A Unified Strategy toward the Synthesis of Acerogenin-Type Macrocycles: Total Syntheses of Acerogenins A, B, C, and L and Aceroside IV

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A general strategy for the synthesis of acerogenin-type diarylheptanoids containing an endocyclic biaryl ether bond has been developed, and convergent total syntheses of acerogenin A, B, C, and L and aceroside IV have been accomplished. Cycloetherification of the linear diarylheptanoid 1-(4-fluoro-3-nitrophenyl)-7-(3-hydroxy-4-methoxyphenyl)heptan-3-one (**18**) under mild conditions (CsF, DMF, 0.01 M, rt, 5 h) gave the macrocycle 4-methoxy-17-nitro-2-oxatricyclo[13.2.2^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexaen-12-one (**19**) in 95% yield. Removal of the nitro group followed by O-demethylation gave acerogenin C (**2**), whose reduction afforded acerogenin A (**1**). Glucosidation of **2** with 2,3,4,6-α-D-tetrabenzoylglucopyranosyl bromide followed by saponification gave aceroside IV (**3**) in excellent overall yield. Acerogenins B (**4**) and L (**5**) were synthesized in a similar fashion featuring a key intramolecular S_NAr reaction of linear compound **29**. The entropy driving force resulting from the preorganization of cyclization precursors in favor of the bent conformation was proposed to contribute significantly to the efficiency of this cyclization. Both computational studies and spectroscopic data (NOE) supported this hypothesis. Experimentally, it was observed that even at high concentration (1 M of **18** in DMF) the analytically pure macrocycle **19** could still be obtained in 45−50% isolated yield. Furthermore, when the cyclization of **18** was carried out in the presence of an external nucleophile (4-methoxyphenol, **33**) or an electrophile (4-fluoro-3-nitrotoluene, **34**), only the 15-membered cyclophane **19** was isolable. This provides experimental evidence that compound **18** is indeed preorganized in such a way that intramolecular reaction was highly competitive with the alternative intermolecular process.

Introduction

Diarylheptanoids are a family of natural plant metabolites whose characteristic structural feature is the presence of two hydroxylated aromatic rings tethered by a linear seven-carbon chain. They could be further divided into three subgroups, namely, linear (**I**), biaryl macrocycles (**II**), and *m*,*p*-cyclophane (**III**) (Figure 1).[1] Evidence has been accumulated suggesting that the linear diarylheptanoids **I** are the biogenetic precursors of the macrocyclic congeners **II** and **III**.[2] The diarylheptanoids exhibit a broad range of potent biological activities that include antiinflammatory, antihepatoxic, antifungal, antibacterial, and related effects.[1] Very recently, compounds possessing an inhibitory activity against nitric oxide production in activated murine macrophages have been identified from the seeds of *A. blepharocalyx*.[3]

Since the isolation of acerogenin A (**1**) by Nagai et al. in 1976 (Figure 2),[4] several dozen structurally related products with an endocyclic biaryl ether bond have been identified from the stem bark of *Acer nikoense* Maxim (Aceraceae),[5] a tree indigenous to Japan that has been used in folk medicine as a remedy for hepatic disorders and for eyewash. Related natural products such as galeon,[6] garuganin,[7] maximowicziol,[8] etc. have also been identified from other plant sources.

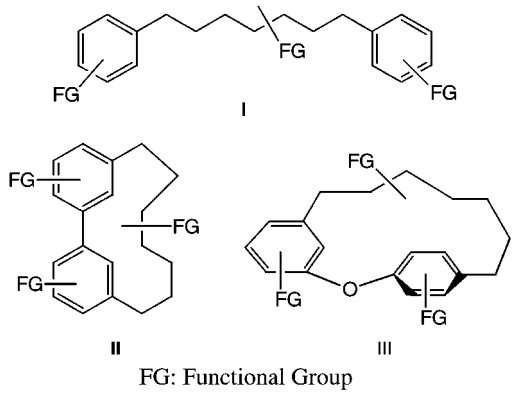

Figure 1.

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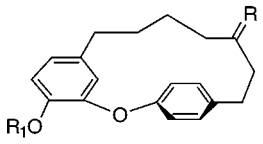
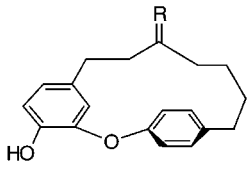


1 R = H, OH, R_1 = H acerogenin A
2 R = O, R_1 = H, acerogenin C
3 R = O, R_1 = β-D-glycopyranosyl, aceroside IV



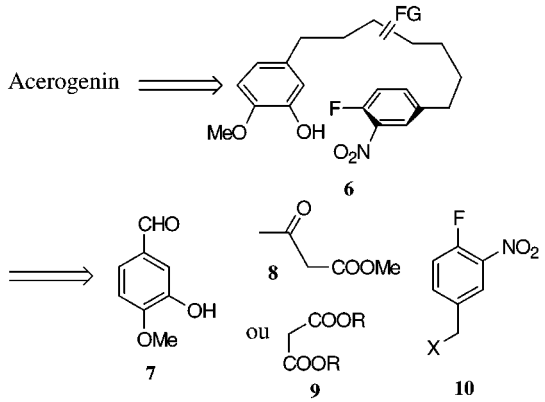
4 R = H, OH acerogenin B
5 R = O, acerogenin L

Figure 2.

Total synthesis of macrocyclic diarylheptanoids has attracted synthetic chemists for decades. Thus, Semmelhack et al.[9] and Whiting et al.[10] have developed an ingenious macrocyclization methodology by way of Ni^0-catalyzed intramolecular biaryl coupling reaction for the synthesis of type II macrocycles such as alnusone[9] and myricanol.[10] On the other hand, intramolecular Wurtz reaction[11] and Wittig reaction[12] have been employed by Nógrádi et al. as the key cyclization step for the total synthesis of *m*,*p*-cyclophane, garugamblin 1, and garuganin III.[13] Although structurally simple, previous synthetic efforts have clearly revealed the difficulties associated with the construction of biaryl ether containing macrocycles (type III)[14] and underscored the requirement of new macrocyclization methodology.

The intramolecular S_NAr reaction developed recently in this laboratory has proved to be an efficient methodology for the construction of *polypeptide macrocycles* with endo *aryl*−*aryl*[15] and *aryl*−*alkyl ether*[16] bond(s). We have attributed the success of this remarkable cycloetherification to an intramolecular recognition phenomenon.[15−18] Several structural elements found in our previously studied substrates could indeed help their preorganization[19] in such a way that a folded conformation was a predominant low energy one, thus favoring the desired cyclization.[20] To evaluate the influence of intramolecular H-bonding[21] on the outcome of cyclization and to further expand the generality of this methodology, we were interested in investigating the cyclization of a linear compound wherein the two reactive sites are linked by *an aliphatic hydrocarbon chain* (e.g., compound **6**). The acerogenin-type natural diarylheptanoids seemed to be appropriate synthetic targets for this purpose. The successful implementation of this strategy as exemplified by the first total synthesis of acerogenin A (**1**), acerogenin C (**2**), aceroside IV (**3**) as well as acerogenin B (**4**) and L (**5**) is the subject of the present paper.[22] A unified synthetic plan for these compounds featuring a key cycloetherification of linear diarylheptanoids **6** is shown in Scheme 1. Parallel to our efforts, Nógrádi et al.[23] have very recently reported a synthesis of acerogenin A via an intramolecular Ullman reaction.

Scheme 1



Results and Discussion

Synthesis of Acerogenins A (1) and C (2) and Aceroside IV (3). The preparation of linear diarylheptanoids **18**, a projected common cyclization precursor for the synthesis of acerogenins A and C and aceroside IV is summarized in Scheme 2. Methyl 3-(3-hydroxy-4-methoxyphenyl)propanoate (**11**) was prepared from isovanillin according to literature procedures.[24] Protection of the phenol function of **11** as an isopropyl ether followed by reduction of the ester afforded alcohol **12**, which was transformed into the corresponding iodide **13** via a tosylate intermediate. Double deprotonation of methyl acetoacetate using LDA[25] (2.1 equiv) as base in THF followed by addition of the iodide **13** gave the β-keto ester **14** in 80% yield with complete regioselectivity. Generation of the monoanion of **14** (1 equiv of NaH in THF) followed by addition of 4-fluoro-3-nitrobenzyl iodide (**15**), in turn prepared from the known 4-fluoro-3-nitrobenzyl

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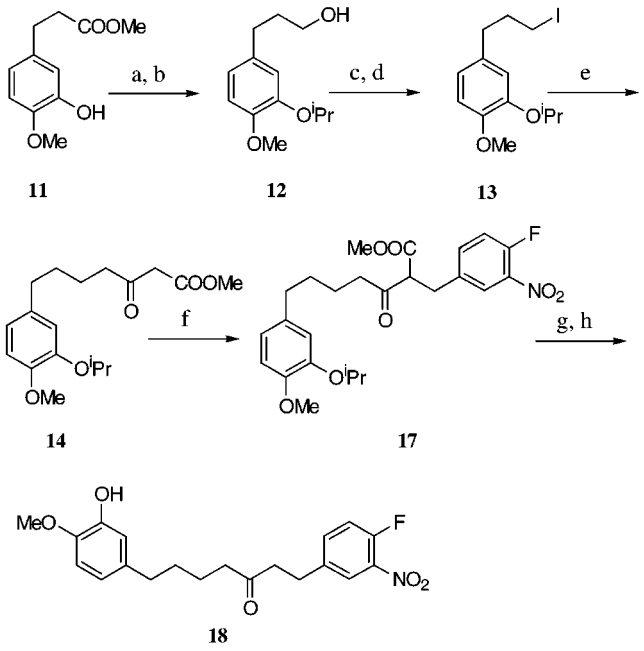
Scheme 2[a]

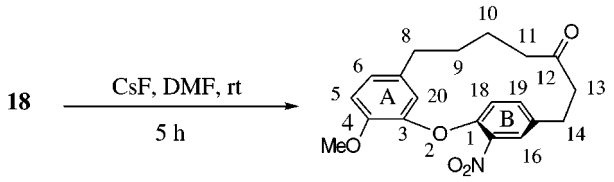


[a] Key: (a) ^{i}PrBr, K_2CO_3, DMF, 96%; (b) LAH−THF, 97%; (c) TsCl, Py; (d) NaI, Me_2CO, 87%; (e) methyl acetoacetate, LDA, then iodide **13**, 80%; (f) NaH, THF, then 4-fluoro-3-nitrobenzyl iodide **15**, 76%; (g) BCl_3, CH_2Cl_2; (h) 6 N HCl, 93%.

bromide (**16**)[26] using a Finkelstein reaction, afforded compound **17** in 75% yield. Other bases such as LDA,[25] Cs_2CO_3,[27] and TBAF[28] gave either lower yields of **17** or substantial amounts of dialkylated compound. Chemoselective removal of the isopropyl protecting group from **17** (BCl_3, CH_2Cl_2, 0 °C)[29] followed by decarboxylation under acidic conditions furnished the cyclization precursor **18** in 93% isolated yield.

