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Total synthesis of acerogenins E, G and K, and centrolobol

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ABSTRACT

The first total synthesis of the diarylheptanoid acerogenins E and K, isolated from *Acer nikoense* MAXIM., is described. Formation of the 13-membered *m*,*m*-cyclophane skeleton was successfully achieved on the basis of a domino process involving a Miyaura arylborylation–intramolecular Suzuki reaction. The cyclization precursor was prepared via a Wittig reaction and Claisen–Schmidt condensation, which proceeded in moderate yields. The total synthesis of acerogenin G and centrolobol was also achieved from a common synthetic intermediate.

1. Introduction

The stem bark of *Acer nikoense* MAXIM. ('megusuri-no-ki' in Japanese) is said to be traditionally used as a folk medicine for the treatment of eye-related diseases and hepatic disorders since the Sengoku period in Japan. Acerogenins, isolated from the stem bark by Nagai and co-workers,[1] mainly consists of diarylheptanoid skeletons. It is known to exert interesting biological activity, such as an anti-inflammatory effect,[2] antitumor promoting activity,[2] an inhibitory effect on nitric oxide production,[3] osteogenic activity,[4] and so on.[5] However, the detailed biological mechanisms for the activity of acerogenins family compounds related to eye and hepatic diseases still remains unclear.

Diarylheptanoid acerogenins are structurally classified into three major types as follows: linears (acyclics), cyclic diaryl ethers, and cyclic biaryl cyclophanes.[6] While the total synthesis of linear and cyclic biaryl ether acerogenins has been reported,[7] the chemical synthesis of cyclic biaryl-type acerogenins E (**1**, Fig. 1)[1h] and K (**2**),[1i] which consist of a 13-membered *m*,*m*-cyclophane skeleton, has not been reported to date, as far as we know. The fact including the interesting biological activity led us to conduct a study on the total synthesis of the cyclic biaryl acerogenins.

In the synthesis of such biaryl natural products, intramolecular cyclization to form the aryl–aryl bond would be attractive and challenging as the key step.[8] Indeed, formation of biaryl bridged macrocycles has been achieved via intramolecular cyclizations, such as the nickel(0)-promoted Ullmann coupling,[9] Suzuki–Miyaura coupling,[10] and domino Miyaura arylborylation–Suzuki reaction.[11] Herein, we report the first total synthesis of **1** and **2** from commercially available starting materials via an intramolecular cyclization to form the aryl–aryl bond. In addition, from one synthetic intermediate, the effective synthesis of linear-type acerogenin G (**3**,

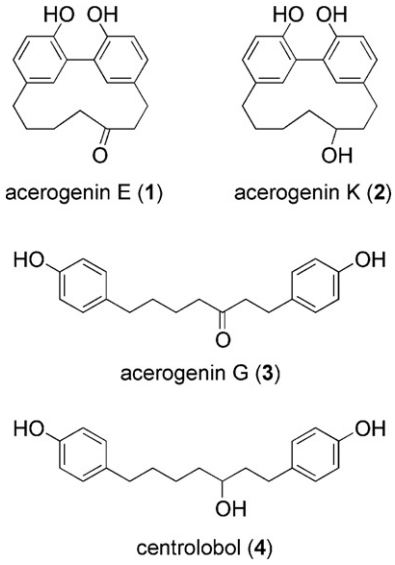

Fig. 1. Structures of diarylheptanoid acerogenins E (**1**), K (**2**), G (**3**), and centrolobol (**4**).

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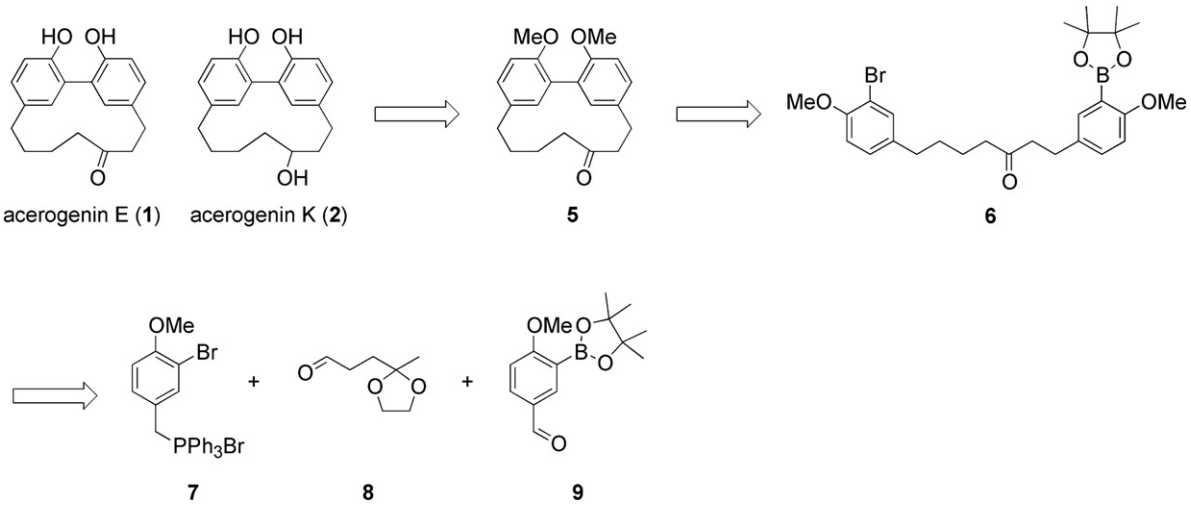
Fig. 1),[1f] an aglycon of aceroside IX, and centrolobol (**4**),[12] which is isolated from *Centrolobium* species, is also described.

2. Results and discussion

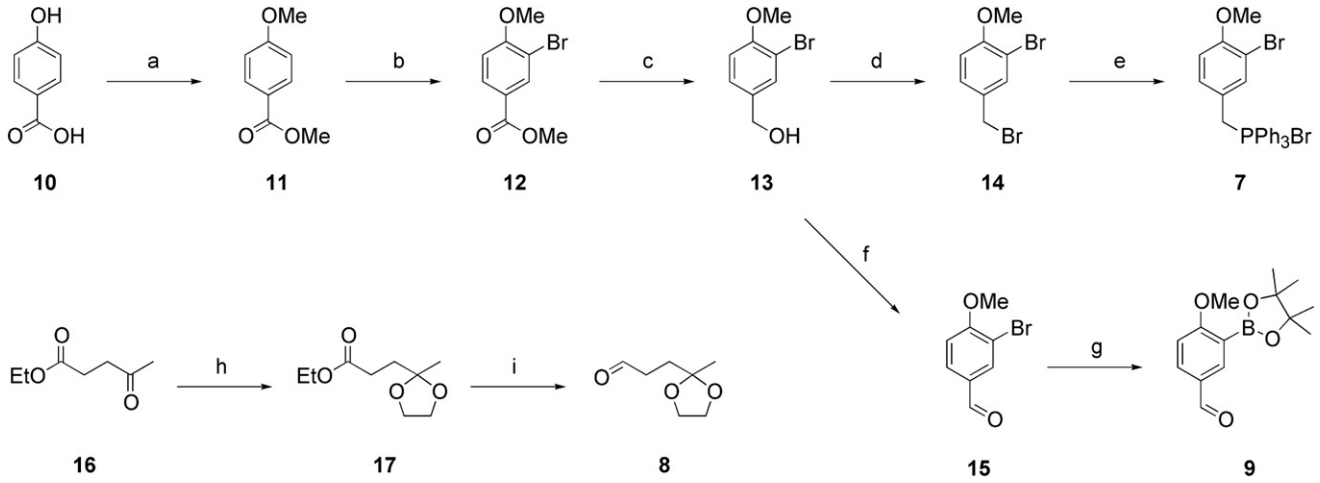
Our initial retrosynthetic analysis of **1** and **2** is outlined in Scheme 1. An intramolecular Suzuki–Miyaura coupling reaction, which has been used as the key step in the total synthesis of isoplagiochin D[10a] and arylomycins,[10b] was chosen in order to form the 13-membered *m*,*m*-cyclophane skeleton **5**. A methyl group was selected as the protective group for the two phenols because it was expected to have a smaller steric affect during the intramolecular coupling reaction. The coupling substrate **6** would then be prepared via a Wittig reaction and a Claisen–Schmidt condensation between the segments **7**, **8**, and **9**. These segments can be readily obtained from commercially available starting materials.



