First Total Synthesis of Acerogenin C and Aceroside IV

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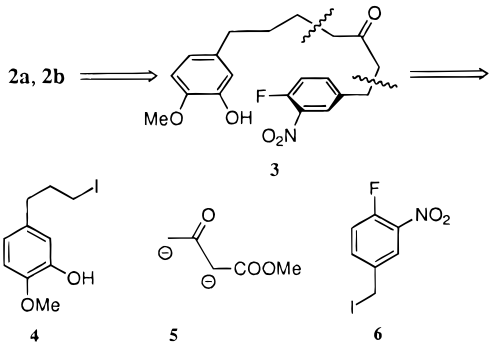
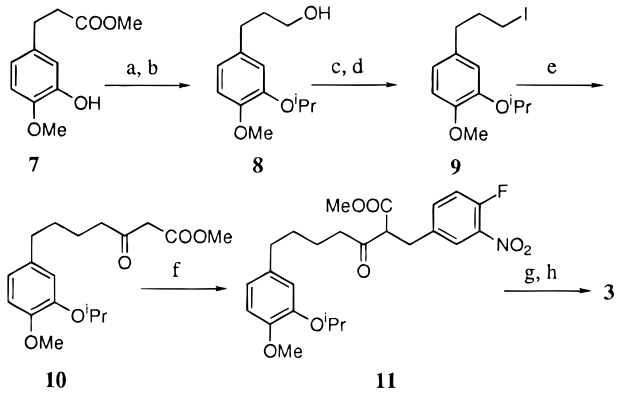
The stem bark of *Acer nikoense* Maxim (Aceraceae), a tree indigenous to Japan, has been used in folk medicine as a remedy for hepatic disorder and for eyewash.[1] Since the isolation of acerogenin A (**1a**) by Nagai et al. in 1976,[2] several dozens of structurally related products with an endocyclic biaryl ether bond have been identified from the same plant.[3] They all belong to a growing family of metabolites called diarylheptanoids, which are characterized by the presence of two aromatic rings connected by an oxygenated seven-carbon aliphatic chain.[4] No total synthesis[5] of acerogenin-type compounds has yet appeared in the literature probably due to the lack of an efficient ring closure reaction. Previously, an intramolecular Wurtz reaction[6] and Wittig reaction[7] have been employed by Nogradi et al.[6,7] as the key cyclization step for the total synthesis of related natural products garugamblin 1 and garuganin III.[4]

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*[8] and *aryl*−*alkyl ether*[9] bond(s). We have attributed the success of this remarkable cycloetherification to an intramolecular recognition phenomenon.[8−11] Several structural elements found in our previously studied substrates could indeed help their preorganization[12] in such a way that a folded conformation was a predominant low energy one, thus favoring the desired cyclization.[13] To evaluate the influence of intramolecular H-bonding[14] 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 **3**). 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 C (**2a**) and aceroside IV (**2b**)[3c] is the subject of the present paper.

Scheme 1



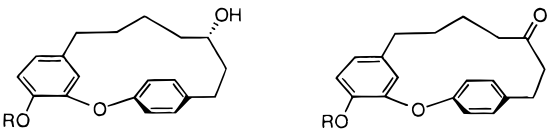
Scheme 2[a]



[a] Key: (a) ^{i}PrBr, K_2CO_3, DMF; (b) LAH−THF, 95%; (c) TsCl, Py; (d) NaI, Me_2CO, 87%; (e) methyl acetoacetate, LDA, then iodide **9**, 80%; (f) NaH, THF, then 4-fluoro-3-nitrobenzyl iodide (**6**), 75%; (g) BCl_3, CH_2Cl_2; (h) 6 N HCl, 90%.

As shown in the retro-synthetic scheme (Scheme 1), our plan calls for the macrocyclization of substrate **3** as a key ring closure step via an intramolecular S_NAr reaction. While many different strategies may be envisaged for the synthesis of type **3** linear diarylheptanoids, a convergent and flexible approach via a "3 + 3 + 1" strategy taking advantage of the dianion chemistry of methyl acetoacetate[15] was attempted in this study.

The linear cyclization precursor **3** was synthesized without event following standard procedures (Scheme 2). Cyclization of **3** occurred smoothly in DMF (0.01 M, room



1a R = H, Acerogenin A, **2a** R = H, Acerogenin C
1b R = β-D-glycopyranosyl, Aceroside I **2b** R = β-D-glycopyranosyl, Aceroside IV

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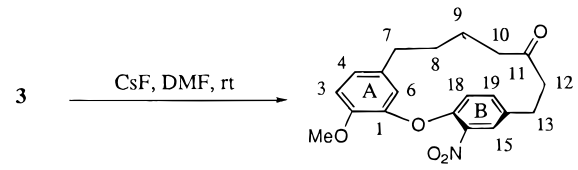
Scheme 3