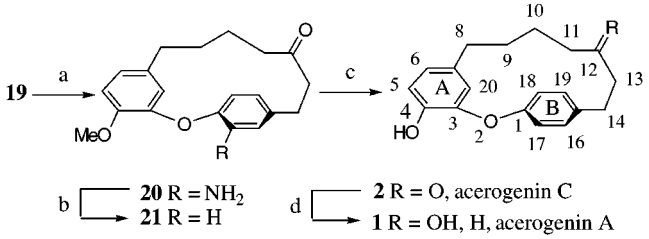
Cyclization of **18** occurred smoothly in DMF (0.01 M, CsF, room temperature, 5 h),[30] providing the desired 15-membered macrocycle **19** in almost quantitative yield (based on the ^{1}H NMR spectrum of the crude product, Scheme 3). The cyclic structure of **19** was easily discernible from the characteristic high-field shift of the H-20 proton in the ^{1}H NMR spectrum, due to the anisotropic effect of the aromatic B ring (δ_{H20} = 5.61 ppm in **19** vs δ_{H20} = 6.71 ppm in **18**). Potassium carbonate[31] was also effective in promoting this cyclization, though a relatively longer time (10 h) was required. The cycloetherification rate could be accelerated by heating the reaction mixture at 60 °C without diminishing the yield of cyclophane **19**. To examine the effect of concentration on the outcome of the cyclization (Scheme 3), compound **18** was treated with CsF in DMF at 0.01, 0.05, 0.1, and 1 M. *It was observed that even at high concentration (1 M of **18** in DMF), the analytically pure macrocycle **19** could still be obtained*

Scheme 3



Concentration	isolated yield (average of two runs)
0.01 M	90-95%
0.05M	90-95%
0.1M	75-80%
1M	45-50%

Scheme 4[a]



[a] Key: (a) H_2, Pd/C, MeOH; (b) ^{t}BuONO, DMF, 90%; (c) $AlCl_3$, CH_2Cl_2, 88%; (d) $NaBH_4$, EtOH, 100%.

in 45−50% isolated yield.[32] This provides experimental evidence that the intramolecular reaction of compound **18** is indeed facile and highly competitive with the alternative intermolecular process (vide infra).

The transformation of 15-membered macrocycle **19** to the natural acerogenin A (**1**) and C (**2**) was accomplished as shown in Scheme 4. Reduction of the nitro group of **19** was carried out by hydrogenolysis under conventional conditions (Pd/C, MeOH, 1 atm) to afford the amino compound **20**, which was converted into compound **21** (90% overall yield) employing Doyle's one-step deamination procedure.[33] The O-demethylation of **21** was realized with $AlCl_3$ in refluxing CH_2Cl_2, without the need of adding soft nucleophiles such as thiol, to afford acerogenin C (**2**). Reduction of the keto function with $NaBH_4$ gave then the racemic acerogenin A (**1**) in excellent yield. The physical data of these two synthetic substances were identical in all respects to those of the natural products.

The synthesis of aceroside IV (**3**) is shown in Scheme 5. Glycosidation of **2** was first attempted with 2,3,4,6-α-D-tetrabenzylglucopyranose under Mitsunobu conditions.[34] While the reaction proceeded cleanly to give the desired aryl glucoside, the conversion was low (<30%) even under forcing conditions (e.g., excess of glycosyl donor, heating at 60 °C in different solvents). The desired transformation was finally realized using a two-phase glycosidation methodology.[35] Thus, 2,3,4,6-α-D-tetrabenzoylglucopyranosyl bromide was allowed to react with acerogenin C (**2**) in the presence of tetrabutylammonium bromide (CH_2Cl_2−aqueous NaOH) to afford stereospecifically the β-aryl glucoside **22** in 93% yield. The anchi-

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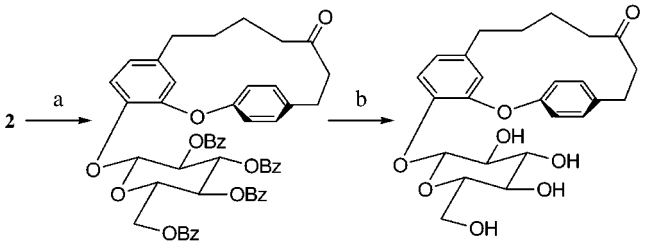
Scheme 5[a]



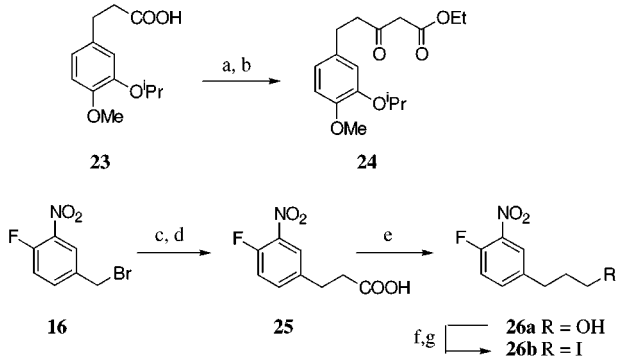
[a] Key: (a) 2,3,4,6-tetrabenzoylglucopyranosyl bromide, CH_2Cl_2–NaOH, Bu_4NBr, 93%; (b) MeOH–H_2O, NaOH, 95%.

meric participation of the neighboring ester function may be responsible for the high stereoselectivity observed during the glucosidation process. Subsequent saponification (MeOH–H_2O, NaOH) of the benzoyl groups gave the aceroside IV (**3**) in 95% isolated yield. The spectral data of our synthetic material were identical with those of the natural product.[36]

The splitting pattern of the para disubstituted aromatic protons (H_{16}, H_{17}, H_{18} and H_{19}) of acerogenin A (**1**) and C (**2**) in ^1H NMR spectra are considerably different. Thus, only two signals were found for these protons, which appeared as an AB quartet (J = 8.3 Hz) in the spectrum of compound **2**, while four signals, each being a doublet of doublet, were observed for these same protons in the spectrum of compound **1**. This observation indicated that the rotational barrier around the biaryl ether bond of **2** is lower than that of **1**. Since the bond angle of an sp^2 carbon is larger than that of an sp^3 carbon, we speculated that the presence of an sp^2 carbon (carbonyl group) in the heptyl chain tether of acerogenin C (**2**) reduced both angle strain and H–H steric interactions inside the ring of compound **2** leading to a ring system more flexible than that of compound **1**. It is interesting to note that once acerogenin C (**2**) was glucosylated to give aceroside IV (**3**), the four protons (H_{16}, H_{17}, H_{18}, and H_{19}) became chemically and magnetically nonequivalent. We thought that the rotation of biaryl ether bond was hindered in the case of aceroside IV (**3**) because of the presence of buttressed ortho function adjacent to the aryl ether linkage.[37]

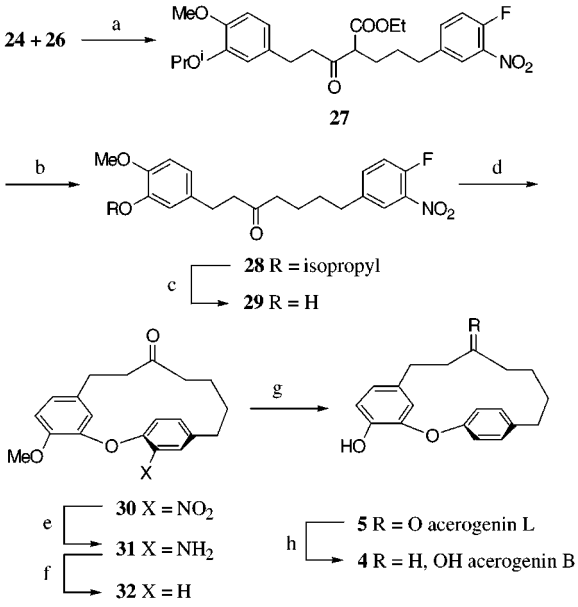
Synthesis of Acerogenins B (4) and L (5). Acerogenins B (**4**) and L (**5**) are structually very similar to acerogenins A and C. They differ from each other only by the position of the carbonyl or hydroxy group in the carbon chain. The two fragments required for the synthesis of the linear precursor are shown in Scheme 6. Reaction of acid **23** with carbonyl diimidazole (CDI) in THF gave the corresponding imidazolide, which was reacted with magnesium ethyl malonate[38] to give keto ester **24** in excellent yield. Other conditions employing

Scheme 6[a]



[a] Reagents and conditions: (a) CDI, THF; (b) $(EtOOCCOO)_2Mg$, 90%; (c) $CH_2(COOEt)_2$, DMF, NaH, 73%; (d) 6 N HCl, 100%; (e) BH_3–THF, 84%; (f) TsCl, Py; (g) NaI, Me_2CO, 91%.

Scheme 7[a]



[a] Reagents and conditions: (a) K_2CO_3–20% Cs_2CO_3, MeCN, 86%; (b) LiCl, DMSO–10% H_2O, 83%; (c) BCl_3, CH_2Cl_2, 81%; (d) CsF, DMF, 0.01 M, 88%; (e) H_2, Pd/C, MeOH, 87%; (f) (1) BF_3·OEt, ^{t}BuONO, (2) DMF, $FeSO_4$, 77%; (g) $AlCl_3$, CH_2Cl_2, reflux, 80%; (h) $NaBH_4$, EtOH, 100%.

the lithium enolate of ethyl acetate, Meldrum's acid, etc. as nucleophiles gave lower chemical yields in this case. On the other hand, alkylation of ethyl malonate with bromide **16** (NaH, DMF) followed by decarboxylation under acidic conditions gave the acid **25**, which was transformed into the other building block 3-(4-fluoro-3-nitro)phenyl propyl iodide (**26b**) in three straightforward steps, namely, chemoselective reduction of acid to alcohol, tosylation, and iodination.

The synthesis of acerogenins B (**4**) and L (**5**) was accomplished as shown in Scheme 7. Alkylation of keto ester **24** with 3-(4′-fluoro-3′-nitrophenyl)propyl iodide **26b** afforded compound **27**. This coupling reaction was found to be very sensitive to the reaction parameters, and the optimal conditions we found were to reflux a MeCN solution of compounds **24** and **26b** in the presence of K_2CO_3 (1 equiv) and Cs_2CO_3 (0.2 equiv). When DMSO was used as cosolvent,[39] a significant amount of dialkylated product was formed, while in CH_2Cl_2 the reaction proceeded too slowly to be synthetically useful. Other

(36) We thank Professor Nagai for kindly sending us the NMR spectra of natural acerogenin C and aceroside IV.

(37) One of the reviewers pointed out that hindered rotation of the para-disubstituted aromatic ring cannot be excluded in acerogenin A. The lack of anisochrony can be attributed to the absence of any of the following three effects: (1) hindered rotation of the aromatic ring; (2) hindered interconversion of planary chiral conformations associated with the flipping of the seven-membered chain; (3) the center of chirality at C-12. Note that the second effect interconverts in the case of acerogenin A enantiomers while it does not in the case of acerogenin C diastereomers.