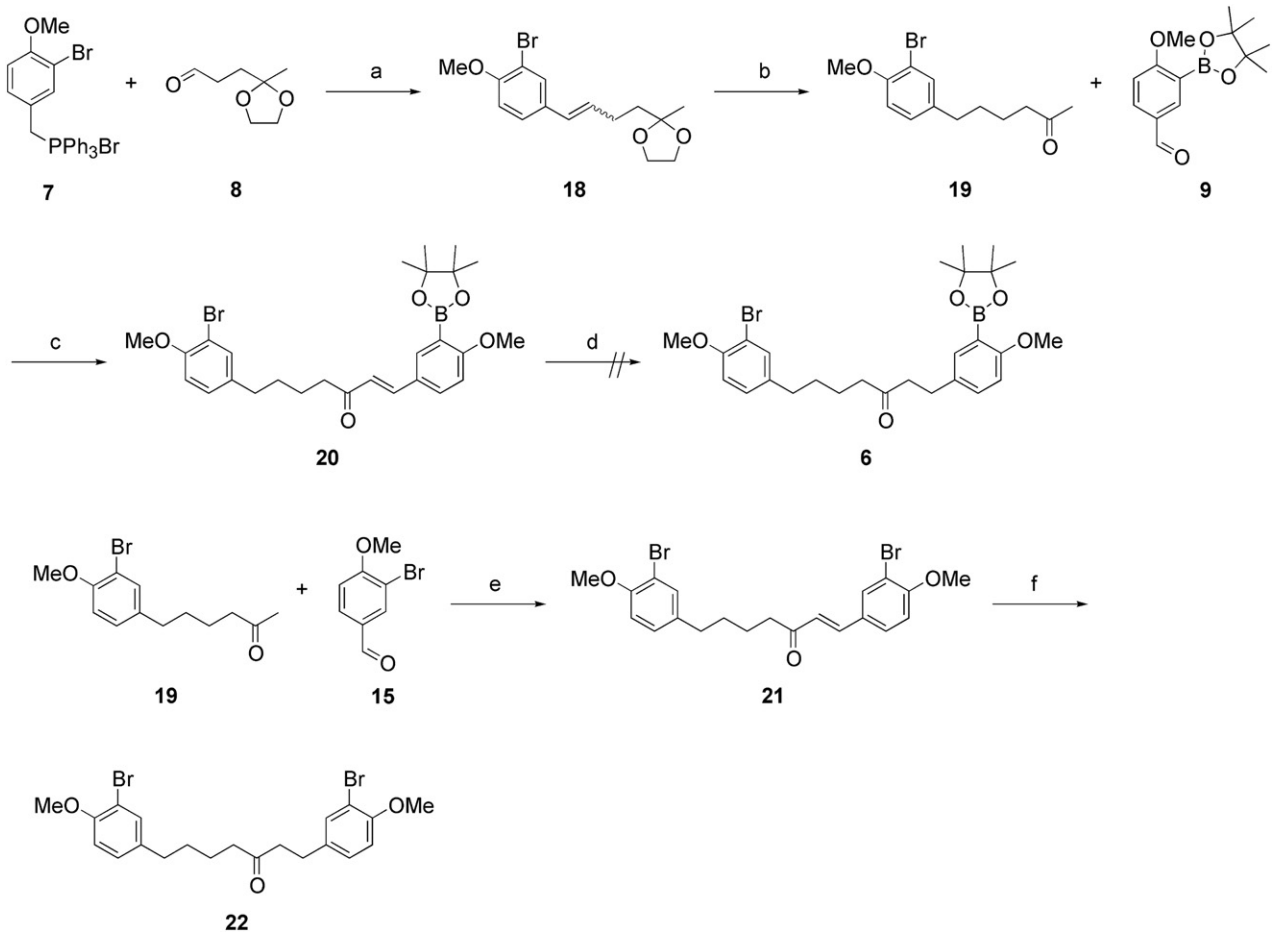
Scheme 1. Initial retrosynthesis.

We commenced the study with the preparation of the three segments **7**, **8**, and **9** (Scheme 2). Commercially available starting material 4-hydroxybenzoic acid (**10**) was dimethylated to give **11** quantitatively via treatment with $(MeO)_2SO_2$ in the presence of K_2CO_3.[13] The *ortho*-position of the methoxy group was then regioselectively monobrominated to afford **12** using NBS and $HBF_4{\cdot}Et_2O$ in 98% yield.[14] Treatment of **12** with $LiAlH_4$ resulted in reduction not only of the methyl ester, but also partially of the aryl bromide; however, reduction of **12** using DIBAL–H afforded alcohol **13** in 98% yield, which was a useful common intermediate for the preparation of the two aromatic segments. First, the primary alcohol of **13** was replaced using the Appel reaction to give dibromide **14** in 83% yield, followed by refluxing with PPh_3 to generate phosphonium salt **7** quantitatively. Separately, Swern oxidation of **13** afforded aldehyde **15** in 98% yield, followed by substitution of the bromine with a boronate group via Miyaura arylborylation[15] to afford **9** in 74% yield. The aliphatic segment **8** was synthesized from readily available ethyl levulinate (**16**). The carbonyl group was protected by refluxing in benzene in the presence of ethylene glycol and *p*-TsOH using a Dean–Stark apparatus to give **17** in 98% yield. Treatment of ethyl ester **17** with DIBAL–H then gave aldehyde **8** in 88% yield.

Wittig reaction of phosphonium salt **7** and aldehyde **8** was then examined to afford **18** in 61% yield (Scheme 3). NaH was found to act as a better base than *n*-BuLi, which may cause lithiation of **7**. The obtained olefin **18** was then hydrogenated and deprotected in two steps in 83% yield to afford ketone **19**. Subsequently, the Claisen–Schmidt condensation of **19** and **9** was then attempted, and



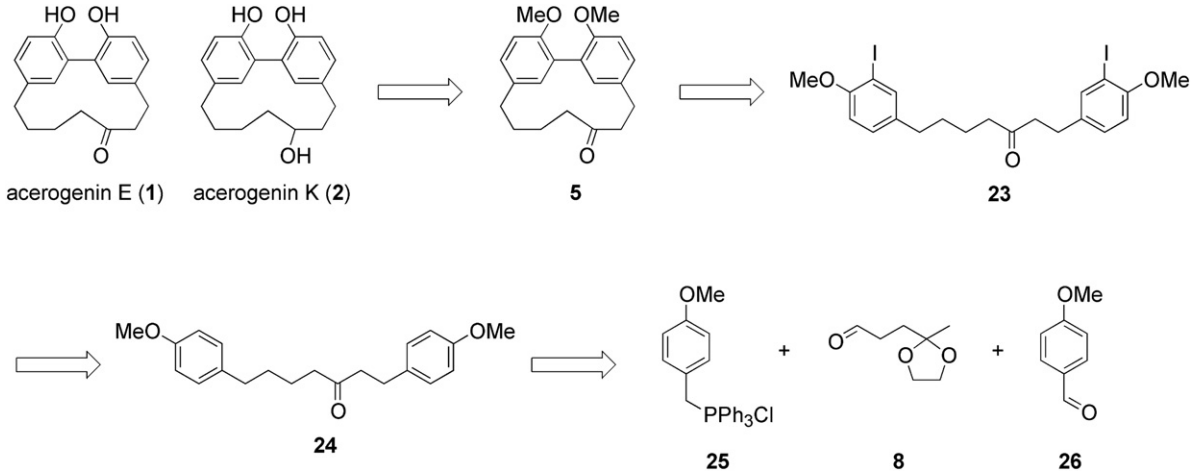
Scheme 2. Synthesis of segments **7**, **8**, and **9**. Reagents and conditions: (a) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux, 4 h, quant; (b) NBS, $HBF_4{\cdot}Et_2O$, MeCN, −20 °C to rt, 23 h, 98%; (c) DIBAL–H, THF, −78 °C to 0 °C, 1 h, 98%; (d) PPh_3, CBr_4, CH_2Cl_2, −78 °C, 2 h, 83%; (e) PPh_3, benzene, reflux, 5 h, quant; (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 3 h, 98%; (g) $PdCl_2(dppf)$, $(Bpin)_2$, AcOK, DMSO, 80 °C, 24 h, 74%; (h) $HO(CH_2)_2OH$, *p*-TsOH, benzene, reflux, 18 h, 98%; (i) DIBAL–H, CH_2Cl_2, −78 °C, 30 min, 88%.



