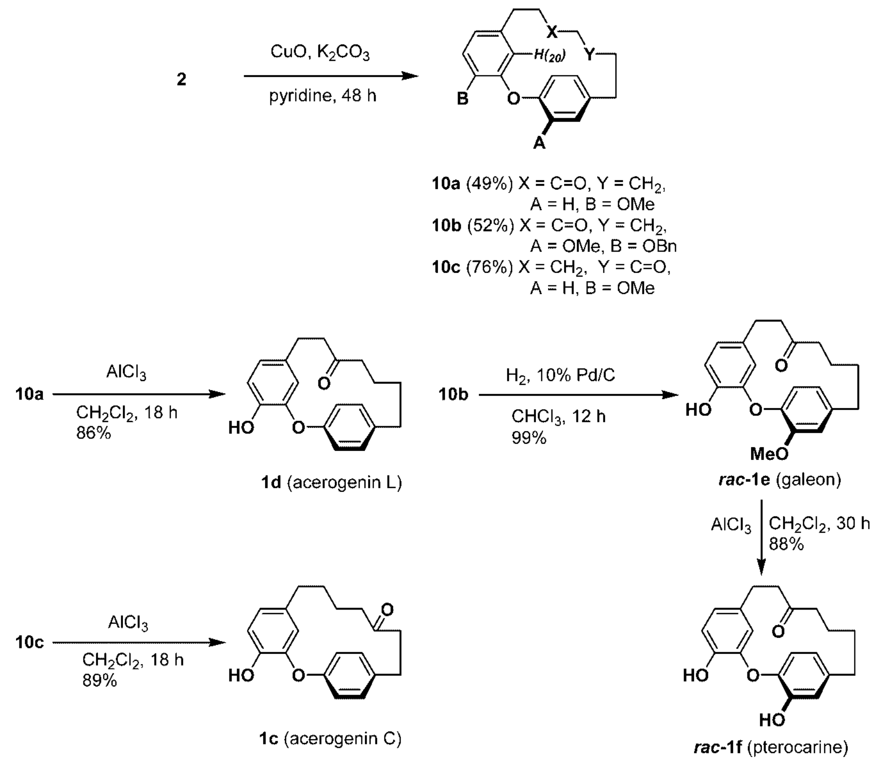
led to much lower yields. Catalytic hydrogenation of **6** under a molecular hydrogen atmosphere at room temperature for 24 h afforded saturated compounds **7** in 96–99% yield. Compounds **7** were then subjected to the second aldol condensation reaction with aromatic aldehydes **3** to give **8**. In some cases, the yields of the second cross aldol condensation were quite low (30–40%) under the same conditions employed for the preparation of **6**. Thus, an alternate procedure which was introduced by Cope[12] for the Knoevenagel reaction was employed to improve the yields consistently up to 73–75% for **8a** and **8c**. Notably, the catalytic hydrogenation of **6b** under an atmosphere of molecular hydrogen at room temperature for 24 h not only reduced the double bonds, but also cleaved the protecting benzyl group to afford **7b** in 99% yield. Similarly, catalytic hydrogenation of **8a** and **8c** under an atmosphere of molecular hydrogen for 2.5 h reduced the double bond to afford **2a** and **2c** in quantitative yields. Unlike the case of **6b**, the catalytic hydrogenation of **8b** under the same conditions for 2 h reduced only the double bond to afford corresponding **2b** in 51% yield without cleavage of the benzyl group. It should be noted that the benzyl moiety in compound **2b** can be kept in position by adjusting the reaction time.[13] Cleavage of the benzyl group begins after a reaction time of 2.5 h.

Although several different approaches for the formation of diaryl ethers have been attempted,[14] the classical Ullmann procedure is still the method of choice (Scheme 3).[15] Compounds **2a**, **2b**, and **2c** were subjected to the Ullmann reaction conditions, that is by using catalytic CuO/K_2CO_3,[16] to yield the corresponding diphenyl ethers **10a**, **10b**, and **10c** in 49, 52, and 76% yield, respectively. The cyclic structures of **10** were easily confirmed by the characteristic high-field shift of the H^{20} resonances shown in the ^1H NMR spectrum, which is due to the anisotropic effect of the neighboring aromatic ring ($\delta_{H^{20}}$ = 5.42 ppm in **10a** vs. $\delta_{H^{2'}}$ = 7.32 ppm in **2a**, $\delta_{H^{20}}$ = 5.55 ppm in **10b** vs. $\delta_{H^{2'}}$ = 7.32 ppm in **2b**, and $\delta_{H^{20}}$ = 5.61 ppm in **10c** vs. $\delta_{H^{2'}}$ = 7.32 ppm in **2c**).