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alkylation conditions varying the base (NaH, LDA), the solvent (THF, DMF), and the temperature were also examined but all gave a less than satisfactory yield of the desired product. Strikingly, no decarboxylation occurred when keto ester **27** was heated under acidic conditions (6 N, HCl, reflux), despite the structural similarity between **27** and **17** (cf. Scheme 2). Fortunately, Krapcho decarboxylation[40] went smoothly to give ketone **28** without interference of intermolecular S_NAr reaction as possible side reaction. Selective removal of isopropyl ether from **28** furnished the linear diarylheptanoid **29**. Macrocylization via formation of aryl−aryl ether bond was carried out under previously established conditions (CsF, DMF, 0.01M) to give the 15-membered *m*,*p*-cyclophane **30** in 88% yield. TBAF[16] (DMF, 0.01 M) was also effective in promoting this cyclization to afford **30** in excellent yield. No dimer or oligomer can be isolated under these two sets of conditions. Reduction of nitro group to amine followed by hydrodeamination, and cleavage of methyl ether gave then the acerogenin L (**5**) in good overall yield. It is worth noting that the one-pot deamination of compound **31** as prescribed for **20** gave in this case a low yield of the desired product. However, formation of diazonium salt from **31** (BF_3·OEt_2, ^{t}BuONO, CH_2Cl_2)[41] followed by dediazonation ($FeSO_4$, DMF)[42] gave cleanly the reduced product **32**. Acerogenin B (**4**) was readily obtained in quantitative yield by reduction of **5** with $NaBH_4$ under standard conditions. The physical data of synthetic **4** and **5** were in complete agreement with those of the natural products.

As for acerogenin A (**1**) and C (**2**), the same difference in splitting pattern of four protons (H_{16}, H_{17}, H_{18}, and H_{19}) of acerogenin B (**4**) and L (**5**) in the ^{1}H NMR spectra was once again observed (vide supra).

Discussion

Conformational properties of a given bifunctionalized substrate can influence dramatically the reaction outcome of an intramolecular process, especially when one deals with a macrocyclization.[20] Techniques such as template-directed synthesis,[43] protecting group tuning,[44] etc. have been developed and frequently applied in order to favor one particular conformation conducive to cyclization. Unbranched polyhydrocarbon chains have a great number of populated low energy conformers.[45] However, for minimizing unfavorable gauche interaction, the extended conformation (zigzag) was generally the lowest energy one.[46] If such conformational preference persisted in our cyclization substrate, then one would expect that the cyclization will be entropically disfavored and that the alternative intermolecular process will prevail. Conversely, the experimental evidence is strongly against this prediction as cycloetherification dominated even at 1 M concentration (vide supra). We reasoned that the presence of electron-rich and electron-poor aromatic rings at chain terminals alters the conformational properties of **18** and **29** leading to a folded conformer conducive to cyclization. To gain information regarding the solution conformation of the cyclization precursor, a computational study of compound **18** was performed. Five thousand conformations were generated by the random search Monte Carlo method[47] and optimized by molecular mechanics minimization using the Macromodel (version 5.5) program[48] with the MM2* force field[49] (water set). The conformational search was carried out on blocks of 1000 Monte Carlo steps until no additional conformation was found to be of lower energy than the current minimum.[50]

From this search, 20 conformations were found within 3 kcal/mol from the global minimum. Interestingly, all these 20 conformers adopted turn structure, and the distance between hydroxyl oxygen and the carbon bearing the fluoro atom ranged from 3.7 to 5.5 Å. Figure 3 showed the three lowest energy conformers. Assuming Boltzman distribution,[51] the population of these bent conformers should be greater than 99%. Taking into account the proximity theory, this calculation partially explains the observed facile cyclization encountered.

To obtain some spectroscopic evidence of such conformational property, a UV−vis spectrum of compound **18** was recorded in acetonitrile (1×10^{-4} M). However, we were unable to detect any absorption resulting from the charge-transfer (CT) complex.[52] From the molecular modeling studies, the relative orientation of two aromatic rings (edge to face vs face to face) and the relative long distance between them (greater than 3 Å) were indeed against formation of a through-space charge complex. That the turn structure was the preferred solution conformation of **18** was nevertheless evidenced by examination of 2D NOESY spectrum ($CDCl_3$, 400 MHz). Thus, among the numerous cross-peaks observed (H_{16}−H_{14}, H_{16}−H_{13}, H_{19}−H_{14}, H_{19}−H_{13}, H_5−H_{OMe}, H_{20}−H_{11}, H_{20}−H_9 (H_{10}), H_6−H_{11}, H_6−H_9 (H_{10}), H_{14}−H_{11}, H_{14}−H_8, H_{13}−H_8), that of H_{20}−H_{11}, H_{20}−H_9 (H_{10}), H_6−H_{11}, H_6−H_9 (H_{10}), H_{14}−H_8, H_{13}−H_8 can be explained only if compound **18** adopted a bent conformation.

Two additional control experiments wherein the intermolecular process was statistically favored by addition

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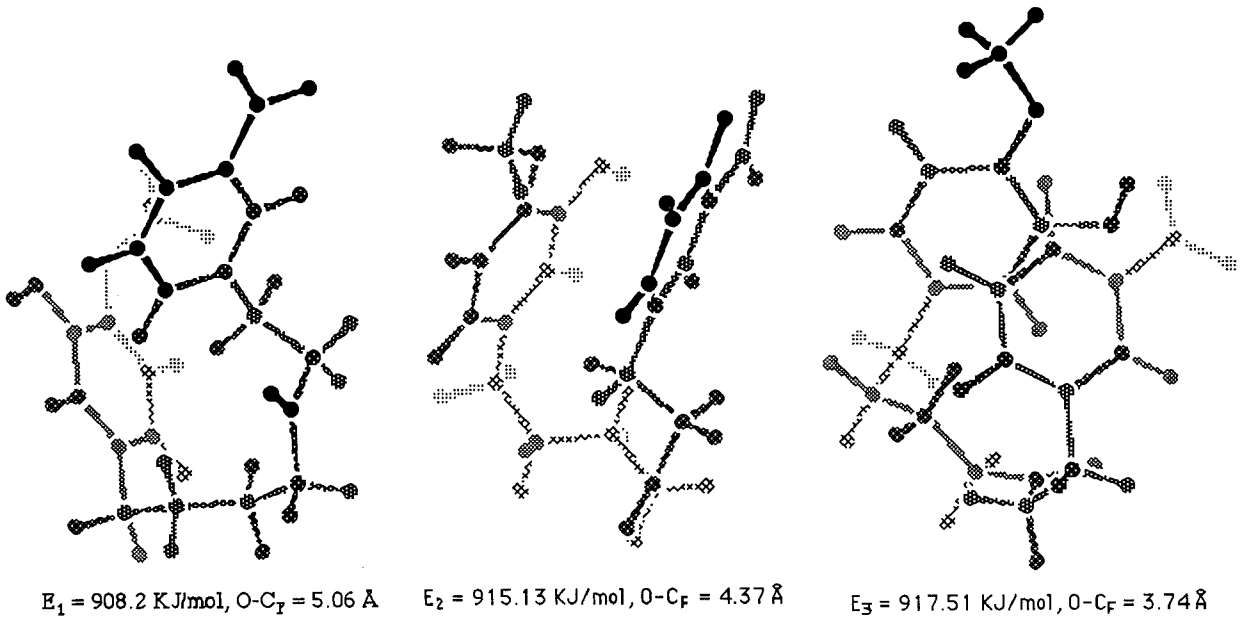


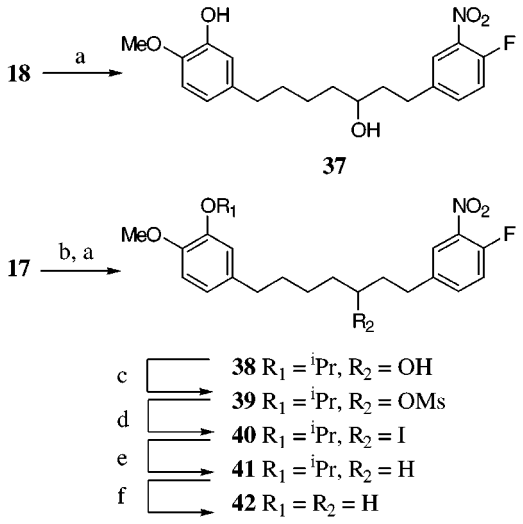
Figure 3. Three lowest energy conformations of compound **18**.

of an external nucleophile or an electrophile were performed. When equimolar amounts of compounds **18** and 4-methoxyphenol (**33**) (DMF, 0.01 M) were treated with CsF at room temperature, a clean spot to spot transformation was observed and the cyclophane **19** was the only new product formed. Neither dimerization (oligomerization) nor intermolecular reaction between **18** and **33** was observed in the crude ^{1}H NMR spectrum. Similarly, the presence of an external electrophilic partner such as 4-fluoro-3-nitrotoluene (**34**) did not interfere with the reaction pathway of **18**, and no trace of cross-coupled product was detected when a mixture of **18** and **34** was treated with CsF in DMF (0.01 M). These experimental results are in accord with the hypothesis that the molecules of type **18** and **29** were preorganized in such a way that the intramolecular reaction was highly favored compared to the intermolecular process.

To eliminate the possible contribution of carbonyl function in the preorganization of cyclization precursor, compounds **37** and **42** were prepared as shown in Scheme 8. Reduction of ketone **18** with $NaBH_4$ gave the secondary alcohol **37** in 93% yield. Alternatively, decarboxylation of **17** (LiCl, DMSO) followed by reduction afforded **38**, which was then transformed into iodide **40** via mesylate intermediate **39**. Attempted Bu_3SnH mediated radical dehalogenation of **40** failed to give the desired compound, and instead, extensive degradation was observed. However, treatment of iodide **40** with $NaBH_4$ in DMSO,[53] seldom employed reductive dehalogenation conditions, furnished compound **41** in reproducible high yields. Deprotection of isopropyl ether was carried out under standard conditions to provide **42** in excellent yield.

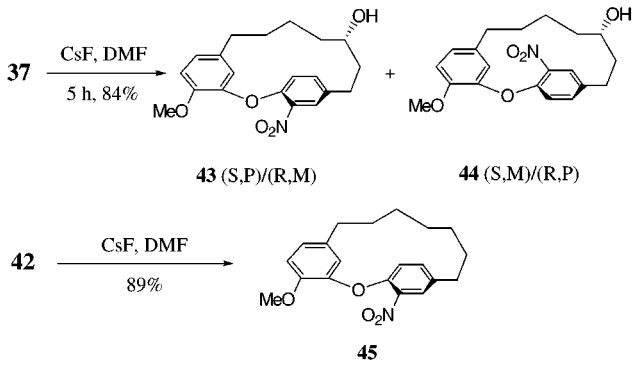
As shown in Scheme 9, cycloetherification of **37** and **42** under standard conditions (CsF, DMF, 0.01 M, 5 h) was once again very efficient to give the corresponding cyclophane in excellent yields. Due to the presence of a stereogenic center in compound **37**, and the creation of a planar chirality upon cyclization, two pairs of atropisomers **43** and **44** were isolated in equal amounts.[54] These

Scheme 8[a]



[a] Key: (a) $NaBH_4$, EtOH, 93%; (b) LiCl, DMSO; (c) MsCl, Et_3N; (d) NaI, Me_2CO, 85%; (e) $NaBH_4$, DMSO, 88%; (f) BCl_3, 92%.