Scheme 3. Wittig reaction and Claisen–Schmidt condensation. Reagents and conditions: (a) NaH, THF, rt, 4 h, 61%; (b) H_2, Pd/C, THF, rt, 15 h, then, PPTS, acetone, H_2O, reflux, 4 h, 83%; (c) AcOH, pyrrolidine, Et_2O, THF, 60 °C, 5 h, 73%; (d) H_2, Pd/C, solvent; (e) AcOH, pyrrolidine, Et_2O, THF, 60 °C, 20 h, 72%; (f) H_2, Pd/C, $CHCl_3$, rt, 22 h, 81%.

gave the coupling product **20** in 73% yield.[7c,16] Although the hydrogenation of **20** was examined in various solvents, such as MeOH, $CHCl_3$, and THF, the reaction gave complex mixtures. However, when dibromine compound **21**, which was prepared from **19** and **15** via a Claisen–Schmidt condensation, was subsequently reduced using Pd/C under a hydrogen atmosphere in $CHCl_3$. Compound **22** was obtained in 81% yield. These results suggest that the bulky boronate in **20** prevents coordination of the olefin to the Pd/C and/or that arylboronate was unstable under the hydrogenation conditions. Due to the difficulty in obtaining the hydrogenated product **6**, direct intramolecular Suzuki–Miyaura coupling reaction for the obtained enone **20** was investigated. However, no cyclized products were identified. This synthetic route was thus ruled out.

The second retrosynthetic analysis is shown in Scheme 4. Installation of the functional groups in the aryl substrates for the intramolecular coupling reaction would be conducted at a late stage. Diiodination of compound **24** would thus provide diiodide **23**. Accordingly, instead of an intramolecular Suzuki–Miyaura coupling reaction, we decided to utilize alternative intramolecular aryliodide–aryliodide coupling reactions, including an Ullmann

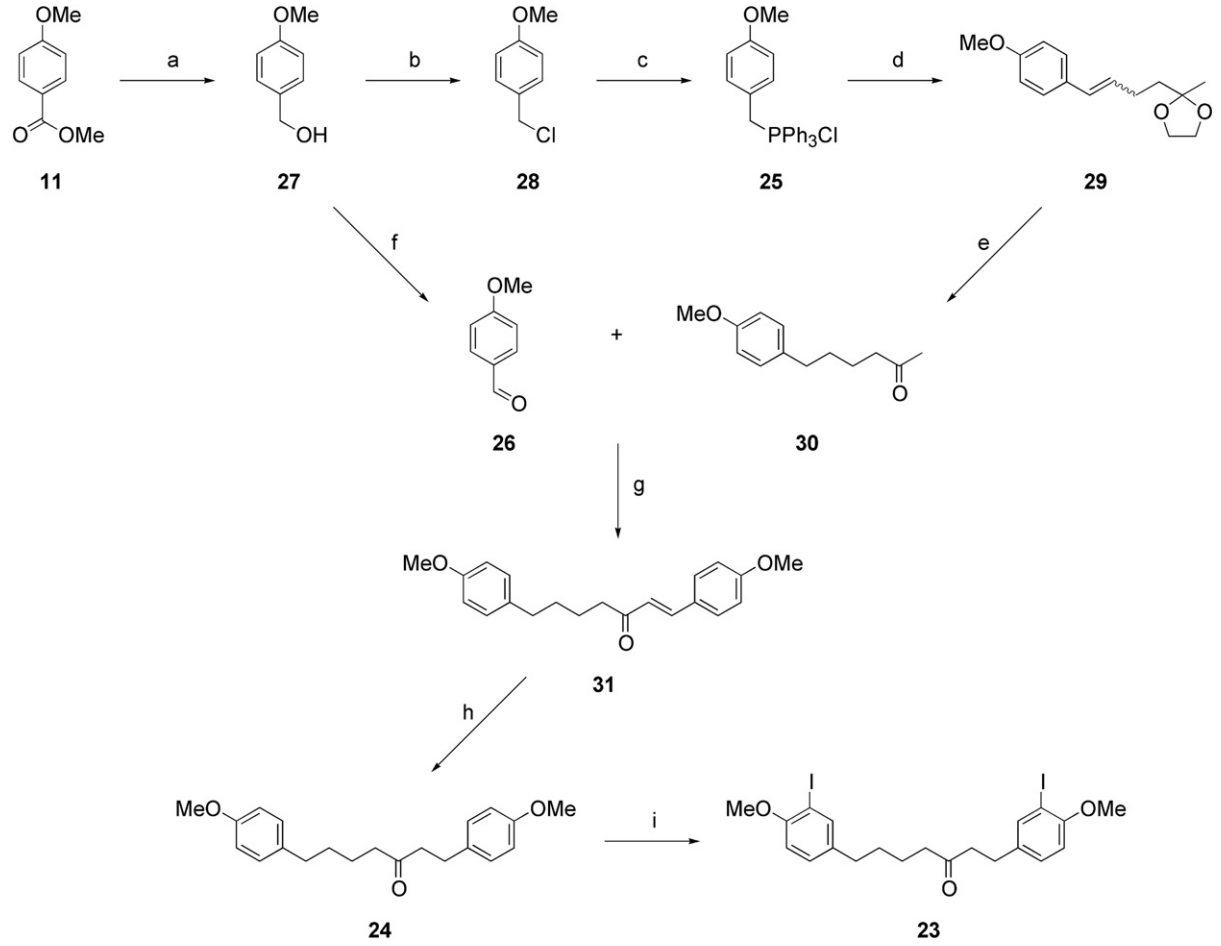


Scheme 4. Second retrosynthesis.

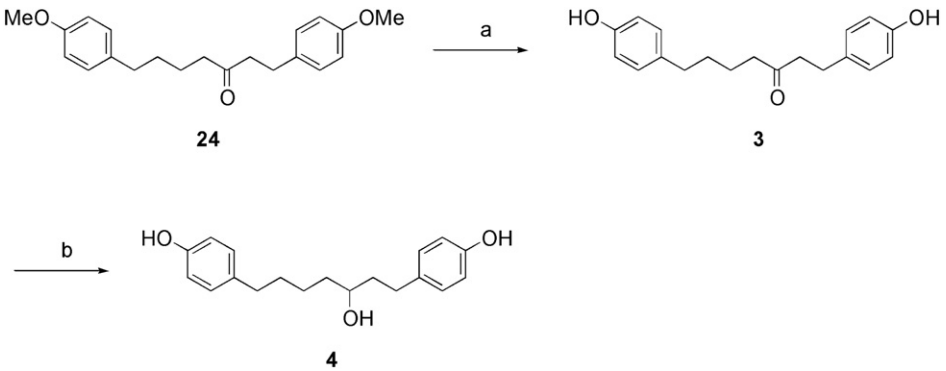
coupling and a domino process involving the Miyaura arylborylation–Suzuki reaction. The coupling substrate **24** would then be prepared from **25**, **8**, and **26** in the same manner as proposed for the initial synthetic pathway.