O-demethylation of **10a** and **10c** by $AlCl_3$ heated at reflux in CH_2Cl_2 afforded acerogenin L (**1d**) and acerogenin C (**1c**) in 86 and 89% yield, respectively. The physical and spectroscopic data of the synthetic substances were identical in all respects to those of the natural products.[4,7] Similarly, the selective cleavage of the benzyl ether of **10b** by catalytic hydrogenation quantitatively yielded the desired galeon (**1e**) as a mixture of rotamers, which was then subjected to O-demethylation by $AlCl_3$ to afford (±)-pterocarine (**1f**) in 88% yield. Demethylation reagents such as pyr-



Scheme 2. Synthesis of the 1,7-diphenylheptanoids **2**.



Scheme 3. Synthesis of acerogenins, (±)-galeon, and (±)-pterocarine.

idinium chloride heated at 180–200 °C for 10–30 min, and BBr_3 and $AlCl_3$ heated at reflux in CH_2Cl_2 were tested. $AlCl_3$ heated at reflux in CH_2Cl_2 was the best with respect to not only the simplicity of the reaction and the work up, but also yield and economical sense.

In addition, **1c** and **1d** were reduced by $NaBH_4$ to afford corresponding alcohols acerogenin A (**1a**) and acerogenin B (**1b**), respectively, whose physical and spectroscopic data were identical to those of the literature values.[4,7]

In conclusion, a simple and practical synthetic procedure for the preparation of diphenyl ether-type diarylheptanoids **1** was established by using the Ullmann diaryl ether formation reaction of linear diarylheptanoids **2**. The diarylheptanoids were assembled from readily available starting materials through a series of cross-aldol condensation reactions. Studies on the synthesis and biological properties of the other derivatives of diarylheptanoids are currently in progress.

Experimental Section

Melting points were determined with a Fischer–Jones melting point apparatus and are not corrected. IR spectra were obtained with a Perkin–Elmer 1330 spectrophotometer. NMR spectra were obtained with a Bruker-250 spectrometer and are reported in parts per million (ppm) from the internal standard tetramethylsilane (TMS). Chemicals and solvents were of commercial reagent grade and used without further purification. Electrospray ionization mass spectrometry (ESI-MS) experiments were performed with a LCQ advantage-trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA). Elemental analyses were measured with a Hewlett–Packard Model 185B elemental analyzer.

6-(4′-Benzyloxyphenyl)hexa-3,5-dien-2-one (6a): To a solution of **5a** (2.01 g, 8.45 mmol) in acetone (50 mL), a solution of 10% NaOH (8 mL) was slowly added. The resulting mixture was stirred at room temperature for 12 h. The solution was then rendered acidic to litmus by the addition of dilute HCl and extracted with EtOAc. The combined organic layers were washed with water and dried with $MgSO_4$. Evaporation of the solvent afforded a crude solid that was recrystallized from *n*-hexane/ EtOAc, 1:1 to give **6a** (2.18 g, 93%) as pale yellow crystals. M.p. 132–133 °C. IR (KBr): $\tilde{\nu}$ = 2913, 1652, 1619, 1593 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 7 H), 7.24 (dd, J = 15.4, 1.5 Hz, 1 H, H^5), 6.95 (d, J = 8.7 Hz, 2 H, $H^{2'}$ and $H^{6'}$), 6.90 (d, J = 15.4 Hz, 1 H, H^3), 6.74 (m, 1 H), 6.20 (d, J = 15.4 Hz, 1 H, H^4), 5.07 (s, 2 H, ph-CH_2), 2.29 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.51, 159.69, 143.99, 141.00, 136.50, 129.48, 128.98, 128.76, 128.64, 128.11, 127.45, 124.62, 115.18, 70.03, 27.30 ppm. MS (ESI): m/z = 279 $[M + H]^+$.

6-(4′-Benzyloxy-3′-methoxyphenyl)hexa-3,5-dien-2-one (6b): The same procedure described for **6a** was applied to **5b** (0.28 g, 1.05 mmol) to give **6b** (0.30 g, 93%) as yellow needles (*n*-hexane/ EtOAc, 1:1). M.p. 105–106 °C. IR (KBr): $\tilde{\nu}$ = 1661, 1508, 1137, 988 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 6 H), 7.00 (d, J = 2.0 Hz, 1 H, $H^{2'}$), 6.96–6.74 (m, 4 H), 5.17 (s, 2 H, ph-CH_2), 3.92 (s, 3 H, OCH_3), 2.29 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.44, 149.71, 149.35, 143.81, 141.21, 136.61, 129.54, 129.38, 128.58, 127.95, 127.16, 124.79, 121.20, 113.52, 109.53, 70.80, 55.97, 27.30 ppm. MS (ESI): m/z = 309 $[M + H]^+$.