Scheme 9



results indicated that the cyclization outcome was insensitive to the functionality present in the tethered chain and should thus find wide applications in the synthesis of related natural or nonnatural cyclophanes.

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Conclusion

We describe herein a unified synthetic strategy for the synthesis of acerogenins A, B, C, and L and aceroside IV featuring a high-yielding cycloetherification reaction as the key ring-closure step. The synthesis is convergent and flexible and should be easily amenable to other members of this family. Experimental evidence has been provided, indicating that the intramolecular reaction of substrates **18** and **29** was a highly favorable process. The entropy driving force resulting from the preorgnization of these cyclization precursors in favor of the bent conformation was thought to contribute significantly the efficiency of this cyclization. Both computational studies and spectroscopic data supported this hypothesis. We anticipate that the proper use of the principle of intramolecular recognition phenomena will help to design new macrocyclization techniques.

Experimental Section

3-(3-Isopropyloxy-4-methoxyphenyl)propanol-1 (12). To a solution of methyl ester **11** (2.44 g, 11.6 mmol) in DMF (40 mL) were added K_2CO_3 (4.80 g, 34.8 mmol) and isopropyl bromide (2.77 mL, 30.11 mmol). After being stirred at 60 °C for 24 h, the reaction mixture was cooled to room temperature, diluted with 1 N HCl solution, and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 5/1) afforded methyl 3-(3′isopropyloxy-4′-methoxyphenyl)propanoate (2.81 g, 96%): IR ($CHCl_3$) 3012, 2982, 2956, 1732, 1513, 1442, 1259, 1137, 1031, 985 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (d, J = 6.0 Hz, 6H), 2.60 (t, J = 7.6 Hz, 2H), 2.90 (t, J = 7.6 Hz, 2H), 3.60 (s, 3H), 3.80 (s, 3H), 4.50 (heptet, J = 6.0 Hz, 1H), 6.72 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 22.0, 30.4, 35.9, 51.5, 55.9, 71.3, 112.1, 116.3, 120.6; 132.9, 147.1, 148.9, 173.3; MS (EI) m/z 252, 210. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.91; H, 8.12. To a solution of LAH (0.84 g, 22.2 mmol) in THF (30 mL) was added, at 0 °C, a solution of methyl 3-(3′isopropyloxy-4′-methoxyphenyl)propanoate (2.8 g, 11.1 mmol) in THF (5 mL). After being stirred at 0 °C for 45 min, the reaction mixture was diluted with 1 N HCl solution. The precipitate was filtered off, and the filtrate was extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 3/1) afforded methyl 3-(3′isopropyloxy-4′-methoxyphenyl)propanol-1 **12** as an oil (2.40 g, 97%): IR ($CHCl_3$) 3020, 2401, 1505, 1215, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (d, J = 6.0 Hz, 6H), 1.90 (quintet, J = 6.4 Hz, 2H), 2.63 (t, J = 6.4 Hz, 2H), 3.68 (t, J = 6.4 Hz), 3.80 (s, 3H), 4.50 (heptet, J = 6.0 Hz, 1H), 6.75 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.8, 31.2, 34.0, 55.7, 61.8, 71.1, 111.8, 116.2, 120.5, 134.0, 146.7, 148.3; MS (EI) m/z 224, 181, 136. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.33; H, 9.01.

3-(3-Isopropyloxy-4-methoxyphenyl)propyl Iodide (13). A solution of alcohol (**12**) (1.01 g, 4.50 mmol) and *p*-toluenesulfonyl chloride monohydrate (1.02 g, 5.40 mmol) in pyridine (45 mL) was stirred at room-temperature overnight. The reaction mixture was diluted with 1 N HCl solution, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. To the solution of so obtained tosylate in acetone (45 mL) was added NaI (0.80 g, 5.40 mmol), and the resulting reaction mixture was refluxed overnight. After being cooled to room temperature, the mixture was filtered, and volatile of the filtrate was evaporated. The residue was dissolved in water and extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 3/1) afforded product **13** as an oil (1.31 g, 87%): IR ($CHCl_3$) 3020, 2978, 2937, 1511, 1258, 1135 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38 (d, J = 6.2 Hz, 6H), 2.10 (quintet, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 3.14 (t, J = 7.2 Hz, 2H), 3.80 (s, 3H), 4.25 (septet, J = 6.2 Hz, 1H), 6.77 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 6.9, 22.6, 35.4, 35.9, 56.5, 71.9, 112.6, 117.1, 121,4; 133.3, 147.6, 149.3; MS (EI) m/z 334, 292. Anal. Calcd for $C_{13}H_{19}IO_2$: C, 46.72; H, 5.73. Found: C, 46.86; H, 5.71.

7-(3-Isopropoxy-4-methoxyphenyl)-3-oxoheptanoic Acid Methyl Ester 14. To a solution of LDA (54.3 mmol) in THF, cooled at 0 °C, was added methyl acetoacetate (1.9 mL, 18.0 mmol) dropwise. Stirring was continued at 0 °C for 20 min and the iodide **13** (3.0 g, 9.0 mmol) was then added. After being stirred at 0 °C for another 20 min, the reaction mixture was diluted by addition of 1 N HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 3/1) afforded product **14** as an oil (2.3 g, 80%): IR ($CHCl_3$) 3015, 2982, 2934, 1748, 1710, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.35 (d, J = 6.0 Hz, 6H), 1.62 (m, 4H), 2.56 (m, 4H), 3.42 (s, 2H), 3.72 (s, 3H), 3.81 (s, 3H), 4.51 (septet, 1H, J = 6.0 Hz), 6.7 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 22.2, 23.1, 30.9, 35.2, 42.9, 49.0, 52.4, 56.1, 71.4, 112.1, 116.5, 120.8, 134.7, 147.1, 148.6, 167.0, 204.1; MS (EI) m/z 322, 290, 280. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.58; H, 8.27.

2-(4-Fluoro-3-nitrobenzyl)-7-(3-isopropoxy-4-methoxyphenyl)-3-oxoheptanoic Acid Methyl Ester 17. To a suspension of NaH (0.16 g, 80% in paraffin, 5.33 mmol) in THF (30 mL) was added, at 0 °C, a solution of compound **14** (1.78 g, 5.52 mmol) in THF (20 mL). Stirring was continued at 0 °C for 20 min, and 4-fluoro-3-nitrobenzyl iodide **15** (1.56 g, 5.55 mmol) was then added. After being stirred at 0 °C for another 1 h, the reaction mixture was diluted with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 1/4) afforded product **17** as an oil (1.99 g, 76%): IR ($CHCl_3$) 3024, 2936, 2848, 1743, 1714, 1538 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.36 (d, J = 6.1 Hz, 6H), 1.55 (m, 4H), 2.5 (m, 4H), 3.19 (m, 2H), 3.7 (s, 3H), 3.78 (t, J = 7.4 Hz, 1H), 3.82 (s, 3H), 4.51 (septet, J = 6.1 Hz, 1H), 6.68 (dd, J = 2.1, 7.9 Hz, 1H), 6.7 (d, J = 2.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 7.19 (dd, J = 8.5 Hz, 10.5 Hz, 1H), 7.47 (ddd, J = 2.3, 4.2, 8.5 Hz, 1H), 7.88 (dd, J = 2.3, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.9, 23.7, 31.6, 33.3, 35.8, 43.3, 53.5, 56.8, 60.6, 72.3, 112.9, 117.4, 119.2 (d, J = 20.1 Hz), 121.6, 126.9, 135.2, 136.2 (d, J = 4.5 Hz), 137.0 (d, J = 8.3 Hz), 147.8, 149.5, 154.8 (d, J = 262.8 Hz), 169.6, 204.0; MS (IE) m/z 475**.** Anal. Calcd for $C_{25}H_{30}NFO_7$: C, 63.15; H, 6.36. Found: C, 63.19, H 6.54.

1-(4-Fluoro-3-nitrophenyl)-7-(3-hydroxy-4-methoxyphenyl)heptan-3-one 18. To a solution of compound **17** (1.70 g, 3.57 mmol) in CH_2Cl_2 (50 mL) was added, at 0 °C, BCl_3 (1 M in CH_2Cl_2, 18.4 mL, 18.4 mmol) dropwise. After being stirred at 0 °C for another 1 h, the reaction was quenched by addition of MeOH, and the volatile was removed under reduced pressure. The residue was redissolved in EtOAc, and the organic extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crude product was dissolved in 6 N HCl and heated to reflux for 24 h. After being cooled to room temperature, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 1/4) afforded product **18** (1.25 g, 93%): mp 60−61 °C; IR ($CHCl_3$) 3027, 2939, 2865, 1741, 1711, 1618, 1594, 1535 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, TMS) δ 1.58 (m, 4H, H8, H9), 2.42 (t, J = 6.7 Hz, 2H, H7), 2.5 (t, J = 6.7 Hz, 2H, H10), 2.75 (t, J = 7.0 Hz, 2H, H12), 2.94 (t, J = 7.0 Hz, 2H, H13), 3.84 (s, 3H, OMe), 5.6 (s, 1H, OH), 6.6 (dd, J =1.8, 8.5 Hz, 1H, H4), 6.71 (m, 2H, H3, H6),

(54) Although the physical data (^1H NMR, ^{13}C NMR, elemental analysis and HRMS) are in accord with the structural assignment of **43** and **44**, the planar chiralities of these two compounds were not thoroughly determined. The physical data described in the Experimental Section were arbitrary assigned for **43** and **44**.

7.16 (dd, J = 10.8, 8.4 Hz, 1H, H18), 7.45 (ddd, J = 2.2, 4.0, 8.4 Hz, H19), 7.86 (dd, J = 2.2, 6.9 Hz, 1H, H15); ^{13}C NMR ($CDCl_3$) δ 22.9, 27.9, 30.5, 34.4, 42.4, 42.9, 55.6, 110.2, 114.1, 117.8 (d, J = 20.1 Hz), 119.2, 125.1, 125.7, 135.1 (d, J = 11.3 Hz), 135.7 (d, J = 8.9 Hz), 137.9, 144.3, 145.0, 153.5 (d, J = 260.6 Hz), 208.5; MS (EI) m/z 376.

