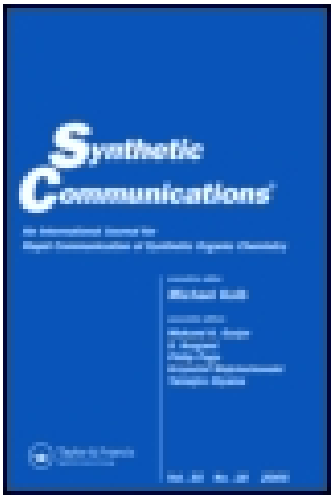

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First Total Synthesis of Cytotoxic Diarylheptanoids, Galeon, and Pterocarine

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First Total Synthesis of Cytotoxic Diarylheptanoids, Galeon, and Pterocarine

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Abstract: The first total synthesis of cytotoxic diphenyl ether-type diarylheptanoids, galeon and pterocarine, was described in which the Ullmann reaction was employed at the final step for the diaryl ether formation of key intermediate, 1-(3-bromo-4-benzyloxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptan-3-one, assembled by a series of cross-aldol condensation from 3-methoxy-4-benzyloxybenzaldehyde.

Keywords: aldol, cytotoxicity, diatrylheptanoid, galeon, pterocarine, Ullmann reaction

INTRODUCTION

Diarylheptanoids are a class of natural products containing the 1,7-diphenylheptane skeleton and 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 studied extensively on account of their unique structures[2–5] and wide variety of biological properties,[6–19] studies on diphenyl ether-type cyclic diarylheptanoids such as acerogenins (**1a–d**),[20–26] galeon (**1e**),[27,28] and pterocarine (**1f**)[29] are mostly 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.[30–32] However, there are no reported synthetic pathways for **1e** or **1f**. The methods reported previously from readily available compounds, however, are somewhat

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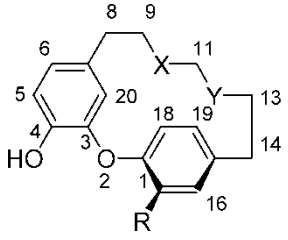
lengthy and are not suitable to apply to the synthesis of galeon and its related diarylheptanoids.



1a X = CH_2, Y = CH(OH), R = H (acerogenin A)
b X = CH(OH), Y = CH_2, R = H (acerogenin B)
c X = CH_2, Y = C=O, R = H (acerogenin C)
d X = C=O, Y = CH_2, R = H (acerogenin L)
e X = C=O, Y = CH_2, R = OCH_3 (galeon)
f X = C=O, Y = CH_2, R = OH (pterocarine)

Recent findings on the potent cytotoxic activity of **1e** against selected cancer cell lines[33] and the inhibitory activity to the cell cycle at the G_0/G_1 phase as well as the apoptosis inducing activity[29] of **1f** spurred us to devise a general and versatile synthetic method. This article described the first total synthesis of **1e** and **1f** from readily available starting materials.