6-(3′-Bromo-4′-methoxyphenyl)hexa-3,5-dien-2-one (6c): The same procedure described for **6a** was applied to **5c** (2.04 g, 7.26 mmol) to give **6c** (1.47 g, 91%) as yellow needles (*n*-hexane/EtOAc, 1:1). M.p. 86–87 °C. IR (KBr): $\tilde{\nu}$ = 1661, 1618, 1590 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.67 (d, J = 2.0 Hz, 1 H, $H^{2'}$), 7.35 (dd, J = 8.5, 2.0 Hz, 1 H, $H^{6'}$), 7.23 (dd, J = 15.0, 10.0 Hz, 1 H, H^5), 6.86 (d, J = 8.5 Hz, 1 H, $H^{5'}$), 6.78–6.74 (m, 2 H, H^4 and H^6), 6.22 (d, J = 15.5 Hz, 1 H, H^3), 3.90 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.41, 156.51, 143.29, 139.29, 131.76, 130.16, 127.87, 125.75, 112.25, 111.84, 56.35, 27.43 ppm. MS (ESI): *m/z* = 282 [M + H]$^+$.

6-(4′-Hydroxyphenyl)hexan-2-one (7a): A mixture of **6a** (2.18 g, 7.84 mmol) and 10% Pd/C (0.22 g) in $CHCl_3$ (60 mL) was stirred under an atmosphere of H_2 at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was evaporated to give **7a** (1.49 g, 99%) as a colorless oil. IR (KBr): $\tilde{\nu}$ = 3363, 1701, 1614, 1594 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.99 (d, J = 8.4 Hz, 2 H, $H^{2'}$ and $H^{6'}$), 6.24 (d, J = 8.4 Hz, 2 H, $H^{3'}$ and $H^{5'}$), 6.03 (s, 1 H, OH, D_2O exchangeable), 2.51 (t, J = 7.0 Hz, 2 H), 2.43 (t, J = 7.0 Hz, 2 H), 2.12 (s, 3 H), 1.58–1.52 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 210.47, 153.87, 133.91, 129.32, 115.13, 43.59, 34.71, 31.09, 29.87, 23.32 ppm. MS (ESI): *m/z* = 193 [M + H]$^+$.

6-(4′-Hydroxy-3′-methoxyphenyl)hexan-2-one (7b): The same procedure described for **7a** was employed with **6b** (4.16 g, 14 mmol) to give **7b** (2.97 g, 99%) as colorless needles (*n*-hexane/EtOAc, 1:1). M.p. 43 °C. IR (KBr): $\tilde{\nu}$ = 3625, 1714, 988 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.80 (d, J = 7.6 Hz, 1 H, $H^{5'}$), 6.64 (d, J = 2.0 Hz, 1 H, $H^{2'}$), 6.63 (d, J = 7.6 Hz, 1 H, $H^{6'}$), 5.62 (s, 1 H, OH, D_2O exchangeable), 3.84 (s, 3 H, OCH_3), 2.52 (t, J = 7.0 Hz, 2 H), 2.42 (t, J = 7.0 Hz, 2 H), 2.09 (s, 3 H), 1.56 (overlapped quintet, J = 7.0 Hz, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 208.92, 145.97, 143.13, 133.44, 120.44, 113.77, 110.54, 55.18, 42.84, 34.73, 30.56, 29.17, 22.76 ppm. MS (ESI): *m/z* = 223 [M + H]$^+$.

6-(3′-Bromo-4′-methoxyphenyl)hexan-2-one (7c): The same procedure described for **7a** was applied to **6c** (2.04 g, 7.26 mmol) to afford **7c** (2.00 g, 97%) as a colorless oil after column chromatography (hexane/EtOAC, 8:1, R_f = 0.2). IR (KBr): $\tilde{\nu}$ = 2938, 1714, 1603 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32 (d, J = 2.0 Hz, 1 H, $H^{2'}$), 7.02 (dd, J = 8.4, 2.0 Hz, 1 H, $H^{6'}$), 6.78 (d, J = 8.4 Hz, 1 H, $H^{5'}$), 3.84 (s, 3 H), 2.51 (t, J = 6.8 Hz, 2 H), 2.41 (t, J = 6.8 Hz, 2 H), 2.10 (s, 3 H), 1.56–1.53 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 208.87, 153.89, 135.79, 132.98, 128.21, 111.77, 111.28, 56.20, 43.42, 34.40, 30.87, 29.89, 23.18 ppm. MS (ESI): *m/z* = 286 [M + H]$^+$.