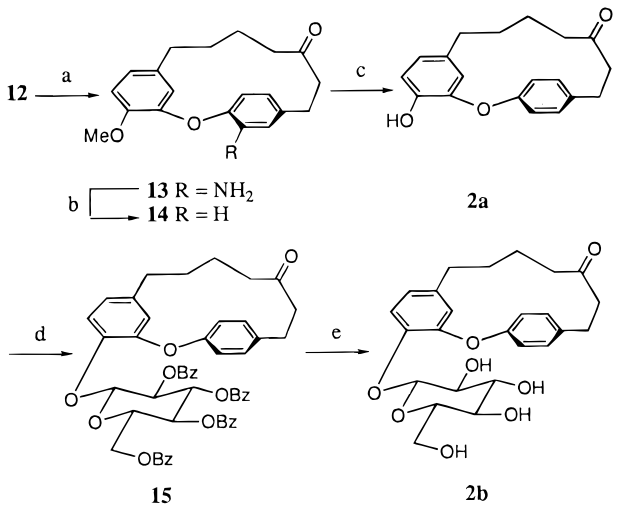
12

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

temperature, 3 h) using cesium fluoride[16] as base, providing the desired macrocycle **12** in almost quantitative yield (based on the ^{1}H NMR spectrum of the crude product, Scheme 3). The cyclic structure of **12** was evident from the characteristic high-field shift of the H-6 proton in the ^{1}H NMR spectrum, due to the anisotropic effect of the aromatic B ring. Potassium carbonate[17] was also found to be 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 to 60 °C without diminishing the yield of cyclized product. To examine the effect of concentration on the outcome of the cyclization (Scheme 3), compound **3** was treated with CsF in DMF at 0.01, 0.05, 0.1, and 1 M. *We observed that even at high concentration (1 M of **3** in DMF), the analytically pure macrocycle **12** could still be obtained in 45−50% isolated yield.*[18] This provides experimental evidence that the intramolecular reaction of compound **3** is indeed facile and highly competitive with the alternative intermolecular process. This result is quite instructive considering the fact that the aliphatic carbon chain usually adopts an extended conformation.[19] We reasoned that the presence of electron-rich and electron-poor aromatic rings at the two chain terminals alters the conformational properties of **3** leading to a folded conformer conducive to cyclization.[20−22] We anticipate that, in the future, the proper use of the principle of intramolecular recognition phenomena[8−11,14] will help to design new macrocyclization techniques.

The syntheses of acerogenin C (**2a**) and aceroside IV (**2b**) were accomplished as shown in Scheme 4. Reduction of the nitro group of **12** was carried out by hydrogenolysis under conventional conditions (Pd/C, MeOH, 1 atm) to afford the amino compound **13**, which was converted into compound **14** (90% overall yield) employing Doyle's one-step deamination procedure.[23] The *O*-demethylation of **14** with $AlCl_3$ in refluxing CH_2Cl_2 gave acerogenin C (**2a**), whose spectral data were identical in all respects to the literature values.[3c]

Scheme 4[a]



[a] Key: (a) H_2, Pd/C, MeOH; (b) ^{t}BuONO, DMF, 90%; (c) $AlCl_3$, CH_2Cl_2, 88%; (d) 2,3,4,6-tetrabenzoylglucopyranosyl bromide, CH_2Cl_2-NaOH, Bu_4NBr, 85%; (e) MeOH-H_2O, NaOH, 92%.

Glycosidation of **2a** was first attempted with 2,3,4,6-α-D-tetrabenzylglucopyranose under Mitsunobu conditions.[24] While the reaction proceeded cleanly to give the desired aryl glucoside, the conversion was low (<30%) even under forced conditions (e.g., excess of glycosyl donor, heating to 60 °C in different solvents). The desired transformation was finally realized using a two-phase glycosidation methodology.[25] Thus, 2,3,4,6-α-D-tetrabenzoylglucopyranosyl bromide was allowed to react with acerogenin C (**2a**) in the presence of tetrabutylammonium bromide (CH_2Cl_2−aqueous NaOH) to afford stereospecifically the β-aryl glucoside **15** in 85% yield. Subsequent saponification (MeOH−H_2O, NaOH) of the benzoyl groups gave the aceroside IV (**2b**) in 92% isolated yield. The spectral data of our synthetic material were identical with those of the natural product.

In summary, we have accomplished the first total synthesis of acerogenin C and aceroside IV[26] featuring a high-yielding cycloetherification reaction as the key ring-closure step. The synthesis is convergent and flexible. It should be easily amenable to other members of this family and should allow for the generation of libraries of cyclic diarylheptanoids for biological investigations.

Acknowledgment. We thank Professor Nagai for kindly sending us the NMR spectra of natural acerogenin C and aceroside IV. Financial support from the CNRS and a SFERE-CONACYT doctoral fellowship funded jointly by the Mexican and French governments to G. Islas Gonzalez are gratefully acknowledged.

Supporting Information Available: Experimental procedure and complete characterization of natural products acerogenin C (**2a**) and aceroside IV (**2b**) as well as the key synthetic intermediates **3** and **10**−**15** (7 pages).

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(20) Molecular modeling [MM2 (Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127−8134), water set)] of compound **3** showed that the lowest energy conformation was indeed the folded one. Similar computational studies have been carried out by Abramovitch's group; see ref 11.

(21) At the present time, we have failed to observe a CT absorption band in the UV−vis spectrum of compound **14** (1×10^{-4} M, MeCN). However, further studies are required before drawing any conclusion. Detailed NMR studies are in progress.

(22) As suggested by one of the reviewers, it would be interesting to check the outcome of an alternative synthetic strategy, i.e., formation of the biaryl ether followed by macrocyclization via intramolecular alkylation of the keto ester. The cyclization results will provide a direct evidence of our hypothesis as intramolecular recognition phenomena will be absent in this case. This study will be incorporated in a future full account.

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(26) We have been informed that Professor Nogradi has also accomplished, very recently, a total synthesis of acerogenin C.