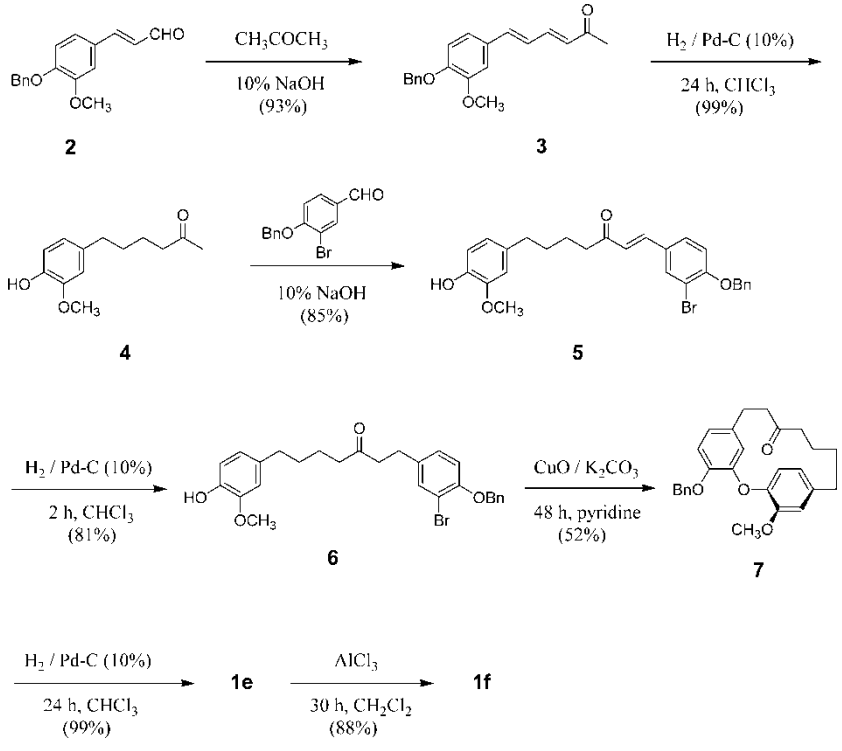
RESULTS AND DISCUSSION

The previous synthesis of acerogenin C and/or L employed two different methodologies. One[30,31] used the S_NAr reaction for ether formation and the acetoacetate ester synthesis for constructing diarylheptanoid skeleton, whereas the other[32] used the Ullmann reaction and the Wittig reaction, respectively. Novelty of the present strategy for synthesizing **1e** lies in the preparation of a suitably substituted 1,7-diphenylheptane derivative (**6**) by a series of cross-aldol condensation reactions and the formation of a diarylether bond at the late stage of synthesis via the Ullmann reaction.

The prerequisite 4-benzyloxy-3-methoxycinnamaldehyde (**2**) was prepared from commercially available 4-hydroxy-3-methoxybenzaldehyde in quantitative yield.[34,35] The cross-aldol condensation of **2** with acetone in the presence of 10% NaOH gave **3** in 93% yield, whereas such condensation of unprotected 4-hydroxy-3-methoxy-cinnamaldehyde led to much a lower yield. Catalytic hydrogenation of **3** under an H_2 atmosphere at room temperature for 24 h not only the reduced double bonds but also removed the protecting benzyl group to afford the corresponding **4** in quantitative yield, which was then subjected to a second aldol condensation reaction with 3-bromo-4-benzyloxybenzaldehyde to give the linear diphenylheptenoid **5** in 85% yield. The catalytic hydrogenation of **6** under an H_2 atmosphere for 2.5 h reduced only the double bond to afford the corresponding compound **6** as pale yellow oil in 81% yield. It should be noted that the benzyl moiety in compound **6** can be kept in protection by adjusting the reaction time.

Although several approaches to the formation of biaryl ethers have been introduced,[36] the Ullmann procedure is the best in some cases.[37] Thus the classical Ullmann condition i.e, using CuO/K_2CO_3[38] as a catalyst was

applied to compound **6** to yield the corresponding cyclic diphenylheptanoid, 4-benzylgaleon (**7**), in 52% yield. The cyclic structure of **7** was confirmed by the characteristic high-field shift of the H-20 resonance in the ^{1}H NMR spectrum due to the anisotropic effect of the neighboring orthogonal benzene ring ($\delta H_{20} = 5.55$ in **7** vs. $\delta H_{20} = 7.32$ in **6**). The selective cleavage of the benzyl ether by catalytic hydrogenation afforded the desired galeon (**1e**) in quantitative yield, of which the spectral (^{1}H and ^{13}C NMR as well as distortionless enhancement by polarization transfer (DEPT), infrared (IR), and ultraviolet (UV) as well as the physical data were identical to those reported in the literature.



The *O*-demethylation of **1e** by a previously reported procedure[27] afforded pterocarine (**1f**) in 88% yield. The physical and spectral data of the synthetic substances were identical to those of the natural products.

In conclusion, a simple and practical synthetic procedure for preparing diphenyl ether-type diarylheptanoid, galeon, was developed using the Ullmann diaryl ether formation of linear diarylheptanoid, which was prepared from readily available starting materials via a series of cross-aldol condensation reactions. Studies on resolving each enantiomer and applying this method to the synthesis of related diarylheptanoids, acerogenin C and L, are currently in progress.

EXPERIMENTAL

Melting points were determined using a Fischer-Jones melting-point apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-(250 spectrometer 250 MHz or 400 MHz for ^{1}H NMR and 62.5 MHz or 100 MHz for ^{13}C NMR) and are reported as parts per million (ppm) from the internal standard tetramethylsilane (TMS). Chemicals and solvents were commercial reagent grade and used without further purification. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a LCQ advantage-trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA). Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

All the spectral data of the compounds prepared are consistent with their structures.