1-(3′-Bromo-4′-methoxyphenyl)-7-(4′′-hydroxyphenyl)hept-1-en-3-one (8a): Compound **7a** (0.20 g, 1.04 mmol) was added to a stirred mixture of acetic acid (0.060 mL) and pyrrolidine (0.090 mL) in Et_2O (10 mL). To the resulting solution, a solution of **3a** (0.225 g, 1.05 mmol) in THF (7 mL) was slowly added at room temperature, and the mixture was stirred for 1 d. The mixture was then rendered acidic to litmus by the addition of 3 N HCl and extracted with EtOAc. The organic layers were combined and washed successively with water, saturated $NaHSO_3$, and water, and then dried with $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (hexanes/EtOAc, 3:1) on silica gel to afford **8a** (0.296 g, 73%) as a colorless oil. IR (KBr): $\tilde{\nu}$ = 3365, 1646, 1592 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.71 (d, J = 2.0 Hz, 1 H, $H^{2'}$), 7.43–7.39 (m, 2 H, H^1 and $H^{6'}$), 7.00 (d, J = 7.8 Hz, 2 H, $H^{2''}$ and $H^{6''}$), 6.86 (d, J = 8.0 Hz, 1 H, $H^{5'}$), 6.76 (d, J = 7.8 Hz, 2 H, $H^{3''}$ and $H^{5''}$), 6.59 (d, J = 16.0 Hz, 1 H, H^2), 6.46 (br. s, 1 H, OH, D_2O exchangeable), 3.88 (s, 3 H), 2.64 (t, J = 6.8 Hz, 2 H), 2.54 (t, J = 6.8 Hz, 2 H), 1.68–1.56 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 201.14, 157.47, 153.95, 141.20, 133.80, 132.71, 129.31 (2 C), 128.26, 124.66, 115.16, 112.19, 111.76, 56.29, 40.77, 34.70, 31.17, 23.89 ppm. MS (ESI): *m/z* = 390 [M + H]$^+$.

1-(4′-Benzyloxy-3′-bromophenyl)-7-(4′′-hydroxy-3′′-methoxyphenyl)hept-1-en-3-one (8b): To a solution of **7b** (0.63 g, 7.88 mmol) and **3b** (2.30 g, 0.013 mol) in EtOH (200 mL), a solution of 10% NaOH (10 mL) was slowly added. The resulting mixture was stirred at room temperature for 7 h. The solution was then rendered acidic to litmus by the addition of 3 N HCl and extracted with EtOAc. The combined organic layers were washed and dried with $MgSO_4$. Evaporation of the solvent afforded an oily material which was purified by flash silica gel column chromatography (hexanes/EtOAc, 8:1) to give **8b** (1.20 g, 85%) as yellow crystals after slow evaporation of the eluent. M.p. 88–89 °C. IR (KBr): $\tilde{\nu}$ = 3530, 1644, 1593, 1496 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.76 (d, J = 1.9 Hz, 1 H, $H^{2'}$), 7.46–7.31 (m, 7 H), 6.91 (d, J = 8.0 Hz, 1 H, $H^{5'}$), 6.80 (d, J = 8.0 Hz, 1 H, $H^{5''}$), 6.67 (d, J = 2.0 Hz, 1 H, $H^{2''}$), 6.66 (d, J = 8.0 Hz, 1 H, $H^{6'}$), 6.58 (d, J = 16.3 Hz, 1 H, H^2), 5.44 (s, 1 H, OH, D_2O exchangeable), 5.19 (s, 2 H, Ph-CH_2), 3.85 (s, 3 H, OCH_3), 2.63 (t, J = 6.8 Hz, 2 H), 2.56 (t, J = 6.8 Hz, 2 H), 1.69–1.60 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.05, 156.56, 146.28, 143.56, 140.53, 135.87, 134.17, 132.81, 129.04, 128.73, 128.67, 128.14, 126.92, 125.05, 120.85, 114.09, 113.45, 112.99, 110.87, 70.79, 55.82, 40.90, 35.43, 31.32, 23.93 ppm. MS: *m/z* (%) = 497 (65) [M + 2]$^+$, 495 (70) [M]$^+$, 359 (100), 341 (70), 331 (39). MS (ESI): *m/z* = 496 [M + H]$^+$.

1-(4′-Hydroxyphenyl)-7-(3′′-bromo-4′′-methoxyphenyl)hept-1-en-3-one (8c): The same procedure described for **8a** was applied to **7c** (0.84 g, 2.94 mmol) and **3c** (0.41 g, 3.36 mmol) to afford **8c** (0.86 g, 75%) as white crystals (hexanes/EtOAc, 3:1). M.p. 113 °C. IR (KBr): $\tilde{\nu}$ = 3359, 2932, 1635, 1600 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49 (d, J = 16.0 Hz, 1 H, H^1), 7.43 (d, J = 8.6 Hz, 2 H, $H^{2'}$ and $H^{6'}$), 7.34 (d, J = 2.0 Hz, 1 H, $H^{2''}$), 7.04 (dd, J = 8.6, 2.0 Hz, 1 H, $H^{6''}$), 6.86 (d, J = 8.6 Hz, 2 H, $H^{3'}$ and $H^{5'}$), 6.78 (d, J = 8.4 Hz, 1 H, $H^{5''}$), 6.59 (d, J = 16.0 Hz, 1 H, H^2), 6.17 (s, 1 H, OH, D_2O exchangeable), 3.83 (s, 3 H), 2.65 (t, J = 6.7 Hz, 2 H), 2.54 (t, J = 6.7 Hz, 2 H), 1.68–1.58 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 201.15, 158.24, 153.90, 142.92, 135.88, 133.05, 130.31, 128.28, 126.94, 123.66, 116.02, 111.83, 111.32, 56.24, 40.46, 34.45, 31.04, 23.98 ppm. MS (ESI): *m/z* = 390 [M + H]$^+$.