New segments **25** and **26** were prepared from **11** (Scheme 5). Reduction of **11** using $LiAlH_4$ provided alcohol **27** in 94% yield as a common intermediate. Bromination via the Appel reaction of **27** did not proceed well, because the product readily decomposed on silica gel. Alternatively, chlorination using $SOCl_2$ generated **28**, which was then refluxed with PPh_3 to afford phosphonium salt **25** in 90% yield. Wittig reaction of **25** and aldehyde **8** using *n*-BuLi gave **29** in 86% yield. Olefin **29** was then hydrogenated and deprotected in two steps in 91% yield to afford ketone **30**. Enone **31** was obtained in 69% yield from the Claisen–Schmidt condensation of aldehyde **26**, which was prepared from **27** via Swern oxidation, and ketone **30**. Hydrogenation of **31** gave the desired product **24** in 83% yield. Finally, treatment of **24** with I_2 and CF_3COOAg gave diiodide **23** in 76% yield.[9,17]

Prior to completing the synthesis of **1** and **2**, dimethoxy ether **24** was investigated as an intermediate for the total synthesis of linear-type diarylheptanoids **3** and **4** (Scheme 6). Deprotection of **24** by careful addition of BBr_3 at −78 °C afforded acerogenin G (**3**) in 82%



Scheme 5. Synthesis of **23**. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 30 min, 94%; (b) $SOCl_2$, Et_2O, rt, 3 h, 95%; (c) PPh_3, toluene, reflux, 7 h, 90%; (d) **8**, *n*-BuLi, THF, 0 °C to rt, 2 h, 86%; (e) H_2, Pd/C, THF, rt, 20 h, then, PPTS, acetone, H_2O, reflux, 4 h, 91%; (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 3 h, 92%; (g) AcOH, pyrrolidine, Et_2O, THF, 60 °C, 3 h, 69%; (h) H_2, Pd/C, $CHCl_3$, rt, 10 h, 83%; (i) I_2, CF_3COOAg, $CHCl_3$, rt, 30 min, 76%.

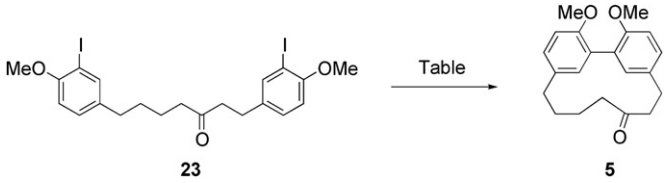


Scheme 6. Total synthesis of **3** and **4**. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 °C to 0 °C, 4 h, 82%; (b) $NaBH_4$, MeOH, 0 °C to rt, 20 min, 97%.

yield.[18] Subsequently, reduction of **3** using 10 equiv of $NaBH_4$ gave racemic centrolobol (**4**) in 97% yield. The spectroscopic data (^1H NMR, ^{13}C NMR, HRMS) of synthetic **3** and **4** were identical to those reported for the natural products.[1f,12] Thus, the total synthesis of **3** and **4** was achieved in 41% yield over six steps and in 39% yield over seven steps, respectively, starting from 4-hydroxybenzoic acid (**10**).

The intramolecular coupling reaction of diiodide **23** was then investigated (Table 1). Various reagents were tested in the Ullmann

Table 1
Optimization of the domino process involving a Miyaura arylborylation–intramolecular Suzuki reaction[a]



23 5

Entry	Pd cat	$(Bpin)_2$/equiv	Additive	Solvent	Concn/M	Yield/%
1	$PdCl_2$(dppf)	1.2	AcOK	Dioxane	0.01	0
2	$PdCl_2$(dppf)	1.2	Cs_2CO_3	DMSO	0.01	0
3	$PdCl_2$(dppf)	1.2	K_2CO_3	DMSO	0.01	26
4	PEPPSI	1.2	AcOK	DMSO	0.01	0
5	$PdCl_2$(dppf)	1.2	AcOK	DMSO	0.01	34
6	$PdCl_2$(dppf)	1.4	AcOK	DMSO	0.01	18
7	$PdCl_2$(dppf)	1.1	AcOK	DMSO	0.01	29
8	$PdCl_2$(dppf)	1.2	AcOK	DMSO	0.02	5
9	$PdCl_2$(dppf)	1.2	AcOK	DMSO	0.005	29

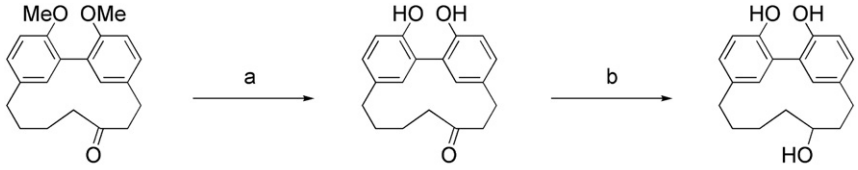
[a] Reaction condition: Pd cat (10 mol %), $(Bpin)_2$ (1.1–1.4 equiv), base (10 equiv), solvent, 100 °C, 24 h.

examined, and it was found that 0.02 and 0.005 M gave the product in 5% and 29% yields, respectively (entries 8 and 9), suggesting that 0.01 M would be the best concentration in the reaction to prevent oligomerization and/or polymerization. Meanwhile, when the intramolecular reaction was run with dibromo compound **22** under the conditions used in entry 5, no coupling products were obtained. As a result, a domino-type intramolecular coupling reaction was optimized to the conditions listed for entry 5.

Eventually, dimethyl ether **5** was deprotected with BBr_3 to provide the desired natural product acerogenin E (**1**) in 94% yield (Scheme 7). Reduction of **1** to acerogenin K (**2**) was achieved in 95% yield, but required many more equivalents (50 equiv) of $NaBH_4$ than was needed (10 equiv) for the reduction of **3** to **4**. This result indicates that the carbonyl carbon of **1** may be surrounded by the cyclophane moiety, which inhibits the nucleophilic attack of the hydride. The spectroscopic data (^1H NMR, ^{13}C NMR, HRMS) and melting points of synthetic **1** and **2** were identical to those reported for the natural products.[1h,i] The total synthesis of **1** and **2** was achieved in 12% yield over eight steps and in 11% yield over nine steps, respectively.

3. Conclusion

The first total synthesis of acerogenins E (**1**) and K (**2**) was achieved in 12% yield over eight steps and in 11% yield over nine steps, respectively, starting from 4-hydroxybenzoic acid (**10**). The diarylheptanoid skeleton was prepared via a Wittig reaction and a Claisen–Schmidt condensation. The total synthesis of the linear-type diarylheptanoids, acerogenin G (**3**), and centrolobol (**4**) was also accomplished from a common synthetic intermediate. A domino process involving a Miyaura arylborylation–intramolecular Suzuki reaction using $PdCl_2$(dppf)/$(Bpin)_2$/AcOK gave the desired 13-



5 1 2

Scheme 7. Total synthesis of **1** and **2**. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 °C to 0 °C, 3 h, 94%; (b) $NaBH_4$, MeOH, 0 °C to rt, 3 h, 95%.

coupling reaction, including $Pd(PPh_3)_4$,[9] $Ni(PPh_3)_4$,[9] $Pd(OAc)_2$/K_2CO_3,[19] and $Pd_2(dba)_3$/TBAF,[20] but resulted in no reaction or the production of complex mixtures, even though the reactions were performed at relatively high dilution (0.01–0.02 M). These results thus encouraged us to apply alternative intramolecular coupling reactions. A domino process involving a Miyaura arylborylation–intramolecular Suzuki reaction, which was reported by Zhu and co-workers[11a] and Hutton and co-workers[11b] for the synthesis of macrocycles, was chosen as the key reaction. Our optimization of the cyclization is summarized in Table 1. When the reaction was run using 10 mol % of $PdCl_2$(dppf), 1.2 equiv of $(Bpin)_2$, 10 equiv of AcOK in 1,4-dioxane, no coupling product was obtained at all (entry 1). Use of Cs_2CO_3 in DMSO did not lead to the reaction either (entry 2), while use of K_2CO_3 gave the desired coupling product **5** in 26% yield (entry 3). In addition, when Pd-PEPPSI-IPr, developed by Organ and co-workers,[21] was used as the Pd catalyst, the reaction did not proceed (entry 4). The best conditions for the generation of **5** were found to be 10 mol % of $PdCl_2$(dppf), 1.2 equiv of $(Bpin)_2$, and 10 equiv of AcOK in DMSO, which provided the desired product in 34% yield (entry 5). Use of 1.4 and 1.1 equiv of $(Bpin)_2$ caused a decrease in the yield to 18% and 29%, respectively (entries 6 and 7). Optimization of the concentration was also membered *m*,*m*-cyclophane product **5** in 34% yield, enabling the preparation of **1** and **2**. This approach is the first example of the formation of an aryl–aryl bond containing an aliphatic cyclophane group via a domino intramolecular Suzuki–Miyaura coupling. Further application of this reaction to the synthesis of other cyclophane natural products will be carried out. In addition, this achievement will lead to the preparation of a range of acerogenin derivatives for structure–activity relationship studies in order to elucidate the biological mechanisms of action of *A. nikoense* MAXIM. (megusurino-ki).