4-Methoxy-17-nitro-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexaen-12-one 19. To a solution of compound **18** (0.80 g, 2.13 mmol) in DMF (213 mL) was added CsF (1.62 g, 10. 66 mmol). After being stirred at room temperature for 5 h, the reaction mixture was diluted with EtOAc. The organic phase was washed with H_2O and brine, dried, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 1/3) afforded product **19** (0.68 g, 90%): mp 75−77 °C IR ($CHCl_3$) 2941, 2839, 1711, 1539, 1511, 1353, 1270, 1121 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz, TMS) δ 0.95 (m, 1H, H10), 1.20 (m, 1H, H10), 1.40 (m, 2H, H9), 1.9−2.1 (m, 2H, H11), 2.45 (t, J = 6.0 Hz, 2H, H8), 2.5−2.7 (m, 2H, H13), 3.05 (m, 2H, H14), 3.95 (s, 3H, OMe), 5.61 (d, J = 1.9 Hz, 1H, H20), 6.72 (dd, J = 1.9, 8.3 Hz, 1H, H6), 6.86 (d, J = 8.3 Hz, 1H, H5), 7.08 (d, J = 8.4 Hz, 1H, H18), 7.35 (dd, J = 2.1, 8.4 Hz, 1H, H19), 7.85 (d, J = 2.1 Hz, 1H, H16); ^{13}C NMR ($CDCl_3$) δ 21.2, 28.1, 32.1, 32.2, 44.8, 46.6, 57.2, 113.8, 118.0, 124.2, 125.9, 127.5, 134.3, 136.4, 139.3, 144.7, 148.0, 150.3, 151.2, 211.5; MS (EI) m/z 355, 325.

17-Amine-4-methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexaen-12-one 20. A solution of compound **19** (270 mg, 0.76 mmol) in MeOH was hydrogenated in the presence of Pd/C (10%) for 1 h. The reaction mixture was filtered through a short pad of Celite. Evaporation of the filtrate gave the analytically pure product **20** (quantitative): mp 129−131 °C; IR ($CHCl_3$) 3300, 3028, 2943, 1705, 1620, 1507, 1261, 1229, 1121 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (m, 2H, H10), 1.40 (m, 2H, H9), 1.97 (t, J = 8.2 Hz, 2H, H11), 2.46 (m, 2H, H8), 2.61 (m, 2H, H13), 2.88 (m, 2H, H14), 3.73 (brs, 2H, NH_2), 3.94 (s, 3H, OMe), 5.91 (d, J = 1.9 Hz, 1H, H20), 6.55 (m, 2H, H16, H19), 6.67 (dd, J = 1.9, 8.2 Hz, 1H, H6), 6.82 (d, J = 8.2 Hz, 1H, H5), 6.91 (d, J = 8.6 Hz, 1H, H18); ^{13}C NMR ($CDCl_3$) δ 20.2, 28.2, 31.7, 32.5, 44.4, 46.0, 56.2, 112.2, 116.7, 117.3, 119.3, 122.2, 124.1, 133.9, 138.3, 139.9, 143.1, 146.9, 148.6, 212.0; MS (EI) m/z 325.

4-Methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7-(20),15(19),16-hexaen-12-one 21. To a solution of *tert*-butylnitrite (0.6 mmol, 79 μL) in dry DMF (2 mL), heated at 50 °C, was added a solution of amine **20** (130 mg, 0.4 mmol) in DMF (1 mL) dropwise. After being stirred for 1 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL), and washed with H_2O and aqueous NH_4Cl successively. The organic phase was dried and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 1/6) gave the product **21** (112 mg, 90%): mp 124−126 °C; IR ($CHCl_3$) 3012, 2934, 2833, 1703, 1519, 1261, 1117 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (m, 2H, H10), 1.37 (m, 2H, H9), 1.90 (m, 2H, H11), 2.45 (brt, J = 6.0 Hz, 2H, H8), 2.61 (brt, J = 7.0 Hz, 2H, H13), 2.99 (brt, J = 7.0 Hz, 2H, H14), 3.95 (s, 3H, OMe), 5.64 (d, J = 2.0 Hz, 1H, H20), 6.64 (dd, J = 2.0, 8.2 Hz, 1H, H6), 6.82 (d, J = 8.2 Hz, 1H, H5), 7.02, 7.20 (AB q, J = 8.4 Hz, 4H, H16, H17, H18, H19); ^{13}C NMR ($CDCl_3$) δ 21.1, 28.2, 32.0, 32.9, 45.2, 46.8, 57.0, 113.1, 118.1, 122.6, 124.3, 131.2, 134.3, 137.8, 147.5, 151.6, 157.6, 212.6; MS (EI) m/z 310 (M^+). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.59; H, 7.17.

Acerogenin C (2). To a solution of compound **21** (120 mg, 0.38 mmol) in freshly redistilled CH_2Cl_2 (20 mL) was added $AlCl_3$ (257 mg, 1.93 mmol). The reaction mixture was heated to reflux for 18 h. After being cooled to room tempearature, the reaction was quenched by careful addition of water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 1/4) afforded acerogenin (**2**) (100 mg, 88%) as a white solid: mp 114−115 °C [lit.,[5c] mp 116 °C]; IR ($CHCl_3$) 3556, 3024, 2936, 1703, 1516, 1504, 1434, 1352, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.00 (m, 2H, H10), 1.48 (m, 2H, H9), 1.95 (m, 2H, H11), 2.48 (t, J = 5.8 Hz, 2H, H8), 2.62 (t, J = 6.5 Hz, 2H, H13), 2.98 (t, J = 6.5 Hz, 2H, H14), 5.60 (d, J = 1.8 Hz, 1H, H20), 5.80 (s, 1H, OH), 6.58 (dd, J = 1.8, 8.1 Hz, 1H, H6), 6.85 (d, J = 8.1 Hz, 1H, H5), 6.95 (d, J = 8.4 Hz, 2H, H17, H18), 7.15 (d J = 8.4 Hz, 2H, H16, H19); ^{13}C NMR ($CDCl_3$) δ 20.2, 27.2, 31.3, 32.0, 44.3, 46.1, 115.4, 116.9, 122.6, 123.3, 130.5, 132.7, 137.4, 143.1, 148.5, 156.7, 212.0; MS (EI) m/z 296. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.69; H, 6.91.

Acerogenin A (1). Sodium borohydride (75.0 mg, 2.0 mmol) was added to a solution of acerogenin C (**2**) (60.0 mg, 0.2 mmol) in MeOH (2.5 mL) cooled at 0 °C. After being stirred at room temperature for 20 min, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification of the crude product by preparative TLC (SiO_2, eluent: heptane/EtOAc = 3/1) afforded acerogenin A (**1**) (60 mg, quantitative): mp 147−149 °C [lit,[4] mp 151−152 °C]; IR ($CHCl_3$) 4215, 3618, 3558, 3027, 2938, 2400, 1511, 1504, 1242, 1048, 929, 802, 735 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 0.90−1.25 (m, 4H), 1.27−1.48 (m, 1H), 1.50−1.52 (m, 1H) 1.53−1.59 (m, 1H), 1.58−2.10 (m, 1H), 2.4−2.55 (m, 2H), 2.76 (td, J = 4.0, 12.8 Hz, 1H), 3.0 (dt, J = 3.8, 13 Hz, 1H), 3.19 (q, J = 4.8 Hz, 1H), 5.74 (d, J = 1.8 Hz, 1H), 6.51 (dd, J = 1.8, 8.1 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 7.01 (dd, J = 2.5, 8.2 Hz, 1H), 7.23 (dd, J = 2.5, 8.2 Hz, 1H), 7.34 (dd, J = 2.0, 8.2 Hz, 1H), 7.40 (dd, J = 2.0, 8.2 Hz, 1H); ^{13}C NMR (CD_3OD) δ 26.0, 29.4, 32.7, 33.4, 40.0, 41.4, 71.3, 117.0, 117.4, 123.1, 124.0, 125.2, 131.2, 132.8, 134.5, 140.6, 144.8, 151.2, 157.8; MS (EI) m/z 298.

Perbenzoate of Aceroside IV 22. To a solution of acerogenin C (**2**) (11 mg, 0.037 mmol), α-D-glucopyranosyl bromide (48 mg, 0.07 mmol) in CH_2Cl_2 (1 mL), and NaOH (1 N, 1 mL) was added catalytic amount of tetrabutylammonium bromide. After being stirred at room temperature for 5 h, the reaction mixture was diluted by addition of aqueous HCl (2 N) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification of crude product by preparative TLC (SiO_2, eluent: toluene/heptane/EtOAc = 1/3/1) afforded product **22** (30.0 mg, 93%) as a white solid: mp 170−172 °C; $[\alpha]_D$ = +19.5 (c 0.5, $CHCl_3$); IR ($CHCl_3$) 3027, 2932, 1734, 1693, 1456, 1195, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (m, 2H, H10), 1.32 (m, 2H, H9), 1.82 (m, 2H, H11), 2.40 (m, 2H, H8), 2.55 (brt, J = 6.5 Hz, 2H, H13), 2.92 (brt, J = 6.5 Hz, 2H, H14), 4.28 (m, 1H, H5′), 4.55 (dd, J = 5.8, 12.1 Hz, 1H, H6′), 4.65 (dd, J = 3.3, 12.1 Hz, 1H, H6′), 5.41 (d, J = 7.7 Hz, 1H, H1′), 5.56 (d, J = 1.9 Hz, 1H, H20), 5.75 (t, J = 9.4 Hz, 1H, H4′), 5.86 (dd, J = 7.7, 9.4 Hz, 1H, H2′), 6.02 (t, J = 9.4 Hz, 1H, H3′), 6.48 (dd, J = 1.9, 8.3 Hz, 1H, H6), 6.60 (dd, J = 2.5, 8.5 Hz, 1H, H18), 6.72 (dd, J = 2.5, 8.5 Hz, 1H, H17), 7.0−8.0 (m, 23H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.4, 27.2, 31.6, 32.4, 44.6, 46.3, 63.3, 69.9, 76.5, 77.3, 77.8, 102.2, 118.0, 121.3, 122.2, 123.2, 123.6, 128.2, 128.5, 128.9, 129.3, 129.5, 129.7, 129.9, 130.4, 133.0, 133.2, 133.3, 133.6, 137.0, 137.7, 143.8, 152.4, 156.7, 165.4, 166.4, 166.2, 188.7, 212.1; FABMS (LiCl) m/z 881 (M + Li)$^+$.

Aceroside IV (3). To a suspension of compound **22** (14 mg, 0.016 mmol) in MeOH (4 mL) and water (1 mL) was added an excess of NaOH. The reaction mixture was heated to 80 °C, and the solution gradually became clear. After 12 h, the reaction was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification by preparative TLC (SiO_2, eluent: CH_2Cl_2/MeOH = 1/6) afforded aceroside IV (**3**) (7.0 mg, 95%) as a white solid: $[\alpha]_D$ = −34 (c 0.5, MeOH) (lit.[5c] $[\alpha]_D$ −39.5, EtOH); mp 148−150 °C (lit.,[5c] mp 153 °C); ^{1}H NMR (CD_3OD, 300 MHz, TMS) δ 0.8−1.0 (m, 2H, H10), 1.2−1.4 (m, 2H, H9), 1.9−2.0 (m, 2H, H11), 2.42 (br$t$, J = 5.8 Hz, 2H, H8), 2.62 (m, 2H, H13), 2.95 (br$t$, J = 6.5 Hz, 2H, H14), 3.4−3.6 (m, 4H, H2′,H3′, H4′, H5′), 3.71 (ddd, J = 1.3, 3.7, 12.0 Hz, 1H, H6′), 3.88 (dd, J = 1.3, 12.0 Hz, 1H, H6′), 5.00 (d, J = 7.3 Hz, 1H, H1′), 5.73 (d, J = 2.1 Hz, 1H, H20), 6.65 (dd, J = 2.1, 8.3 Hz, 1H, H6), 6.98 (dd, J = 2.1, 8.1 Hz, 1H, H17),7.03 (dd, J = 2.1, 8.1 Hz, 1H, H18), 7.08 (d, J = 8.3 Hz, 1H, H5), 7.15 (dd, J = 1.6, 8.1 Hz, 1H, H16), 7.22 (dd, J = 1.6, 8.1 Hz, 1H,

H19); ^{13}C NMR (CD_3OD) δ 21.3, 28.5, 32.4, 33.1, 45.3, 46.9, 62.5, 71.3, 75.0, 77.9, 78.2, 103.3, 119.0, 119.5, 123.6, 124.6, 131.7, 131.9, 137.0, 138.8, 145.7, 152.7, 158.5, 214.9; MS (FAB) *m/z* 481 ($M + Na^+$).