1-(3′-Bromo-4′-methoxyphenyl)-7-(4′′-hydroxyphenyl)heptan-3-one (2a): A mixture of **8a** (0.49 g, 1.26 mmol) and 10% Pd/C (0.05 g) in $CHCl_3$ (15 mL) was stirred under an atmosphere of H_2 at room temperature for 10 h. The reaction mixture was filtered through a pad of Celite. The filtrate was evaporated to give an oily material which was purified by silica gel flash column chromatography (hexanes/EtOAc, 3:1) to give **2a** (0.49 g, 99%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32 (d, J = 2.0 Hz, 1 H, $H^{2'}$), 7.05 (dd, J = 8.5, 2.0 Hz, 1 H, $H^{6'}$), 7.99 (d, J = 8.5 Hz, 2 H, $H^{2''}$ and $H^{6''}$), 6.78 (d, J = 8.5 Hz, 1 H, $H^{5'}$), 6.72 (d, J = 8.5 Hz, 2 H, $H^{3''}$ and $H^{5''}$), 4.83 (br. s, 1 H, OH, D_2O exchangeable), 3.84 (s, 3 H, OCH_3), 2.78 (dd, J = 13.5, 7.0 Hz, 2 H), 2.64 (dd, J = 13.5, 7.0 Hz, 2 H), 2.50 (t, J = 6.8 Hz, 2 H), 2.37 (t, J = 6.8 Hz, 2 H), 1.54–1.49 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 210.07, 154.15, 153.57, 134.71, 134.27, 132.99, 129.40, 128.37, 115.09, 111.87, 111.42, 56.23, 44.14, 42.88, 34.74, 32.18, 28.41, 23.27 ppm. MS (ESI): *m/z* = 392 [M + H]$^+$.

1-(4′-Benzyloxy-3′-bromophenyl)-7-(4′′-hydroxy-3′′-methoxyphenyl)heptan-3-one (2b): The same procedure described for **2a** was applied to **8b** (1.29 g, 2.61 mmol) to give an oily material which was flash column chromatographed on silica gel (hexanes/EtOAc, 7:1) to afford **2b** (0.66 g, 51%) as a colorless oil. IR (KBr): $\tilde{\nu}$ = 3563, 1714 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.57–7.30 (m, 6 H), 7.00 (dd, J = 8.2, 2.0 Hz, 1 H, H$^{6'}$), 6.80 (d, J = 8.8 Hz, 2 H), 6.64 (d, J = 2.0 Hz, 1 H, H$^{2''}$), 6.63 (dd, J = 8.5, 1.5 Hz, 1 H, H$^{6''}$), 5.48 (s, 1 H, OH, D$_2$O exchangeable), 5.10 (s, 2 H, Ph-CH_2), 3.85 (s, 3 H, OCH_3), 2.78 (t, J = 7.3 Hz, 2 H), 2.65 (t, J = 7.0 Hz, 2 H), 2.51 (t, J = 7.0 Hz, 2 H), 2.40 (t, J = 7.3 Hz, 2 H), 1.63–1.51 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 209.78, 153.26, 146.25, 143.54, 136.54, 135.09, 134.05, 133.01, 128.49, 128.22, 127.83, 126.92, 120.77, 114.08, 113.83, 112.27, 110.85, 70.90, 56.23, 44.50, 42.80, 34.40, 30.89, 28.91, 23.15 ppm. MS (ESI): m/z = 498 [M + H]$^+$.

1-(4′-Hydroxyphenyl)-7-(3′′-bromo-4′′-methoxyphenyl)heptan-3-one (2c): The same procedure described for **2a** was applied to **8c** (0.64 g, 1.65 mmol) to afford **2c** (0.64 g, 99%) as a colorless oil after column chromatography (hexanes/EtOAc, 3:1). IR (KBr): $\tilde{\nu}$ = 3411, 1699, 1616 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.31 (d, J = 2.0 Hz, 1 H, H$^{2''}$), 7.45–6.99 (m, 3 H, H$^{5'}$, H$^{2''}$ and H$^{6''}$), 6.78 (d, J = 8.8 Hz, 1 H, H$^{6'}$), 6.73 (d, J = 8.8 Hz, 2 H, H$^{3''}$ and H$^{5''}$), 5.04 (s, 1 H, OH, D$_2$O exchangeable), 3.84 (s, 3 H, OCH$_3$), 2.79 (t, J = 8.0 Hz, 2 H), 2.66 (t, J = 6.8 Hz, 2 H), 2.47 (t, J = 7.2 Hz, 2 H), 2.35 (t, J = 7.2 Hz, 2 H), 1.60–1.49 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 210.61, 153.87 (2 C), 135.82, 133.03, 133.00, 129.40, 128.25, 115.26, 111.80, 111.29, 55.78, 44.04, 42.79, 35.33, 31.16, 28.40, 23.27 ppm. MS (ESI): m/z = 392 [M + H]$^+$.