4. Experimental section

4.1. General

All non-aqueous reactions were conducted under an atmosphere of nitrogen with magnetic stirring. Acetonitrile (MeCN), benzene were dried by distillation and stored over activated molecular sieves. Chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), diethylether (Et_2O), tetrahydrofuran (THF), and toluene were dried by activated molecular sieves. Dehydrated dimethyl sufoxide (DMSO) and methanol (MeOH) were purchased from Kanto

Chemicals (Tokyo, Japan). All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates produced by Merck. Column chromatography was performed with acidic Silica gel 60 (spherical, 40–50 μm) or neutral Silica gel 60N (spherical, 40–50 μm) produced by Kanto Chemicals.

Melting points were measured by an AS one ATM-01 apparatus. Optical rotations were measured on a JASCO P-2200 digital polarimeter at the sodium lamp (λ=589 nm) D line and are reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). Infrared (IR) spectra were recorded on a JASCO FT-IR 4100 spectrometer and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EXC 300 spectrometer (300 MHz) or on a JEOL JNM-ECA 500 spectrometer (500 MHz). ^1H NMR data are reported as follows: chemical shift (δ, ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constants (*J*) in hertz (Hz), assignments. ^{13}C NMR data are reported in terms of chemical shift (δ, ppm). EIMS spectra were recorded on a Shimadzu GCMS QP-5050 instrument or on a JEOL JMS-700 instrument.

4.2. (3-Bromo-4-methoxyphenyl)-methanol (13)

To a solution of methyl 3-bromo-4-methoxybenzoate (**12**, 2.00 g, 8.16 mmol) in THF (20 mL) was added DIBAL–H (1.00 M in hexane, 20.4 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min and 0 °C for 30 min. To the reaction mixture at −78 °C was added methanol (10 mL) dropwisely followed by saturated aqueous Rochelle salt solution (16 mL) and EtOAc (20 mL). After being stirred at room temperature for 2 h, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and then concentrated in vacuo. Purification on silica gel column chromatography (hexane/EtOAc=2:1) gave **13** (1.73 g, 7.96 mmol, 98%) as a colorless solid; R_f 0.17 (hexane/EtOAc=3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, *J*=2.2 Hz, H18), 7.27 (1H, dd, *J*=8.6, 2.2 Hz, H15), 6.88 (1H, d, *J*=8.6 Hz, H16), 4.61 (2H, s, H13), 3.90 (3H, s, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 134.6, 132.4, 112.0, 111.8, 64.4, 56.4; EIMS (*m*/*z*) calcd for $C_8H_9BrO_2$ $[M]^+$ 215.98, found 216.05.

4.3. 2-Bromo-4-bromomethyl-1-methoxybenzene (14)

To a solution of (3-bromo-4-methoxyphenyl)-methanol (**13**, 504 mg, 2.32 mmol) in CH_2Cl_2 (10 mL) was added triphenylposphine (1.23 g, 4.60 mmol) at room temperature. After being stirred at room temperature for 10 min, carbon tetrabromide (1.53 g, 4.61 mmol) was added at −78 °C, and being stirred at −78 °C for 2 h. The reaction mixture was treated with 50% hexane/EtOAc mixture (20 mL), and passed through short silica gel column chromatography (50% hexane/EtOAc, 200 mL). Purification by silica gel column chromatography (hexane/EtOAc=5:1) gave **14** (537 mg, 1.92 mmol, 83%) as a colorless solid; R_f 0.60 (hexane/EtOAc=3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, d, *J*=2.0 Hz, H18), 7.29 (1H, dd, *J*=8.6, 2.0 Hz, H15), 6.86 (1H, d, *J*=8.6 Hz, H16), 4.44 (2H, s, H13), 3.90 (3H, s, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 134.2, 131.5, 129.5, 112.0, 111.9, 56.5, 32.6; EIMS (*m*/*z*) calcd for $C_8H_8Br_2O$ $[M]^+$ 277.89, found 278.00.

4.4. 3-Bromo-4-methoxybenzyltriphenylphosphonium bromide (7)

A mixture of 2-bromo-4-bromomethyl-1-methoxybenzene (**14**, 211 mg, 0.754 mmol) and triphenylphosphine (198 mg, 0.754 mmol) in benzene (2 mL) was stirred under reflux for 5 h, and concentrated in vacuo to give **7** (414 mg, quant) as a colorless powder; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.60 (15H, m, Ph), 7.52–7.45 (1H, m, H18), 6.83–6.78 (1H, m, H15), 6.70 (1H, d, *J*=8.5 Hz, H16), 5.45 (2H, d, *J*=14.2 Hz, H13); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.66, 135.60, 135.08, 135.04, 134.67, 134.54, 132.74, 132.65, 130.33, 130.16, 120.44, 120.33, 118.46, 117.34, 112.05, 112.01, 111.22, 56.29, 29.93.

4.5. 4-Methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (9)

To a mixture of [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (68.0 mg, 92.9 μmol), bis(pinacolato)diboron (283 mg, 1.11 mmol), and potassium acetate (274 mg, 2.79 mmol) was added **15** (202 mg, 0.939 mmol) in DMSO (3 mL). The reaction mixture was stirred at 80 °C for 24 h. After addition of water, the aqueous layer was extracted with toluene. The combined organic layers were washed with water, dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=3:1) gave **9** (182 mg, 0.693 mmol, 74%) as a colorless solid; R_f 0.26 (hexane/EtOAc=3:1); mp 98–101 °C; IR (neat, cm^{-1}) 2979, 1688, 1490, 1427, 1362, 1266, 1201, 1065, 1020, 854, 808; ^1H NMR (300 MHz, $CDCl_3$) δ 9.90 (1H, s, H13), 8.20 (1H, d, *J*=2.4 Hz, H18), 7.96 (1H, dd, *J*=6.4, 2.3 Hz, H15), 6.97 (1H, d, *J*=8.7 Hz, H16), 3.92 (1H, s, OMe), 1.37 (12H, s, Bpin); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 169.0, 140.1, 134.2, 129.5, 110.7, 84.1, 56.2, 25.0; EI-HRMS (*m*/*z*) calcd for $C_{14}H_{19}BO_4$ $[M]^+$ 261.1412, found 261.1383.

4.6. 2-[4-(3-Bromo-4-methoxyphenyl)-but-3-enyl]-2-methyl-[1,3]dioxolane (18)

To a slurry of sodium hydride (60% dispersion in paraffin liquid, 9.8 mg, 0.245 mmol, 1.5 equiv) in THF (1 mL), 3-bromo-4-methoxybenzyltriphenylphosphonium bromide (**7**, 101 mg, 0.186 mmol, 1.1 equiv) was added and stirred at room temperature for 1.5 h. To the yellow ylide slurry was added a solution of 3-(2-methyl-[1,3]dioxolan-2-yl)-propionaldehyde (**8**, 24.2 mg, 0.168 mmol, 1.0 equiv) in THF (0.5 mL). After stirring for 4 h at room temperature, the reaction mixture was diluted with EtOAc, filtered through Celite, and then concentrated in vacuo. Purification by silica gel chromatography (hexane/EtOAc=4:1) gave **18** (33.4 mg, 0.102 mmol, 61%, *E*/*Z*=2.1:1) as a colorless oil; R_f 0.40 (hexane/EtOAc=3:1); IR (neat, cm^{-1}) 2943, 1714, 1597, 1496, 1267, 1147, 1053, 964, 881, 805; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, d, *J*=2.1 Hz, H18-*E*), 7.50 (1H, d, *J*=2.1 Hz, H18-*Z*), 7.21 (1H, dd, *J*=8.6, 2.1 Hz, H15), 6.86 (1H, d, *J*=8.6 Hz, H16-*Z*), 6.82 (1H, d, *J*=8.6 Hz, H16-*E*), 6.34–6.24 (1H, m, H13), 6.17–6.03 (1H, m, H12-*E*), 5.68–5.56 (1H, m, H12-*Z*), 4.01–3.91 (4H, m, OCH_2CH_2O), 3.90 (3H, s, OMe-*Z*), 3.88 (3H, s, OMe-*E*), 2.52–2.24 (2H, m, H11), 1.86–1.75 (2H, m, H10), 1.35 (3H, s, H8-*E*), 1.33 (3H, s, H8-*Z*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 133.6, 132.3, 132.2, 130.7, 130.0, 129.0, 128.0, 127.3, 126.2, 112.0, 111.7, 109.9, 64.9, 56.4, 39.1, 38.8, 27.7, 24.1, 24.0, 23.5; EI-HRMS (*m*/*z*) calcd for $C_{15}H_{19}BrO_3$ $[M]^+$ 326.0518, found 326.0533.