5-(3-Isopropoxy-4-methoxyphenyl)-3-oxopentanoic Acid Ethyl Ester 24. A solution of acid **23** (3.0 g, 12.6 mmol) and carbonyl diimidazole (CDI, 4.0 g, 25.2 mmol) in THF (30 mL) was stirred at room temperature for 2 h. To an another flask containing a solution of monoethyl malonate (3.3 g, 25.0 mmol) in THF (30 mL) was added, at −10 °C, a solution of isopropylmagnesium (2 M, 25.2 mL, 50.4 mmol) dropwise. The reaction mixture was stirred at −10 °C for 30 min and at room temperature for 1.5 h before being recooled at 0 °C. The imidazolide of acid **23**, precooled at 0 °C, was then introduced. After being stirred at 0 °C for 1 h and room temperature for 24 h, the reaction mixture was diluted with aqueous HCl solution, and the volatile was removed under reduced pressure. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 4/1) provided product **24** as an oil (3.5 g, 90%): IR ($CHCl_3$) 3016, 2981, 1741, 1706, 1538, 1510, 1258, 1139, 1034, 768 cm^{-1};^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26 (t, *J* = 7.5 Hz, 3H), 1.29 (d, *J* = 6.1 Hz, 6H), 2.8 (s, 4H), 3.41 (s, 2H), 3.82 (s, 3H), 4.16 (q, *J* = 7.5 Hz, 2H), 4.5 (septet, *J* = 6.1 Hz, 1H), 6.7 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.1, 29.0, 44.7, 49.5, 56.0, 61.3, 71.4, 112.2, 116.5, 120.7, 133.1, 147.2, 149.0, 167.1, 202.0; MS (EI) *m/z* 308. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.79; H, 7.74.

3-(4-Fluoro-3-nitrophenyl)propionic Acid 25. To a solution of NaH (0.69 g, 75% in paraffin, 21.45 mmol) in DMF (100 mL) was added at 0 °C a solution of diethyl malonate (6.5 mL, 43 mmol) in DMF (50 mL), and stirring was continued for 40 min. A solution of 4-fluoro-3-nitrobenzyl bromide (5.0 g, 21.45 mmol) in DMF (120 mL) was introduced. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with aqueous HCl solution and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 10/1) provided diethyl 2-(4′-fluoro-3′-nitrophenyl)ethyl malonate as an oil (3.7 g, 73%): IR ($CHCl_3$) 3023, 2987, 2943, 2904, 1736, 1538, 1283, 1187, 1033, 823, 772, 503 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz, TMS) δ 1.28 (t, *J* = 7.0 Hz, 6H), 3.26 (d, *J* = 7.6 Hz, 2H), 3.60 (t, *J* = 7.6 Hz, 1H), 4.2 (q, *J* = 7.0 Hz, 4H), 7.16 (dd, *J* = 8.6, 10.5 Hz, 1H), 7.4 (ddd, *J* = 2.4, 4.2, 9.2 Hz, 1H), 7.8 (dd, *J* = 2.4, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 33.5, 53.3, 61.9, 118.5 (d, *J* = 20.7 Hz), 126.3, 135.0, 136.3 (d, *J* = 8.6 Hz), 137.4, 154.5 (d, *J* = 261.6 Hz), 168.2; MS (EI) *m/z* 313. Anal. Calcd for $C_{14}H_{16}NFO_5$: C, 53.68; H, 5.15. Found: C, 53.43; H, 5.46. A solution of alkylated malonate (3.5 g, 11.2 mmol) in 6 N HCl (100 mL) was refluxed overnight. After being cooled to room temperature, the solution was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated to give pure acid **25** in quantitative yield: mp 97−99 °C; IR ($CHCl_3$) 3515, 3106, 2938, 1718, 1538, 1350, 1253, 831, 449 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (t, *J* = 9.0 Hz, 2H), 3.00 (*t*, *J* = 9.0 Hz, 2H), 7.20 (dd, *J* = 8.0, 10.0 Hz, 1H), 7.48 (ddd, *J* = 2.2, 4.3, 8.0 Hz, 1H), 7.91 (dd, *J* = 2.2, 6.9 Hz, 1H); ^{13}C NMR (CD_3OD, 200 MHz) δ 30.7, 35.9, 119.2 (d, *J* = 20.9 Hz), 126.7, 136.9 (d, *J* = 8.9 Hz), 137.5, 139.8, 152.2 (d, *J* = 258.8 Hz), 175.9; MS (EI) *m/z* 213, 196, 168, 154. Anal. Calcd for $C_9H_8NFO_4$: C, 50.71; H, 3.78. Found: C, 51.01; H, 4.23.

3-(4-Fluoro-3-nitrophenyl)propanol 26a. To a solution of acid **25** (1.0 g, 4.7 mmol) in THF (25 mL) was added BH_3·THF (1 M solution in THF, 14.0 mL, 14.0 mmol). After being refluxed for 2 h, the reaction mixture was cooled to room temperature, diluted with aqueous HCl solution, and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 2/3) provided product **26a** as an oil (0.78 g, 84%): IR ($CHCl_3$) 3620, 3464, 3022, 2947, 2879, 1629, 1541, 1357, 1242, 1052, 909 cm^{-1};^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.91 (quintet, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 7.20 (dd, *J* = 8.0, 10.5 Hz, 1H), 7.48 (ddd, *J* = 2.2, 4.4, 8.0 Hz, 1H), 7.88 (dd, *J* = 2.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.0, 33.7, 61.5, 118.3 (d, *J* = 20.9 Hz), 125.5, 135.6 (d, *J* = 8.2 Hz), 137.2, 139.0, 153.9 (d, *J* = 260.7 Hz); MS (EI) *m/z* 199, 154. Anal. Calcd for $C_9H_{10}NFO_3$: C, 54.27; H, 5.06. Found: C, 54.21; H, 54.21.

3-(4-Fluoro-3-nitrophenyl)propyl Iodide 26b. To a solution of alcohol **26a** (0.78 g, 3.92 mmol) in pyridine (40 mL) was added *p*-toluenesulfonyl chloride monohydrate (1.50 g, 7.8 mmol). After being refluxed overnight, the reaction mixture was diluted aqueous HCl solution and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. To the crude tosylate in acetone (25 mL) was added NaI (1.2 g, 7.8 mmol), and the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted aqueous HCl solution and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 4/1) provided product **26b** as an oil (1.10 g, 91%): IR ($CHCl_3$) 3011, 2935, 2860, 1625, 1538, 1346, 1213, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.14 (quintet, *J* = 8.0 Hz, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 3.17 (t, *J* = 8.0 Hz, 2H), 7.2 (dd, *J* = 8.5, 10.5 Hz, 1H), 7.49 (ddd, *J* = 2.4, 4.2, 8.5 Hz, 1H), 7.8 (dd, *J* = 2.4, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 2.4, 31.6, 32.6, 115.8 (d, *J* = 19.8 Hz), 123.1, 133.0 (d, *J* = 7.8 Hz), 134.9 (d, *J* = 3.3 Hz), 151.6 (d, *J* = 261.3 Hz); MS (EI) *m/z* 309, 182.

2-[3-(4-Fluoro-3-nitrophenyl)propyl]-5-(3-isopropoxy-4-methoxyphenyl)-3-oxopentanoic Acid Ethyl Ester 27. To a solution of keto ester **24** (770.0 mg, 2.5 mmol) and iodide **26b** (772.0 mg, 2.5 mmol) in acetonitrile (30.0 mL) were added K_2CO_3 (345.0 mg, 2.5 mmol) and Cs_2CO_3 (140.0 mg, 0.5 mmol). After being refluxed for 24 h, the reaction mixture was diluted with water, acidified with aqueous HCl solution, and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 6/1) provided product **27** as an oil (1.05 g, 86%): IR ($CHCl_3$) 3026, 2984, 2937, 1744, 1713, 1541, 1509, 1353, 1213, 1140, 1038, 811 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 6H), 1.55 (td, *J* = 2.0, 7.7 Hz, 2H), 1.81 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.8 (m, 4H) 3.39 (t, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.50 (q, *J* = 6.0 Hz, 1H), 6.70 (dd, *J* = 2.0, 8.2 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.5, 10.5 Hz, 1H), 7.40 (ddd, *J* = 2.2, 4.3, 10.5 Hz, 1H), 7.8 (dd, *J* = 2.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.1, 27.3, 28.6, 29.0, 34.5, 43.8, 56.0, 58.9, 61.5, 71.5, 112.2, 116.7, 118.3 (d, *J* = 20.2 Hz), 120.7, 120.8, 125.4, 133.1, 135.4 (d, *J* = 9.0 Hz), 138.6 (d, *J* = 4.2 Hz), 147.2, 149.0, 153.9 (d, *J* = 260.5 Hz), 169.4, 204.1; MS (EI) *m/z* 490, 472; HRMS calcd for $C_{26}H_{32}NFO_7$ 489.2162, found 489.2187.

7-(4-Fluoro-3-nitrophenyl)-1-(3-isopropoxy-4-methoxyphenyl)heptan-3-one 28. To a solution of keto ester **27** (690.0 mg, 1.41 mmol) in DMSO (7 mL) and water (0.7 mL) was added LiCl (118.0 mg, 2.82 mmol). After being heated at 160 °C for 24 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 4/1) provided product **28** (487.0 mg, 83%): IR ($CHCl_3$) 3021, 2938, 2862, 1707, 1541, 1513, 1354, 1257, 1133, 1029, 808 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (d, *J* = 6.0 Hz, 6H), 1.58 (m, 4H), 2.40 (t, *J* = 6.5 Hz, 2H), 2.69 (m, 4H) 2.8 (t, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 4.50 (q, *J* = 6.0, 1H), 6.72 (dd, *J* = 3.0, 8.8 Hz, 2H), 6.8 (d, *J* = 8.0, 1H), 7.20 (dd, *J* = 8.6, 10.6 Hz, 1H) 7.40 (ddd, *J* = 2.2, 4.2, 8.4 Hz, 1H), 7.80 (dd, *J* = 2.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.1, 29.5, 30.6, 34.8, 42.7, 44.7, 56.2, 71.6, 112.3, 116.7, 118.3 (d, *J* = 20.3 Hz), 120.8, 120.9, 125.5, 133.6, 135.5(d, *J* = 8.0 Hz), 139.2, 147.3, 149.0, 154.0 (d, *J* = 255.0 Hz), 209.9; MS (EI) *m/z* 417, 375. Anal. Calcd for $C_{23}H_{28}NFO_5$: C, 66.17; H, 6.76. Found: C, 66.19; H, 6.81.