4-Methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexaen-10-one (10a): To a dried flask fitted with a stirring bar was added **2a** (0.19 g, 0.49 mmol) and K$_2$CO$_3$ (0.135 g, 0.98 mmol) under an atmosphere of N$_2$, followed by the addition of freshly distilled pyridine (25 mL) by syringe. The mixture was warmed to 90 °C and CuO (97 mg, 1.22 mmol) was added under positive N$_2$ flush. The mixture was heated at reflux for about 48 h under a N$_2$ atmosphere and cooled to room temperature. The solid material was removed by filtration. The filtrate was diluted with EtOAc, washed with 10% NaHSO$_3$, and dried with MgSO$_4$. Evaporation of the solvent afforded a solid material which was purified by flash column chromatography over silica gel (hexanes/EtOAc, 8:1) to afford **10a** (0.18 g, 49%) as a colorless oil which solidified in the refrigerator to give white needles. M.p. 109–110 °C (ref.[7b] 108–110 °C). IR (KBr): $\tilde{\nu}$ = 2927, 2867, 1708, 1514, 1503, 1265, 1231, 1216, 1159, 849 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.27 (d, J = 8.4 Hz, 2 H, H^{16} and H^{19}), 7.00 (d, J = 8.4 Hz, 2 H, H^{17} and H^{18}), 6.78 (d, J = 8.2 Hz, 1 H, H^5), 6.64 (dd, J = 8.2, 2.0 Hz, 1 H, H^6), 5.42 (d, J = 2.0 Hz, 1 H, H^{20}), 3.92 (s, 3 H), 2.86–2.84 (m, 2 H), 2.73 (t, J = 6.0 Hz, 2 H), 2.30–2.56 (m, 2 H), 1.78 (dd, J = 13.0, 7.4 Hz, 2 H), 1.65–1.48 (m, 4 H) ppm. ^{13}C NMR (250 MHz, CDCl$_3$): δ = 209.97, 154.32, 150.58, 146.45, 138.37, 133.81, 131.23, 123.38, 121.12, 113.69, 111.72, 56.16, 46.09, 40.84, 35.41, 27.34, 27.00, 18.97 ppm. MS (ESI): m/z = 311 [M + H]$^+$.

4-Benzyloxy-17-methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3(20),4,6,15(19),16-hexaen-10-one (10b): The same procedure described for **10a** was applied to **2b** (0.41 g, 0.82 mmol) to give **10b** (0.18 g, 52%) as white needles. M.p. 113 °C. IR (KBr): $\tilde{\nu}$ = 1716 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.48 (d, J = 7.0 Hz, 2 H), 7.38–7.27 (m, 3 H), 7.03 (d, J = 8.5 Hz, 1 H), 6.87–6.84 (m, 2 H), 6.66 (d, J = 8.3 Hz, 1 H), 6.55 (dd, J = 8.0, 2.0 Hz, 1 H), 5.55 (d, J = 1.9 Hz, 1 H, H^{20}), 5.38–5.18 (AB quartet, 2 H), 3.72 (s, 3 H), 2.97 (dd, J = 15.5, 8.2 Hz, 1 H), 2.83 (dd, J = 13.0, 5.3 Hz, 1 H), 2.71–2.58 (m, 2 H), 2.41–2.20 (m, 2 H), 2.02 (t, J = 11.6 Hz, 1 H), 2.03–1.75 (m, 1 H), 1.69–1.50 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 210.03, 152.28, 150.23, 145.32, 142.80, 139.67, 137.55, 134.67, 128.43, 127.67, 127.38, 124.25, 122.00, 121.10, 115.66, 115.25, 112.63, 71.68, 56.12, 46.10, 40.97, 36.01, 27.40, 27.03, 19.08 ppm. MS (ESI): m/z = 417 [M + H]$^+$.