4.7. 6-(3-Bromo-4-methoxyphenyl)-hexan-2-one (19)

A mixture of 2-[4-(3-bromo-4-methoxyphenyl)-but-3-enyl]-2-methyl-[1,3]dioxolane (**18**, 298 mg, 0.911 mmol) and 10% Pd/C (30.0 mg) in THF (3 mL) was stirred under an atmosphere of H_2 at room temperature for 15 h. The reaction mixture was filtered through Celite and washed with EtOAc. Concentration of the filtrate in vacuo gave a colorless oil. Then the crude oil and PPTS (39.1 mg, 155 μmol) in acetone (12 mL) and water (160 μL) were refluxed for 4 h. After cooling to room temperature, saturated $NaHCO_3$ solution was added, and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and then

concentrated in vacuo. Purification by silica gel column chromatography gave **19** (215 mg, 0.755 mmol, 83%) as a colorless oil; R_f 0.40 (hexane/EtOAc=3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (1H, d, J=2.1 Hz, H18), 7.06 (1H, dd, J=6.2, 2.3 Hz, H15), 6.81 (1H, d, J=8.3 Hz, H16), 3.87 (3H, s, OMe), 2.54 (2H, t, J=7.0 Hz, H14), 2.44 (3H, t, J=6.9 Hz, H11), 2.12 (3H, s, H10), 1.66–1.51 (4H, m, H12/13); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 154.1, 136.0, 133.2, 128.4, 112.0, 111.5, 56.4, 43.6, 34.6, 31.0, 30.0, 23.4; EIMS (m/z) calcd for $C_{13}H_{17}BrO_2$ $[M]^+$ 284.04, found 283.95.

4.8. 7-(3-Bromo-4-methoxyphenyl)-1-[4-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-hept-1-en-3-one (20)

To a stirred mixture of acetic acid (30 μL) and pyrrolidine (45 μL) in Et_2O (3 mL) was added a solution of 6-(3-bromo-4-methoxyphenyl)-hexan-2-one (**19**, 100 mg, 0.352 mmol, 1.3 equiv) and 3-bromo-4-methoxybenzaldehyde (**9** 72.4 mg, 0.276 mmol, 1.0 equiv) in THF (2.5 mL), and stirred at 60 °C for 5 h. The mixture was then cooled to room temperature and acidified by the addition of 1 N HCl and extracted with EtOAc. The combined organic layers were washed with water, saturated $NaHSO_3$ solution, brine, and dried over Na_2SO_4 and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=5:1) gave **20** (106 mg, 0.201 mmol, 73%) as a colorless amorphous; R_f 0.26 with decomposition (hexane/EtOAc=3:1); IR (neat, cm^{-1}) 2934, 1596, 1496, 1413, 1354, 1259, 1148, 1063, 814; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, d, J=2.4 Hz, H19), 7.58 (1H, dd, J=6.4, 2.4 Hz, H5), 7.51 (1H, d, J=16.1 Hz, H7), 7.37 (1H, d, J=2.1 Hz, H18), 7.07 (1H, dd, J=6.4, 2.1 Hz, H15), 6.87 (1H, d, J=8.5 Hz, H4), 6.81 (1H, d, J=8.3 Hz, H16), 6.64 (1H, d, J=16.1 Hz, H8), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 2.66 (2H, t, J=6.8 Hz, H10), 2.57 (2H, t, J=7.2 Hz, H13), 1.75–1.52 (4H, m, H11/12), 1.37 (12H, s, Bpin), 212.1, 200.5, 166.2, 142.5, 136.2, 133.3, 128.4, 126.7, 124.4, 112.0, 83.9, 56.4, 56.1, 40.4, 34.7, 31.3, 25.0, 24.1; EI-HRMS (m/z) calcd for $C_{27}H_{34}BBrO_3$ $[M]^+$ 528.1683, found 528.1675.

4.9. 1,7-Bis-(3-bromo-4-methoxyphenyl)-hept-1-en-3-one (21)

To a stirred mixture of acetic acid (10 μL) and pyrrolidine (15 μL) in Et_2O (2 mL) was added a solution of 6-(3-bromo-4-methoxyphenyl)-hexan-2-one (**19**, 60.1 mg, 0.211 mmol) in Et_2O (1 mL), and then added a solution of 3-bromo-4-methoxybenzaldehyde (**15**, 46.1 mg, 0.214 mmol) in THF (2 mL). The reaction mixture was stirred at 60 °C for 20 h. The mixture was then acidified by the addition of 1 N HCl and extracted with EtOAc. The combined organic layers were washed with water, saturated $NaHSO_3$ solution, brine, and dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=5:1) gave **21** (73.4 mg, 0.152 mmol, 72%) as a yellow oil; R_f 0.31 (hexane/EtOAc=3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, d, J=2.1 Hz, H19), 7.48–7.39 (2H, m, H5/7), 7.37 (1H, d, J=2.1 Hz, H18), 7.07 (1H, dd, J=8.2, 2.0 Hz, H15), 6.90 (1H, d, J=8.6 Hz, H4), 6.81 (1H, d, J=8.3 Hz, H16), 6.61 (1H, d, J=16.1 Hz, H8), 3.93 (3H, s, OMe), 3.86 (3H, s, OMe), 2.64 (2H, t, J=6.9 Hz, H10), 2.57 (2H, t, J=7.2 Hz, H13), 1.76–1.62 (4H, m, H11/12); EIMS (m/z) calcd for $C_{21}H_{22}Br_2O_3$ $[M]^+$ 479.99, found 479.95.

4.10. 1,7-Bis-(3-bromo-4-methoxyphenyl)-heptan-3-one (22)

A mixture of 1,7-bis-(3-bromo-4-methoxyphenyl)-hept-1-en-3-one (**21**, 68.6 mg, 0.142 mmol) and 10% Pd/C (14.0 mg) in $CHCl_3$ (1.5 mL) was stirred under H_2 atmosphere using a balloon at room temperature for 22 h. The reaction mixture was filtered through a pad of Celite and washed with $CHCl_3$. The filtrate was then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=5:1) afforded **22** (55.7 mg, 0.115 mmol, 81%) as a colorless oil; R_f 0.43 (hexane/EtOAc=3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.32 (2H, m, H18/19), 7.10–7.00 (2H, m, H5/15), 6.83–6.76 (2H, m, H4/16), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 2.80 (2H, t, J=7.2 Hz, H7), 2.66 (2H, t, J=7.3 Hz, H8), 2.51 (2H, t, J=7.2 Hz, H13), 2.38 (2H, t, J=6.9 Hz, H10), 1.62–1.48 (4H, m, H11/12); EIMS (m/z) calcd for $C_{21}H_{24}Br_2O_3$ $[M]^+$ 482.01, found 481.90.

4.11. 2-[4-(4-Methoxyphenyl)-but-3-enyl]-2-methyl-[1,3]dioxolane (29)

To a suspension of 4-methoxybenzyltriphenylphosphonium chloride (**25**, 201 mg, 478 μmol, 1.2 equiv) in THF (2 mL) was added dropwisely 1.65 M n-BuLi in hexane (289 μL, 478 μmol, 1.2 equiv). The ylide suspension was stirred at 0 °C for 15 min. To the suspension was added a solution of 3-(2-methyl-[1,3]dioxolan-2-yl)-propionaldehyde (**8**, 57.4 mg, 398 μmol) in THF (1 mL), and allowed to be stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution at 0 °C, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=5:1) gave **29** (84.9 mg, 342 μmol, 86%, E/Z=1.7:1) as a colorless oil; R_f 0.60 (hexane/EtOAc=3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (2H, m, H15/18), 6.95–6.80 (2H, m, H1/16), 6.40–6.30 (1H, m, H13), 6.14–6.03 (1H, m, H12-*E*), 5.62–5.51 (1H, m, H12-*Z*), 4.04–3.87 (4H, br s, OCH_2CH_2O), 3.81 (3H, s, OMe), 3.80 (3H, s, OMe), 2.50–2.38 (2H, m, H11-*Z*), 2.36–2.20 (2H, m, H11-*E*), 1.84–1,76 (2H, m, H10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.26, 131.22, 130.85, 130.50, 129.71, 128.94, 128.87, 127.57, 114.48, 114.17, 110.39, 65.30, 55.86, 55.83, 39.72, 39.42, 28.18, 24.55, 24.49, 24.00; EIMS (m/z) calcd for $C_{15}H_{20}O_3$ $[M]^+$ 248.14, found 248.15.

