Ellagitannin Chemistry

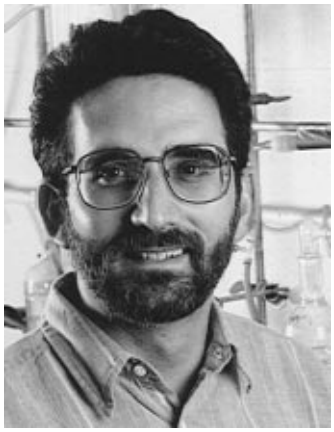
Stéphane Quideau and Ken S. Feldman*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received June 28, 1995 (Revised Manuscript Received August 31, 1995)

Contents

Stéphane Quideau was born on May 28, 1966, in Lannilis, France. After completion of his undergraduate studies in chemistry at the University of Angers and, under the guidance of Professor M. L. Martin, at the University of Nantes, he moved in 1990 to the University of Wisconsin—Madison, where he carried out his Ph.D. studies on oxidative coupling of lignin phenols with Professor J. Ralph. He is currently a postdoctoral fellow with Professor Ken S. Feldman at Penn State. His current fields of interest include the chemistry and biochemistry of plant secondary metabolites and the development of biomimetic approaches to natural products synthesis.



Ken Feldman was born and raised in Miami Beach, FL. In 1978, he obtained his B.S. degree in chemistry while exploring the ipso nitration reaction of substituted aromatics in Philip Myhre's lab at Harvey Mudd College. His Ph.D. work at Stanford University with E. E. van Tamelen focused on biomimetic syntheses of marine and terrestrial natural products. After a year-long stint as a post-doctoral fellow at Dupont, he joined the faculty of the chemistry department at Penn State as an assistant professor in 1984. His current research interests include the chemistry and biology of the ellagitannin class of secondary plant metabolites, and the rational synthesis of multidimensional periodic organic networks that may exhibit "zeolitic" properties.

I. Introduction

Ellagitannins belong to the hydrolyzable tannin class of polyphenol extractives derived from the secondary metabolism of dicotyledonous species of the Angiospermae. Early interest in this class of natural products was confined to the compositional characterization of vegetable tannin extracts used in the leather industry. The first insights into the constitution of the ellagitannins emerged from investigations on the second class of hydrolyzable tannins, the gallotannins, conducted at the turn of the century by Fischer and Freudenberg.[1] Structural elucidation of numerous members of the ellagitannin family awaited the work of Schmidt and Mayer, whose many contributions to the understanding of both the chemistry and biochemistry of the ellagitannins flourished in the German literature from 1950 onward.[2] However, these seminal studies only revealed the tip of the ellagitannin iceberg, as the vast structural diversity of these complex plant isolates had yet to be appreciated. The lack of adequate isolation/purification and analytical techniques, as well as the absence of universal appeal, thwarted further progress in the chemistry and biochemistry of the ellagitannins at that time. However, recent disclosures of the promising anticancer and antiviral activities of select members of this class of natural products engendered a renaissance of interest in their chemistry. Owing primarily to the efforts of Haslam,[3] Okuda,[4] and Nishioka,[5] and the availability of modern NMR techniques, over 500 ellagitannins have been structurally characterized at present.

The foundation of their biogenetic construction consists of the chemically trivial acylation of a carbohydrate core, generally D-glucopyranose, by gallic acid. Structural variation among the ellagitannins principally arises from (1) the differing extent of galloylation, (2) the intramolecular dehydrogenative (oxidative) C−C coupling of galloyl groups, (3) the dehydrogenation and hydrolytic cleavage of galloyl-derived aromatic rings, (4) the formation of aromatic C-glycosides, and (5) oligomerization via

0009-2665/96/0796-0475$25.00/0

oxidative C−O coupling. A complete structural classification of the ellagitannins occurring in the various taxa of the Dicotyledoneae is beyond the scope of this review. The following compendium of structures is based on the chemical diversity and apparent hierarchy of molecular complexity among the major subclasses of ellagitannins in order to highlight the problems which must be addressed in the context of total syntheses efforts.