4-Methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexaen-12-one (10c): The same procedure described for **10a** was applied to **2c** (0.48 g, 1.23 mmol) to give **10c** (0.32 g, 76%) as white needles. M.p. 123–124 °C (ref.[4b] 124 °C). IR (KBr): $\tilde{\nu}$ = 2927, 2845, 1698, 1515, 1260, 1121 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.17 (d, J = 8.4 Hz, 2 H, H^{16} and H^{19}) 7.01 (d, J = 8.4 Hz, 2 H, H^{17} and H^{18}), 6.81 (d, J = 8.1 Hz, 1 H, H^5), 6.63 (dd, J = 8.1, 1.6 Hz, 1 H, H^6), 5.61 (d, J = 1.6 Hz, 1 H, H^{20}), 3.92 (s, 3 H, OCH$_3$), 2.97 (dd, J = 13.2, 6.3 Hz, 2 H, H^{14}), 2.58 (dd, J = 13.2, 6.6 Hz, 2 H, H^{13}), 2.43 (t, J = 5.6 Hz, 2 H, H^8), 1.89 (t, J = 8.1 Hz, 2 H, H^{11}), 1.38–1.34 (m, 2 H, H^{10}), 1.15–1.05 (overlapped t, J = 7.4 Hz, 2 H, H^9) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 212.18, 156.73, 150.74, 146.67, 137.05, 133.55, 130.53 (2 C), 123.67 (2 C), 121.92, 117.22, 112.12, 56.20, 46.23, 44.50, 32.29, 31.23, 27.38, 20.34 ppm. MS (ESI): m/z = 311 [M + H]$^+$.

12-Oxo-2-oxatricyclo[13.2.2.13,7]eicosa-3,5,7(20),15,17,18-hexaen-4-ol, Acerogenin C (1c): A mixture of **10c** (0.40 g, 1.29 mmol) and AlCl$_3$ (0.85 g, 6.38 mmol) in freshly distilled CH$_2$Cl$_2$ (25 mL) was heated at reflux for 18 h. The reaction was quenched by the careful addition of water (10 mL), and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layers were combined and washed with water and dried with MgSO$_4$. Evaporation of the solvent afforded a semisolid which was purified by silica gel column chromatography (hexanes/EtOAc, 3:1) to afford **1c** (0.34 g, 89%) as colorless crystals. M.p. 114–115 °C, (ref.[4c] 116 °C). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.18 (d, J = 8.3 Hz, 2 H, H^{16} and H^{19}), 7.00 (d, J = 8.3 Hz, 2 H, H^{17} and H^{18}), 6.85 (d, J = 8.2 Hz, 1 H, H^7), 6.62 (dd, J = 8.2, 1.8 Hz, 1 H, H^6), 5.64 (d, J = 1.6 Hz, 1 H, H^{20}), 3.00 (t, J = 6.3 Hz, 2 H, H^{14}), 2.61 (t, J = 6.6 Hz, 2 H, H^{13}), 2.45 (t, J = 5.6 Hz, 2 H, H^8), 1.90 (t, J = 8.1 Hz, 2 H, H^{11}), 1.37 (m, 2 H, H^{10}), 1.05 (q, J = 7.4 Hz, 2 H, H^9) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 212.8, 156.8, 149.1, 143.0, 137.6, 133.0, 130.7 (2 C), 123.5 (2 C), 122.8, 117 0, 115.5, 46.3, 44.5, 32.2, 31.5, 27.4, 20.4 ppm. MS (ESI): m/z = 297 [M + H]$^+$.C$_{19}$H$_{20}$O$_3$ (296.4): calcd. C 77.00, H 6.80; found C 69.85, H 6.88.

10-Oxo-2-oxatricyclo[13.2.2.13,7]eicosa-3,5,7(20),15,17,18-hexaen-4-ol, Acerogenin L (1d): The same procedure employed for **1c** was applied to **10a** (29 mg, 0.94 mmol) to give **1d** (24 mg, 86%) after purification by silica gel flash chromatography (hexanes/Et$_2$O, 4:1). M.p. 186–188 °C (ref.[7b] 181–183 °C, ref.[4g] 188–190 °C). IR (KBr): $\tilde{\nu}$ = 3554, 1709 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.27 (d, J = 8.4 Hz, 2 H, H^{16} and H^{19}), 7.00 (d, J = 8.4 Hz, 2 H, H^{17} and H^{18}), 6.80 (d, J = 8.0 Hz, 1 H, H^7), 6.61 (dd, J = 8.0, 1.2 Hz, 1 H, H^6), 5.41 (d, J = 1.2 Hz, 1 H, H^{20}), 2.81 (t, J = 5.0 Hz, 2 H, H^{14}), 2.75 (t, J = 6.0 Hz, 2 H), 2.27 (t, J = 5.0 Hz, 2 H), 1.77 (t, J = 8.0 Hz, 2 H), 1.65 (m, 2 H), 1.58 (m, 2 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 210.2, 154.3, 148.6, 143.1, 139.0, 133.5, 131.4, 123.4, 122.0, 115.1, 113.4, 46.4, 41.2, 35.6, 27.5, 27.4, 19.1 ppm. MS (EI): m/z = 296. MS (ESI): m/z = 297 [M + H]$^+$.