7-(4-Fluoro-3-nitrophenyl)-1-(3-hydroxy-4-methoxyphenyl)heptan-3-one 29. To a solution of compound **28**

(400.0 mg, 0.96 mmol) in CH_2Cl_2 (20 mL) was added BCl_3 (4.8 mL, 1 M solution in CH_2Cl_2, 4.8 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was quenched by careful addition of dry MeOH, and the volatile was removed under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 4/1) provided product **29** as an oil (290.0 mg, 81%): IR ($CHCl_3$) 3548, 3040, 3012, 2942, 2866, 1711, 1537, 1509, 1349, 1266, 1217, 1140, 1029, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (m, 4H), 2.41 (t, J = 6.4 Hz, 2H), 2.69 (m, 4H), 2.80 (m, 2H), 3.85 (s, 3H), 5.58 (s, 1H, OH), 6.60 (dd, J = 1.7, 8.3 Hz, 2H), 6.70 (d, J = 6.8 Hz, 1H) 7.20 (dd, J = 8.7, 10.6 Hz, 1H) 7.40 (ddd, J = 2.2, 4.4, 8.4 Hz, 1H), 7.80 (dd, J = 2.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.0, 29.2, 30.4, 34.6, 42.5, 44.3, 56.0, 110.8, 114.5, 118.1 (d, J = 20.6 Hz), 119.7, 125.3, 134.2, 135.5 (d, J = 7.7 Hz), 136.6, 139.2, 145.0, 145.6, 153.8 (d, J = 263.5 Hz), 210; MS (EI) m/z 375, 345; HRMS calcd for $C_{20}H_{22}NFO_5$ 375.1482, found 375.1492.

4-Methoxy-17-nitro-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexen-10-one 30. To a solution of compound **29** (114.0 mg, 0.30 mmol) in DMF (30 mL, 0.01 M) was added CsF (230.0 mg, 1.33 mmol). After being stirred at room temperature for 4 h, the reaction mixture was diluted with EtOAc, washed with water and brine, and evaporated to dryness. Purification by flash chromatography (SiO_2, eluent: toluene/AcOEt = 2/1) provided product **30** (94.0 mg, 88%): mp 138−139 °C; IR ($CHCl_3$) 3025, 2937, 2864, 1711, 1534, 1519, 1351, 1263, 1237, 1122, 1029, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (m, 4H), 1.85 (m, 1H), 2.10 (m, 1H), 2.2−2.5 (m, 2H), 2.68 (m, 2H), 2.90 (m, 2H), 3.90 (s, 3H), 5.30 (d, J = 1.8 Hz, 1H), 6.61 (dd, J = 1.8, 8.2 Hz, H), 6.80 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.50 (dd, J = 2.0, 8.3 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.9, 26.8, 27.4, 35.3, 40.9, 45.8, 56.7, 113.1, 113.5, 122.9, 126.2, 126.9, 134.1, 136.4, 140.0, 147.2, 148.3, 149.7, 209.2; MS (EI) m/z 355, 324; HRMS calcd for $C_{20}H_{21}NO_5$ 355.14197, found 355.1395.

17-Amino-4-methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexen-10-one 31. A solution of compound **30** (25.0 mg, 0.07 mmol) in MeOH (2 mL) and EtOAc (1 mL) was hydrogenated in the presence of 10% Pd/C under hydrogen atmosphere for 1 h. The reaction mixture was filtered through a short pad of Celite. The filtrate was evaporated to dryness and purified by flash chromatography (SiO_2, eluent: heptane/EtOAc = 3/2) to provide product **31** (19.8 mg, 87%): mp 148−150 °C; IR ($CHCl_3$) 3492, 3400, 3015, 2941, 1712, 1620, 1510, 1443, 1259, 1124, 1027, 953 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 4H), 1.84 (m, 2H), 2.31 (t, J = 5.8 Hz, 2H), 2.63 (m, 2H), 2.82 (m, 2H), 3.92 (s, 3H), 5.70 (d, J = 2.0 Hz, 1H), 6.60 (m, 3H), 6.80 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3, 27.3, 27.5, 35.8, 41.4, 46.5, 56.3, 111.9, 113.1, 117.9, 120.4, 121.7, 123.7, 134.5, 139.5, 139.9, 140.8, 146.8, 148.4, 210.4; MS (EI) m/z 325; HRMS for $C_{20}H_{23}NO_3$ 325.16779, found 325.1697.

4-Methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7-(20),15(19),16-hexen-10-one 32. To a degassed CH_2Cl_2 (5 mL) were added $BF_3{\cdot}Et_2O$ (5 μL) and a solution of compound **31** (10 mg, 0.03 mmol) in CH_2Cl_2 (60 μL). To this solution, cooled to −15 °C, was added ^{t}BuONO (4 μL), and the resulting solution was stirred at −15 °C for 15 min and at 5 °C for 30 min. The volatile was removed at freezing temperature under reduced pressure. The so-obtained crude diazonium salt was dissolved in DMF (0.3 mL) followed by addition of $FeSO_4{\cdot}7H_2O$. After being stirred at room temperature for 1 h, the reaction mixture was diluted with EtOAc, washed with water and brine, and evaporated to dryness. Purification by preparative TLC (SiO_2, eluent: heptane/EtOAc = 3/1) provided product **32** (7.2 mg, 77%): mp 108−110 °C; IR ($CHCl_3$) 2943, 2861, 1711, 1521, 1501, 1265, 1224, 1208, 1126, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.6 (m, 4H), 1.8 (t, J = 6.7 Hz, 2H), 2.3 (t, J = 5.3 Hz, 2H), 2.70 (t, J = 5.1 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H), 3.9 (s, 3H), 5.4 (d, J = 1.9 Hz, 1H), 6.60 (dd, J = 1.9, 8.2 Hz, 1H), 6.8 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.1, 27.0, 27.4, 35.4, 40.9, 46.0, 56.3, 112.1, 113.9, 121.1, 123.4, 131.2, 133.9, 138.3, 146.6, 150.8, 154.5, 209.7; MS (EI) m/z 310.

Acerogenin L (5). A solution of compound **32** (23.0 mg, 0.074 mmol) in CH_2Cl_2 (10 mL) containing anhydrous $AlCl_3$ (49.0 mg, 0.37 mmol) was refluxed for 18 h. The reaction was carefully hydrolyzed by addition of water, and the volatile was evaporated. The aqueous phase was extracted with EtOAC. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 4/1) provided acerogenin L **5** (17.5 mg, 80%): mp 181−183 °C; [lit.[5f] mp 188−190 °C]; IR ($CHCl_3$) 3554, 2941, 1709, 1519, 1505, 1226, 1212, 804, 491 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (m, 2H), 1.65 (m, 2H), 1.77 (t, J = 8 Hz, 2H), 2.27 (t, J = 5.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.81 (t, J = 5.0 Hz, 2H), 5.41 (d, J = 1.2 Hz, 1H), 6.61 (dd, J = 1.2, 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.1, 27.4, 27.5, 35.6, 41.2, 46.4, 113.4, 115.1, 122.0, 123.4, 131.4, 133.5, 139.0, 143.1, 148.6, 154.3, 210.2; MS (EI) m/z 296.

Acerogenin B (4). Sodium borohydride (25.0 mg, 0.67 mmol) was added to a solution of acerogenin L (**5**) (20.0 mg, 0.067 mmol) in MeOH (2.0 mL) cooled at 0 °C. After being stirred at room temperature for 20 min, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification of crude product by preparative TLC (SiO_2, eluent: heptane/EtOAc = 3/1) afforded acerogenin B (**4**) (24 mg, quantitative): mp 170−173 °C (lit.[5b] mp 179 °C); IR ($CHCl_3$) 4213, 3688, 3622, 3023, 2400, 1514, 1423, 1218, 931, 742, 627, 422 cm^{-1}; ^1H NMR (MeOD, 300 MHz) δ 0.65−0.82 (m, 2H), 0.95−1.12 (m, 2H), 1.17−1.62 (m, 3H) 1.70−1.90 (m, 1H), 2.40−2.68 (m, 3H), 2.71−2.89 (m, 1H), 3.19 (m, 1H), 5.48 (d, J = 1.7 Hz, 1H), 6.62 (dd, J = 1.7, 8.1 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H) 6.80 (dd, J = 2.4, 8.2 Hz, 1H) 7.03 (dd, J = 2.4, 8.2 Hz, 1H), 7.13 (dd, J = 2.0, 8.2 Hz, 1H), 7.14 (dd, J = 2.0, 8.2 Hz, 1H); ^{13}C NMR (CD_3OD) δ 23.6, 29.2, 31.4, 36.1, 37.4, 39.8, 72.4, 116.6, 117.1, 123.2, 124.2, 124.3, 131.60, 132.9, 134.5, 140.6, 144.7, 151.2, 157.4; MS (EI)-m/z 298.

5-[7-(4-Fluoro-3-nitrophenyl)-5-hydroxyheptyl]-2-methoxyphenol 37. Compound **18** (115 mg, 0.31 mmol) was reduced with $NaBH_4$ (58 mg, 1.53 mmol) in MeOH (10 mL) under standard conditions to afford product **37** (107 mg, 93%): mp 55−56 °C; IR ($CHCl_3$) 4214, 3029, 1539, 1355, 1210, 722, 656 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25−1.80 (m, 8H), 2.51 (t, J = 7.3 Hz, 2H), 2.65−2.90 (m, 2H), 3.60 (m, 1H), 3.85 (s, 3H), 5.63 (s, 1H, OH), 6.60 (dd, J = 1.8, 7.5 Hz, 1H), 6.73 (d, J = 8.3 Hz, 2H), 7.15 (dd, J = 9.3, 10.6 Hz, 1H), 7.30 (ddd, J = 2.4, 4.2, 8.3 Hz, 1H), 7.8 (dd, J = 2.4, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 31.0, 31.4, 35.2, 37.6, 38.5, 56.1, 70.8, 110.7, 114.7, 118.2 (d, J = 20.5 Hz), 119.7, 125.5, 125.6, 135.6 (d, J = 8.6 Hz), 136.8, 139.4 (d, J = 3.1 Hz), 144.8, 145.4, 153.9 (d, J = 260.8 Hz); MS (EI) m/z 377. Anal. Calcd for $C_{20}H_{24}NFO_5$: C, 63.65; H, 6.41. Found: C, 63.11; H, 6.61.