4.12. 6-(4-Methoxyphenyl)-hexan-2-one (30)

A suspension of 2-[4-(4-methoxyphenyl)-but-3-enyl]-2-methyl-[1,3]dioxolane (**29**, 347 mg, 1.40 mmol) and 10% Pd/C (50.0 mg) in THF (5 mL) was stirred under an atmosphere of H_2 at room temperature for 20 h. The reaction mixture was filtered through Celite and washed with EtOAc. Concentration of the filtrate in vacuo gave a colorless oil. Then the crude oil and PPTS (120 mg, 474 μmol) in acetone (12 mL) and water (160 μL) were refluxed for 4 h. After cooling to room temperature, saturated $NaHCO_3$ solution was added, and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography gave **30** (263 mg, 1.27 mmol, 91%) as a colorless oil; R_f 0.57 (hexane/EtOAc=3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (2H, d, J=8.2 Hz, H15/18), 6.82 (2H, d, J=8.4 Hz, H1/16), 3.78 (3H, s, OMe), 2.56 (2H, t, J=7.0 Hz, H13), 2.44 (2H, t, J=7.0 Hz, H10), 2.11 (3H, s, H8), 1.68–1.50 (4H, m, H11/12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.2, 157.9, 134.4, 129.4, 113.9, 55.4, 43.7, 34.9, 31.3, 30.0, 23.5; EIMS (m/z) calcd for $C_{13}H_{18}O_2$ $[M]^+$ 206.13, found 206.25.

4.13. 1,7-Bis-(4-methoxyphenyl)-hept-1-en-3-one (31)

To a stirred mixture of acetic acid (20 μL) and pyrrolidine (30 μL) in Et_2O (3 mL) was added a solution of 6-(4-methoxyphenyl)-hexan-2-one (**30**, 63.8 mg, 0.309 mmol, 1.1 equiv) in Et_2O (1.5 mL) and added a solution of 4-methoxybenzaldehyde (**26**, 38.3 mg, 0.281 mmol, 1.0 equiv) in THF (3 mL). The mixture was stirred at 60 °C for 3 h. The mixture was then acidified by the addition of 1 N HCl and extracted with EtOAc. The combined organic layers were washed with water, saturated $NaHSO_3$ solution, brine, and dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=5:1) gave **31** (66.3 mg,

0.204 mmol, 69%) as a colorless solid; R_f 0.50 (hexane/EtOAc=3:1); mp 75–76 °C; IR (neat, cm^{-1}) 2932, 1646, 1604, 1507, 1247, 1173, 1035, 981, 818; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.43 (3H, m, H5/7/19), 7.10 (2H, d, J=8.5 Hz, H15/18), 6.91 (2H, d, J=8.6 Hz, H2/4), 6.82 (2H, d, J=8.5 Hz, H1/16), 6.61 (1H, d, J=16.2 Hz, H8), 3.84 (3H, s, OMe), 3.78 (3H, s, OMe), 2.69–2.54 (4H, m, H10/13), 1.80–1.58 (4H, m, H11/12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.6, 161.7, 142.3, 134.5, 130.1, 129.4, 127.4, 124.2, 114.5, 113.9, 55.5, 55.4, 40.8, 35.0, 31.5, 24.2; EI-HRMS (m/z) calcd for $C_{21}H_{24}O_3$ $[M]^+$ 324.1725, found 324.1718.

4.14. 1,7-Bis-(4-methoxyphenyl)-heptan-3-one (24)

A mixture of **31** (185 mg, 0.570 mmol) and 10% Pd/C (74.0 mg) in $CHCl_3$ (3 mL) was stirred under H_2 atmosphere using a balloon at room temperature for 10 h. The reaction mixture was filtered through a pad of Celite and washed with $CHCl_3$. The filtrate was then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=5:1) afforded **24** (154 mg, 0.472 mmol, 83%) as a colorless solid; R_f 0.60 (hexane/EtOAc=3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.13–7.02 (4H, m, H5/15/18/19), 6.81 (4H, d, J=8.6 Hz, H1/2/4/16), 3.78 (6H, s, OMe), 2.83 (2H, t, J=7.5 Hz, H7), 2.67 (2H, t, J=7.6 Hz, H8), 2.54 (2H, t, J=7.1 Hz, H13), 2.38 (2H, t, J=6.9 Hz, H10), 1.66–1.47 (4H, m, H11/12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.4, 158.1, 134.4, 133.3, 129.4, 113.9, 55.4, 44.7, 43.0, 34.9, 31.3, 29.1, 23.5; EIMS (m/z) calcd for $C_{21}H_{26}O_3$ $[M]^+$ 326.19, found 326.20.

4.15. 1,7-Bis-(3-iodo-4-methoxyphenyl)-heptan-3-one (23)

To a solution of 1,7-bis-(4-methoxyphenyl)-heptan-3-one (**24**, 277.6 mg, 0.850 mmol) in $CHCl_3$ (8 mL) was added silver trifluoroacetate (750 mg, 3.40 mmol). To the stirred suspension was added a solution of iodine (863 mg, 3.40 mmol) in $CHCl_3$ (20 mL) dropwise over 15 min. The suspension was stirred at room temperature for 30 min and then filtered through a pad of Celite. To the filtrate was added saturated Na_2SO_3 solution until the reaction mixture turned to colorless. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Twice of purification by silica gel column chromatography (hexane/EtOAc=8:1) afforded **23** (372 mg, 0.644 mmol, 76%) as a colorless powder; R_f 0.43 (hexane/EtOAc=3:1); mp 57–58 °C; IR (neat, cm^{-1}) 2930, 1705, 1600, 1488, 1252, 1050, 805; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.54 (2H, m, H18/19), 7.14–7.04 (2H, m, H5/15), 6.78–6.66 (2H, m, H4/16), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 2.79 (2H, t, J=7.0 Hz, H7), 2.66 (2H, t, J=6.9 Hz, H8), 2.50 (2H, t, J=7.2 Hz, H13), 2.38 (2H, t, J=6.6 Hz, H10), 1.64–1.44 (4H, m, H11/12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.8, 156.7, 139.3, 139.2, 136.6, 135.5, 129.6, 129.5, 111.0, 110.9, 86.1, 86.0, 56.5, 44.4, 42.9, 34.4, 31.1, 28.4, 23.3; EI-HRMS (m/z) calcd for $C_{21}H_{24}I_2O_3$ $[M]^+$ 577.9815, found 577.9823.

4.16. Acerogenin G (3)[1f]

To a solution of 1,7-bis-(4-methoxyphenyl)-heptan-3-one (**24**, 95.6 mg, 0.293 mmol) in CH_2Cl_2 (5 mL) cooled to −78 °C was dropwisely added BBr_3 (1 M in CH_2Cl_2, 1.46 mL, 1.46 mmol). The temperature was gradually raised to 0 °C. After stirring for 4 h, saturated $NaHCO_3$ solution was added at 0 °C. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=2:1) afforded **3** (71.9 mg, 0.241 mmol, 82%) as a colorless amorphous; R_f 0.46 (hexane/EtOAc=1:1); $[\alpha]_D^{25}$ −0.1 (c 0.8, MeOH); IR (neat, cm^{-1}) 3600, 3097, 1644, 1494, 1248, 1047; ^1H NMR (500 MHz, pyridine-d_5) δ 7.24–7.02 (8H, m, H2′/3′/5′/6′/2″/3″/5″/6″), 2.94 (2H, t, J=7.5 Hz, H1), 2.71 (2H, t, J=7.5 Hz, H2), 2.53 (2H, t, J=7.3 Hz, H7), 2.36 (2H, t, J=6.4 Hz, H4), 1.62 (2H, m, H6), 1.57 (2H, m, H5); ^{13}C NMR (125 MHz, pyridine-d_5) δ 209.6 (C3), 157.3 (C4′ or C4″), 157.1 (C4′ or C4″), 133.1 (C1′ or C1″), 132.2 (C1′ or C1″), 130.0 (C2′/6′/2″/6″), 116.2 (C3′/5′/3″/5″), 44.8 (C2), 42.8 (C4), 35.2 (C7), 31.7 (C5), 29.5 (C1), 23.7 (C6); EI-HRMS (m/z) calcd for $C_{19}H_{22}O_3$ $[M]^+$ 298.1569, found 298.1588.