(±)-Galeon (1e): A mixture of **10b** (0.14 g, 0.34 mmol) and Pd/C (10%, 0.034 g) in CHCl$_3$ (20 mL) was stirred under an atmosphere of H$_2$ at room temperature for 12 h. Pd/C was filtered off through a pad of Celite, and the filtrate was concentrated. Pure **1e** (0.108 g, 99%) was obtained as white needles (98%). M.p. 178–180 °C (ref.[5a] 179–181 °C, ref.[5b] 178–180 °C). IR (KBr): $\tilde{\nu}$ = 3636, 1721, 1533 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 6.97 (d, J = 8.4 Hz, 1 H, H^{18}), 6.84 (d, J = 1.9 Hz, 1 H, H^{16}), 6.83 (d, J = 8.3 Hz, 1 H, H^{19}), 6.80 (d, J = 8.0 Hz, 1 H, H^5), 6.57 (d, J = 8.3 Hz, 1 H, H^6), 5.79 (s, 1 H, OH, D$_2$O exchangeable), 5.53 (d, J = 1.9 Hz, 1 H, H^{20}), 3.69 (s, 3 H, OCH$_3$), 2.94 (dd, J = 16.2, 9.0 Hz, 1 H, H^{8A}), 2.84–2.55 (m, 3 H, 2H^{14}, H^{8B}), 2.38–2.16 (m, 2 H, H^{9}), 2.02–1.85 (m, 1 H, H^{11A}), 1.76–1.71 (m, 1 H, H^{13A}), 1.54–1.49 (m, 4 H, H^{11B}, 2H^{12} and H^{13B}) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 210.29, 152.07, 147.21, 143.04, 142.70, 140.03, 133.20, 123.95 (2 C), 121.94 (2 C), 121.86, 115.00, 114.91, 112.18, 56.00, 46.29, 41.25, 35.89, 27.33, 27.25, 18.98 ppm. MS (ESI): *m*/*z* = 327 [M + H]$^+$.

(±)-Pterocarine (1f): A mixture of **1e** (30 mg, 0.092 mmol) and AlCl$_3$ (126 mg, 0.94 mmol) in freshly distilled CH$_2$Cl$_2$ (15 mL) was heated at reflux for 30 h. The reaction was quenched by the careful addition of water (10 mL), and resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 30 mL). The organic layers were combined, washed with water, and dried with MgSO$_4$. Evaporation of the solvent afforded a semisolid which was purified by silica gel column chromatography (hexanes/EtOAc, 3:1) to afford **1f** (25.4 mg, 88 %) as a white powder. M.p. 175 °C. IR (KBr): $\tilde{\nu}$ = 3339, 1696, 1590, 1516 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 6.94 (d, *J* = 1.9 Hz, 1 H, H^{16}), 6.89 (d, *J* = 8.0 Hz, 1 H, H^{18}), 6.82 (d, *J* = 8.0, 1.9 Hz, 1 H, H^{5}), 6.80 (d, *J* = 8.0 Hz, 1 H, H^{19}), 6.57 (d, *J* = 8.0, 2.2 Hz, 1 H, H^{6}), 5.79 (s, 1 H, C^{4}-OH, D$_2$O exchangeable), 5.71 (s, 1 H, C^{17}-OH, D$_2$O exchangeable), 5.57 (d, *J* = 2.2 Hz, 1 H, H^{20}), 2.87 (dd, *J* = 16.2, 9.0 Hz, 1 H, H^{8A}), 2.82 (dd, *J* = 16.2, 9.0 Hz, 1 H, H^{8B}), 2.72–2.65 (m, 2 H, H^{14}), 2.38–2.16 (m, 2 H, H^{9}), 1.89–1.82 (m, 2 H, H^{11}), 1.67–1.63 (m, 2 H, H^{13}), 1.58–1.54 (m, 2 H, H^{12}) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 210.48, 148.76, 146.72, 142.84, 140.63, 140.46, 133.97, 123.36, 122.94, 122.81, 117.81, 115.54, 112.51, 46.46, 41.07, 35.60, 27.26, 27.17, 18.95 ppm. MS (ESI): *m*/*z* = 313 [M + H]$^+$.

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[13] Reaction time is critical to secure yields over 50%. Longer reaction times result in over reduction of the keto moiety, as well as cleavage of the benzyl group to afford byproducts. So far 1-(4′-benzyloxy-3′-bromophenyl)-7-(4′′-hydroxy-3′′-methoxyphenyl)-heptan-3-ol and 1-(4′-hydroxy-3′-bromophenyl)-7-(4′′-hydroxy-3′′-methoxyphenyl)heptan-3-ol were isolated, which may explain the relatively low yield of this step.

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