1-(4-Fluoro-3-nitrophenyl)-7-(3-isopropoxy-4-methoxyphenyl)heptanol-3 38. Decarboxylation of compound **17** followed by reduction under standard conditions provided alcohol **38** in 91% yield: IR ($CHCl_3$) 3600, 2934, 1538, 1512, 1355, 1264, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.3 (d, J = 6.1 Hz, 6H), 1.3−2.0 (m, 8H), 2.50 (t, J = 7.1 Hz, 2H), 2.70 (m, 2H), 3.50 (m, 1H), 3.8 (s, 3H), 4.5 (q, J = 6.1 Hz, 1H), 6.7 (m, 3H), 7.1 (dd, J = 6.0, 8.5 Hz, 1H), 7.4 (ddd, J = 2.3, 4.3, 8.3 Hz, 1H), 7.90 (dd, J = 2.3, 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 22.3, 25.2, 31.0, 31.6, 35.3, 37.7, 38.5, 56.1, 70.8, 71.7, 112.3, 117.1, 118.2 (d, J = 20.5 Hz), 121.0, 125.5, 135.0, 135.2 (d, J = 8.6 Hz), 137.2, 139.4, 147.2, 148.8, 153.9 (d, J = 262 Hz); MS (EI) m/z 419, 377. Anal. Calcd for $C_{23}H_{30}NFO_5$: C, 65.85; H, 7.21. Found: C, 65.64; H, 7.44.

1-(4-Fluoro-3-nitrophenyl)-7-(3-isopropoxy-4-methoxyphenyl)-3-iodoheptane 40. A solution of alcohol **38** (400.0 mg, 0.95 mmol), Et_3N (0.26 mL, 1.9 mmol), and MsCl (150 μL, 1.9 mmol) in CH_2Cl_2 was stirred at 0 °C for 1 h. The reaction mixture was diluted with water and 1 N HCl and extracted with CH_2Cl_2. The combined organic extracts were

washed with aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated to give the crude mesylate. The so-obtained mesylate in acetone (30 mL) was refluxed in the presence of NaI (290.0 mg, 1.9 mmol) for 24 h. The volatile was evaporated, and the residue was dissolved in water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (SiO_2, eluent: heptane/Et_2O = 5/1) provided product **40** as an oil (429.3 mg, 85%): IR ($CHCl_3$) 3012, 2929, 1592, 1542, 1347, 1258, 1135, 1113 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, J = 6.1 Hz, 6H), 1.3−2.0 (m, 8H), 2.3 (t, J = 6.7 Hz, 2H), 2.5−2.9 (m, 2H), 3.60 (s, 3H), 3.8 (m, 1H), 4.3 (q, J = 6.0 Hz, 1H), 6.50 (m, 2H), 6.62 (d, J = 7.8 Hz, 1H), 7.00 (dd, J = 2.2, 8.4 Hz, 1H), 7.30 (ddd, J = 2.3, 4.3, 8.3 Hz, 1H), 7.7 (dd, J = 2.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.2, 29.0, 30.7, 34.7, 35.1, 37.4, 40.6, 41.5, 56.1, 71.6, 112.3, 117.0, 118.4 (d, J = 20.4 Hz), 120.9, 125.5, 134.8, 135.5 (d, J = 8.6 Hz), 137.2, 137.9, 147.2, 148.8, 154.1 (d, J = 261.6 Hz); MS (IC) m/z 530 (M + H), 488, 402, 360. Anal. Calcd for $C_{23}H_{29}NFIO_4$: C, 52.22; H, 5.67. Found: C, 52.18; H, 5.52.

1-(4-Fluoro-3-nitrophenyl)-7-(3-isopropoxy-4-methoxyphenyl)heptane 41. To solution of compound **40** (301.5 mg, 0.57 mmol) in DMSO was added $NaBH_4$ (130.0 mg, 3.4 mmol) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was diluted with 1 N HCl and extracted with EtOAC. The combined organic extracts were washed with water and brine, dried, and evaporated to dryness. Purification by flash chromatography (SiO_2, eluent: heptane/EtOAc = 5/1) provided product **41** as an oil (202.1 mg, 88%): IR ($CHCl_3$) 3010, 2937, 2402, 1540, 1507, 1236, 1195, 793 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (m, 6H), 1.34 (d, J = 7.5 Hz, 6H), 1.58 (m, 4H), 2.52 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 3.82 (s, 3H,), 4.51 (q, J = 7.5 Hz, 1H), 6.69 (m, 2H), 6.78 (d, J = 7.9 Hz, 1H), 7.18 (dd, J = 8.5, 10.7 Hz, 1H), 7.39 (ddd, J = 2.2, 4.3, 8.4 Hz, 1H), 7.83 (dd, J = 2.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 29.1, 29.2, 29.3, 31.1, 31.7, 34.9, 35.5, 56.2, 71.6, 112.2, 117.0, 118.0 (d, J = 20.4 Hz), 121.0, 125.5, 134.6, 135.5 (d, J = 7.3 Hz), 137.1, 139.9, 147.2, 148.7, 153.9 (d, J = 261.4 Hz); MS (IE) m/z 403, 361. Anal. Calcd for $C_{23}H_{30}NFO_4$: C, 68.47; H, 7.49. Found: C, 69.08; H, 7.42.

5-[7-(4-Fluoro-3-nitrophenyl)heptyl]-2-methoxyphenol 42. Treatment of compound **41** (130.0 mg, 0.32 mmol) in CH_2Cl_2 with BCl_3 at 0 °C as described for the preparation of **18** gave **42** as an oil (107.1 mg, 92%): IR ($CHCl_3$) 3545, 2935, 2858, 1535, 1513, 1354, 1271, 1211, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.31 (s, 6H), 1.58 (m, 4H), 2.49 (t, J = 7.4 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 3.85 (s, 3H), 5.57 (d, J = 1.9 Hz, 1H, OH), 6.63 (dd, J = 1.8, 8.2 Hz, 1H), 6.75 (d, J = 7.8 Hz, 2H), 7.25 (dd, J = 9.6, 10.4 Hz, 1H), 7.4 (ddd, J = 2.2, 4.3, 8.4 Hz, 1H), 7.83 (dd, J = 2.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.0, 29.1, 29.3, 31.1, 31.5, 34.9, 35.3, 56.1, 110.7, 114.7, 118.1 (d, J = 20.3 Hz), 119.7, 125.5, 125.6, 135.5 (d, J = 8.1 Hz), 136.2, 139.9, 144.7, 145.5, 153.9 (d, J = 260.5 Hz); MS (IE) m/z 361. Anal. Calcd for $C_{20}H_{24}NFO_4$: C, 66.45; H, 6.69. Found: C, 66.84; H, 6.88.

4-Methoxy-17-nitro-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexen-12-ol 43 and 44. Cyclization of compound **37** (40.0 mg, 0.11 mmol) under standard conditions (CsF, DMF, 0.01 M, room temperature, 5 h) gave after purification (preparative TLC, SiO_2, eluent: toluene/EtOAc = 2/1) two macrocycles **43** (42%) and **44** (42%). ***(S,P)*/*(R,M)*-43:** mp 47−49 °C; IR ($CHCl_3$) 3619, 2936, 1532, 1310, 1267, 1122 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 095−1.31 (m, 2H, H10), 1.43−1.62 (m, 2H, H9), 1.91 (m, 2H, H11) 2.45 (m, 2H, H8), 2.78 (td, J = 3.9, 12.4 Hz, 2H, H13), 3.03 (dt, J = 4.1, 9.3 Hz, 2H, H14), 3.30 (m, 1H, H12), 3.97 (s, 3H, OMe), 5.56 (d, J = 1.8 Hz, 1H, H20), 6.70 (dd, J = 1.7, 8.3 Hz, 1H, H6), 6.81 (d, J = 8.2 Hz, 1H, H5) 7.31 (d, J = 8.5 Hz, 1H, H18) 7.51 (dd, J = 2.1, 8.4 Hz, 1H, H19), 7.87 (d, J = 2.1 Hz, 1H, H16); ^{13}C NMR ($CDCl_3$) δ 24.9, 28.1, 31.6, 32.1, 39.1, 39.5, 56.6, 70.4, 112.9, 114.6, 123.3, 126.9, 127.8, 134.7, 135.3, 140.9, 143.0, 147.0, 149.5, 149.7; MS (EI) m/z 357. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 66.79; H, 6.85.

***(S,M)*/*(R,P)*-4-Methoxy-17-nitro-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexen-12-ol 44:** mp 65−67 °C; IR ($CHCl_3$) 3602, 3022, 2940, 1536, 1353, 1221, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85−1.28 (m, 2H, H10), 1.45−1.60 (m, 2H, H9), 1.86−2.0 (m, 2H, H11), 2.45 (t, J = 5.7 Hz, 2H, H8), 2.73 (td, J = 4.2, 12.4 Hz, 2H, H13), 3.10 (dt, J = 4.1, 9.3 Hz, 2H, H14), 3.25 (m, 1H, H12), 3.95 (s, 3H, OMe), 5.61 (d, J = 1.7 Hz, 1H, H6), 6.60 (dd, J = 1.7, 8.6 Hz, 1H, H6), 6.82 (d, J = 8.3 Hz, 1H, H5) 7.11 (d, J = 8.3 Hz, 1H, H18) 7.40 (dd, J = 2.1, 8.3 Hz, 1H, H19), 7.89 (d, J = 2.1 Hz, 1H, H16); ^{13}C NMR ($CDCl_3$) δ 24.9, 27.9, 31.6, 32.3, 39.4, 39.8, 57.5, 70.9, 113.0, 115.8, 123.3, 125.5, 126.6, 134.7, 136.1, 140.6, 144.7, 147.0, 149.8, 150.1; MS (EI) m/z 357. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 66.99; H, 6.75.

4-Methoxy-17-nitro-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),15(19),16-hexene 45. Cyclization of compound **42** (19.0 mg, 0.52 mmol) under standard conditions (CsF, DMF, 0.01 M, room temperature, 5 h) gave after purification (preparative TLC, SiO_2, eluent: toluene/heptane/EtOAc = 2/1/1) macrocycle **45** (15.9 mg, 89%): mp 98−101 °C; IR ($CHCl_3$) 2931, 2865, 1530, 1516, 1355, 1267, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.70 (m, 2H), 0.82 (m, 2H), 1.15 (m, 2H), 1.30 (m, 2H), 1.60 (m, 2H), 2.43 (m, 2H), 2.74 (m, 2H), 3.97 (s, 3H), 5.73 (d, J = 1.8 Hz, 1H), 6.65 (dd, J = 1.8, 8.2 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 7.2 (d, J = 8.3 Hz, 1H), 7.5 (dd, J = 2.0, 8.3 Hz, 1H), 7.9 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.8, 28.1, 30.0, 31.1, 31.5, 35.3, 56.7, 112.9, 115.5, 123.3, 126.4, 126.7, 134.9, 136.0, 140.9, 143.6, 147.0, 149.5, 149.8; MS (IE) m/z 341. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.46; H, 7.03; N, 3.88.

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Supporting Information Available: ^1H NMR spectra of natural products acerogenins A, B, C, and L, aceroside IV, as well as the key synthetic intermediates lacking microanalyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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