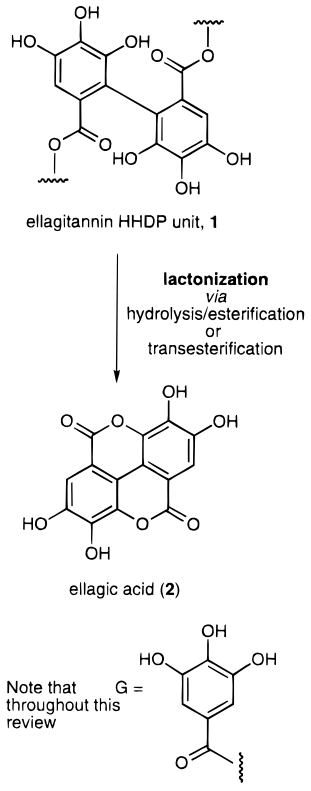
A. Structural Description

1. Monomeric Ellagitannins

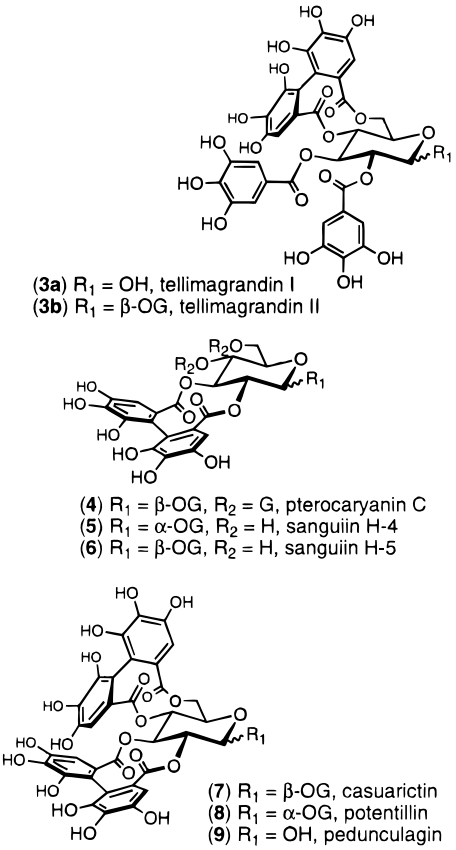
The defining structural characteristic of all monomeric ellagitannins is the 6,6′-dicarbonyl-2,2′,3,3′,4,4′-hexahydroxybiphenyl moiety, commonly designated by the trivial name hexahydroxydiphenoyl (HHDP, **1**), which is surmised to originate from oxidative C−C coupling of phenolic galloyl groups *in vivo*. Hydrolytic release of HHDP ester groups leads to their facile and unavoidable conversion into the bislactone ellagic acid (**2**) for which these natural products are named (Scheme 1). The most common biaryl coupling patterns involve galloyl ester groups located at the 2,3- and 4,6-positions of the glucopyranose core, although coupling across the 1,6-, 1,3-, 3,6-, and 2,4-positions are known (*vide infra*). The level of structural diversity is already remarkable among the monomeric ellagitannins possessing these basic features, as it is expressed not only by the variation in position, frequency, and stereochemistry of HHDP units, but also by the galloylation extent and anomeric stereochemistry of the glucose core.

A roster of monomeric species notable both for their common occurrence in plants and for their involvement in the modular assembly of more complex