6: Colorless oil (83%). IR (KBr) υ 3520, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.57–7.30 (m, 6H), 7.00 (dd, $J = 8.2$, 2.0 Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 2H), 6.64 (s, 1H, H2′), 6.63 (dd, $J = 8.5$, 1.5 Hz, 1H), 5.48 (s, 1H, OH, D_2O exchangeable), 5.10 (s, 2H, Ph-CH_2-), 3.85 (s, 3H, OCH_3), 2.78 (t, $J = 7.3$ Hz, 2H), 2.65 (t, $J = 7.0$ Hz, 2H), 2.51 (t, $J = 7.0$ Hz, 2H), 2.40 (t, $J = 7.3$ Hz, 2H), 1.63–1.51 (m, 4H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 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, 70.80, 55.78, 44.04, 42.79, 35.33, 31.16, 28.40, 23.27. MS (ESI) calcd. for $C_{27}H_{29}O_4Br^+$[M + H$^+$] 498, found 498.

7 (4-Benzylgaleon): Pale yellow needles (52%); mp 113°C. IR (KBr) υ 1714, 1518 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.48 (overlapped d, $J = 7.0$ Hz, 2H), 7.38–7.27 (m, 3H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.87–6.84 (m, 2H), 6.76 (d, $J = 8.3$ Hz, 1H), 6.55 (dd, $J = 8.0$, 2.0 Hz, 1H), 5.55 (d, $J = 1.9$ Hz, 1H), 5.38–5.18 (AB quartet, 2H), 3.72 (s, 3H), 2.97 (dd, $J = 15.5$, 8.2 Hz, 1H), 2.83 (dd, $J = 13.0$, 5.3 Hz, 1H), 2.71–2.58 (m, 2H), 2.41–2.20 (m, 2H), 2.02 (t, $J = 11.6$ Hz, 1H), 2.03–1.75 (m, 1H), 1.69–1.50 (m, 4H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 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. MS (ESI) calcd. for $C_{27}H_{28}O_4^+$[M + H$^+$] 417, found 417.

1e (Galeon): White needles (99%); mp 178–180°C (lit.[27] mp 179–181°C, lit.[28] mp 178–180°C). IR (KBr) υ 3387, 1703, 1517 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.97 (d, $J = 8.4$ Hz, H_{18}), 6.84 (d, $J = 1.9$ Hz, H_{16}), 6.83 (d, $J = 8.3$ Hz, H_{19}), 6.80 (d, $J = 8.0$ Hz, H_5), 6.57 (d, $J = 8.3$ Hz, H_6), 5.79 (s, OH, D_2O exchangeable), 5.53 (d, $J = 1.9$ Hz, H_{20}), 3.69 (s, 3H, OCH_3), 2.94 (dd, $J = 16.2$, 9.0 Hz, H_{8A}), 2.84–2.55 (m, 3H, $2H_{14}$, H_{8B}), 2.38–2.16 (m, 2H, H_9), 2.02–1.85 (m, 1H, H_{11A}), 1.76–1.71 (m, 1H,

H_{13A}), 1.54–1.49 (m, 4H, H_{11B}, $2H_{12}$ & H_{13B}). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 210.29 (C═O), 152.07 (C17), 147.21 (C3), 143.04 (C4), 142.70 (C1), 140.03 (C15), 133.20 (C7), 123.95 (C18, CH), 121.94 (C19, CH), 121.86 (C6, CH), 115.00 (C5, CH), 114.91 (C16, CH), 112.18 (C20, CH), 56.00 (OCH_3), 46.29 (C11, CH_2), 41.25 (C9, CH_2), 35.89 (C14, CH_2), 27.33 (C13, CH_2), 27.25 (C8, CH_2), 18.98 (C12, CH_2). MS (ESI) calcd. for $C_{20}H_{22}O_4^+$ [M+H^+] 327, found 327.

1f (Pterocarine): White powder (88%), mp 175°C. IR (KBr) υ 3339, 1696, 1590, 1516 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 6.93 (d, $J = 1.6$ Hz, H_{16}), 6.87 (d, $J = 8.0$ Hz, H_{18}), 6.82 (d, $J = 8.0$, 1.2 Hz, H_5), 6.77 (d, $J = 8.0$ Hz, H_{19}), 6.62 (d, $J = 8.0$, 1.0 Hz, H_6), 5.62 (br. s, 2H, C_4-OH, C_{17}-OH, D_2O exchangeable), 5.54 (d, $J = 1.0$ Hz, H_{20}), 2.86–2.82 (m, 2H, H_8), 2.72–2.65 (m, 2H, $2H_{14}$), 2.38–2.16 (m, 2H, H_9), 1.89–1.82 (m, 2H, $2H_{11}$), 1.67–1.63 (m, 2H, $2H_{13}$), 1.58–1.54 (m, $2H_{12}$). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 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. MS (ESI) calcd. for $C_{19}H_{20}O_4^+$ [M+H^+] 313, found 313.

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