4.17. Centrolobol (4)[12]

To a solution of acerogenin G (**3**, 30.3 mg, 0.102 mmol) in MeOH cooled to 0 °C was added sodium borohydride (35.1 mg, 0.928 mmol). After being stirred at room temperature for 20 min, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=1:1) afforded **4** (29.7 mg, 98.9 μmol, 97%) as a colorless powder; R_f 0.31 (hexane/EtOAc=1:1); mp 116–119 °C; $[\alpha]_D^{25}$ −1.1 (c 0.9, MeOH); IR (neat, cm^{-1}) 3566, 3483, 1642, 1596, 1495, 1245, 1166, 1030; ^1H NMR (500 MHz, acetone-d_6) δ 8.04 (2H, br s, ArOH), 7.06–6.97 (4H, m, H2′/6′/2″/6″), 6.73 (4H, d, J=8.3 Hz, H3′/5′/3″/5″), 3.54 (1H, m, H3), 3.48 (1H, m, OH), 2.69 (1H, m, H1a), 2.60–2.45(3H, m, H1b/7), 1.78–1.26 (8H, m, H2/4/5/6); ^{13}C NMR (125 MHz, acetone-d_6) δ 156.14 (C4′/4″), 134.25 (C1′ or C1″), 134.20 (C1′ or C1″), 130.04 (C2′/6′ or C2″/6″), 130.01 (C2′/6′ or C2″/6″), 115.87 (C3′/5′ or C3″/5″), 115.83 (C3′/5′ or C3″/5″), 70.81 (C3), 40.74 (C2), 38.32 (C4), 35.68 (C7), 32.80 (C6), 31.87 (C1), 26.09 (C5); EI-HRMS (m/z) calcd for $C_{19}H_{24}O_3$ $[M]^+$ 300.1725, found 300.1714.

4.18. 3,17-Dimethoxy-tricyclo[12.3.1.12,6]nonadeca-1(17),2(19),3,5,14(18),15-hexaen-9-one (5)

To a mixture of 1,7-bis-(3-iodo-4-methoxyphenyl)-heptan-3-one (**23**, 59.8 mg, 0.103 mmol), $PdCl_2$(dppf) (7.6 mg, 10 μmol), bis(pinacolato)diboron (32.0 mg, 0.126 mmol) and AcOK (102 mg, 1.04 mmol) was added degassed DMSO (10.3 mL). The reaction mixture was stirred at 100 °C for 24 h. After cooling to 0 °C, saturated NH_4Cl solution was added and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel short column chromatography (hexane/EtOAc=1:1) and silica gel column chromatography (hexane/EtOAc=5:1) afforded **5** (11.4 mg, 35.1 μmol, 34%) as a colorless powder; R_f 0.41 (hexane/EtOAc=3:1); mp 147–148 °C; IR (neat, cm^{-1}) 2933, 1699, 1505, 1461, 1260, 1032, 816; ^1H NMR (300 MHz, pyridine-d_5) δ 7.16–7.06 (2H, m, H5/15), 7.00–6.82 (4H, m, H4/16/18/19), 3.77 (3H, s, OMe), 3.75 (3H, s, OMe), 3.38–2.34 (8H, m, H7/8/10/13), 1.90–1.56 (4H, m, H11/12); ^{13}C NMR (75 MHz, pyridine-d_5) δ 213.1, 156.2, 155.7, 135.0, 133.0, 131.7, 130.2, 129.6, 129.4, 128.6, 112.1, 111.9, 55.9, 46.5, 42.6, 32.0, 29.6, 25.9, 21.5; EI-HRMS (m/z) calcd for $C_{21}H_{24}O_3$ $[M]^+$ 324.1725, found 324.1718.

4.19. Acerogenin E (1)[1h]

To a solution of 3,17-dimethoxy-tricyclo[12.3.1.12,6]nonadeca-1(17),2(19),3,5,14(18),15-hexaen-9-one (**5**, 13.3 mg, 41.0 μmol) in CH_2Cl_2 (1.5 mL) cooled to −78 °C was added BBr_3 (1 M in CH_2Cl_2, 205 μL, 0.205 mmol). The temperature was allowed to gradually rise to 0 °C. After stirring for 3 h, saturated $NaHCO_3$ solution was added at 0 °C. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=2:1) afforded **1** (11.4 mg, 38.5 μmol, 94%) as a colorless powder; R_f 0.54 (hexane/EtOAc=1:1); mp 230–232 °C; $[\alpha]_D^{25}$ −0.3 (c 0.8, MeOH); IR (neat, cm^{-1}) 3280, 2939, 1694, 1507, 1403, 1243, 819; ^1H NMR (500 MHz, pyridine-d_5) δ 7.26–7.05 (6H, m, H4/5/15/16/18/19), 4.99 (2H, br s, ArOH), 3.08 (2H, m, H7), 2.80 (2H, t, J=5.1 Hz, H8), 2.75–2.61 (4H,

m, H10/13), 1.96–1.78 (4H, m, H11/12); ^{13}C NMR (125 MHz, pyridine-d_5) δ 212.5 (C9), 153.0 (C3 or C17), 152.9 (C3 or C17), 134.3 (C18 or C19), 134.2 (C18 or C19), 132.4 (C6), 131.6 (C14), 129.9 (C15), 129.0 (C5), 127.8 (C1 or C2), 127.3 (C1 or C2), 117.0 (C4 or C16), 116.8 (C4 or C16), 45.1 (C10), 42.2 (C8), 31.7 (C13), 28.5 (C7), 26.1 (C12), 22.4 (C11); EI-HRMS (m/z) calcd for $C_{19}H_{20}O_3$ $[M]^+$ 296.1412, found 296.1404.

4.20. Acerogenin K (2)[1i]

To a solution of acerogenin E (**1**, 4.9 mg, 17 μmol) in MeOH at 0 °C was portionwise added sodium borohydride (33.9 mg, 0.896 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc=1:1) afforded **2** (4.7 mg, 16 μmol, 95%) as a colorless powder; R_f 0.63 (hexane/EtOAc=1:1); mp 239–241 °C; $[\alpha]_D^{25}$ −0.7 (c 1.1, MeOH); IR (neat, cm^{-1}) 3352, 3094, 2913, 2361, 1507, 1417, 1244, 940, 801; ^{1}H NMR (500 MHz, pyridine-d_5) δ 7.56 (1H, s, H19), 7.46 (1H, s, H18), 7.21–7.10 (4H, m, H4/5/15/16), 5.00 (2H, br s, ArOH), 4.46 (1H, t, J=9.5 Hz, H9), 3.31 (1H, m, H7a), 2.99 (1H, m, H7b), 2.87 (1H, m, H13a), 2.55–2.35 (2H, m, H13b/8a), 2.09–1.92 (3H, m, H8b/10a/12a), 1.90–1.83 (1H, m, H10b), 1.83–1.69 (2H, m, H11a/12b), 1.50–1.36 (1H, m, H11b); ^{13}C NMR (125 MHz, pyridine-d_5) δ 152.7 (C3/17), 135.1 (C18 or C19), 134.7 (C18 or C19), 131.6 (C6 or C14), 131.1 (C6 or C14), 130.0 (C5 or C15), 129.8 (C5 or C15), 127.5 (C1 or C2), 127.4 (C1 or C2), 116.9 (C4/16), 68.0 (C9), 40.7 (C10), 35.8 (C8), 30.3 (C13), 27.6 (C7), 27.1 (C12), 23.5 (C11); EI-HRMS (m/z) calcd for $C_{19}H_{22}O_3$ $[M]^+$ 298.1569, found 298.1562.

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Supplementary data

Full experimental procedures, ^{1}H and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.065.

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