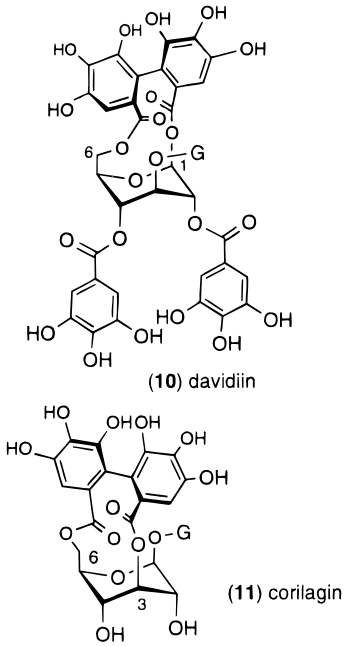
Scheme 1



Scheme 2



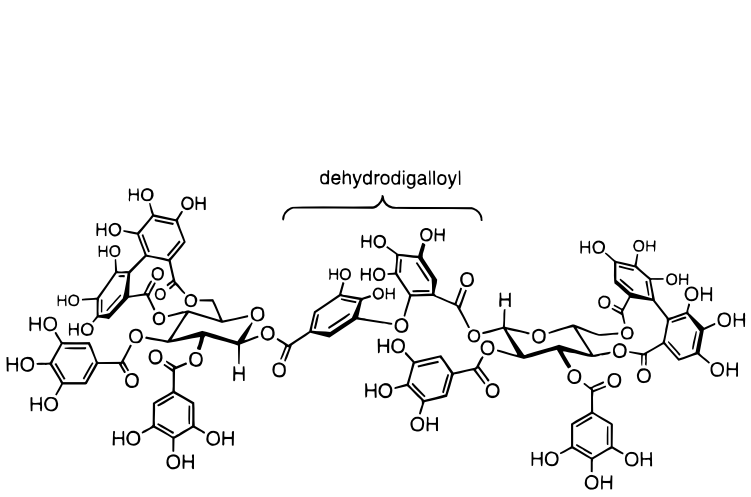
Scheme 3



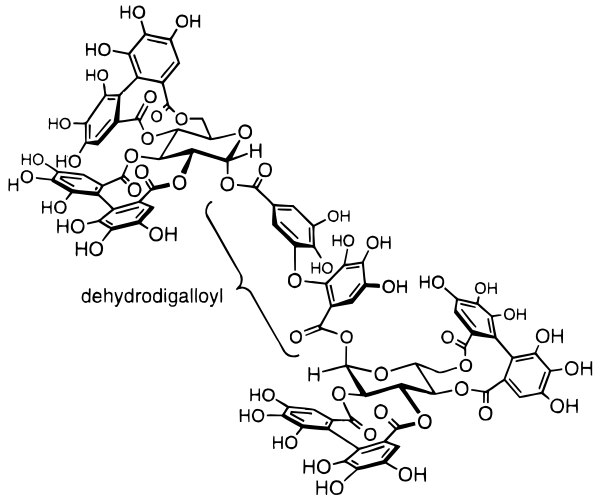
oligomeric ellagitannins includes tellimagrandin I (**3a**)[6] and II (**3b**, eugeniin)[5a,6] featuring a 4,6-coupled (*S*)-HHDP unit, pterocaryanin C (**4**)[5b,7] and the sanguins H-4/H-5 (**5**/**6**)[5c,8] featuring a 2,3-coupled (*S*)-HHDP unit, and casuarictin (**7**),[9] its α-anomer potentillin (**8**),[9a,10] and hemiacetal congener pedunculagin (**9**),[9b,11] all three of which display both 2,3- and 4,6-(*S*)-HHDP ester groups (Scheme 2).

Another subclass of monomeric ellagitannins comprises a group of less commonly encountered but

Scheme 4



(**15**) coriariin A



(**16**) agrimoniin

synthetically more challenging structures in which (*R*)- and/or (*S*)-HHDP moieties bridge the 1,6- or 3,6-positions of the glucopyranose core in the $^1C_4$ conformation, as exemplified in davidiin (**10**),[12] corilagin (**11**),[13] geraniin (**12**),[12a,14] carpinusin (**13**),[5d] and chebulagic acid (**14**)[13b,c,15] (Schemes 3, 9, and 11). Additional complex bridges at the glucose 2,4-positions such as in **12**−**14** would originate from an initially formed HHDP ester group which invariably and characteristically experiences further transformations when generated at these loci in an axial disposition (cf. section I.A.3).

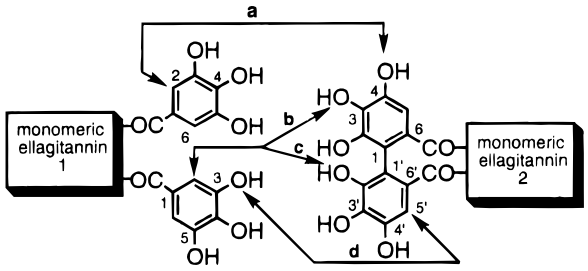
2. Oligomeric Ellagitannins

Oligomerization of ellagitannin molecules is presumed to arise primarily from oxidative C−O coupling between galloyl and hexahydroxydiphenoyl moieties of appropriate monomeric precursors.

Over 150 structurally characterized dimeric-to-tetrameric ellagitannins have been isolated and classified according to the type of monomeric fragments involved and the regiochemistry of the attachment process.[4a] The most prevalent coupling modules are (1) the dehydrodigalloyl ester group evident, for example, in the tellimagrandin II dimer coriariin A (**15**),[16] the potentillin dimer agrimoniin (**16**)[10] (Scheme 4), as well as in the tellimagrandin II/potentillin dimer gemin A,[8] and (2) the valoneoyl ester group.[17] The formation of this latter trigalloyl linking unit involves coupling between C(2) of a galloyl moiety in one monomer and the C(4)-phenol in a HHDP moiety of another monomer (Scheme 5) and is exemplified in the tellimagrandin II dimer rugosin D (**17**),[18] the macrocyclic tellimagrandin I dimer oenothein B (**18**)[19] [and its analog woodfordin C (**19**)][20] (Scheme 6), the pterocaryanin C/casuarictin trimer nobotanin E,[7] and the tellimagrandin I tetramer trapanin B.[21]

The isodehydrodigalloyl species **20** and the dehydrotrigalloyl (hellinoyl) unit **21** shown in Scheme 7 represent further variation among other known C−O-coupled galloyl/galloyl linking units of dimeric ellagitannins.[4a,22] Other galloyl/hexahydroxydiphenoyl interunit linkers are depicted in Scheme 5. For

Scheme 5



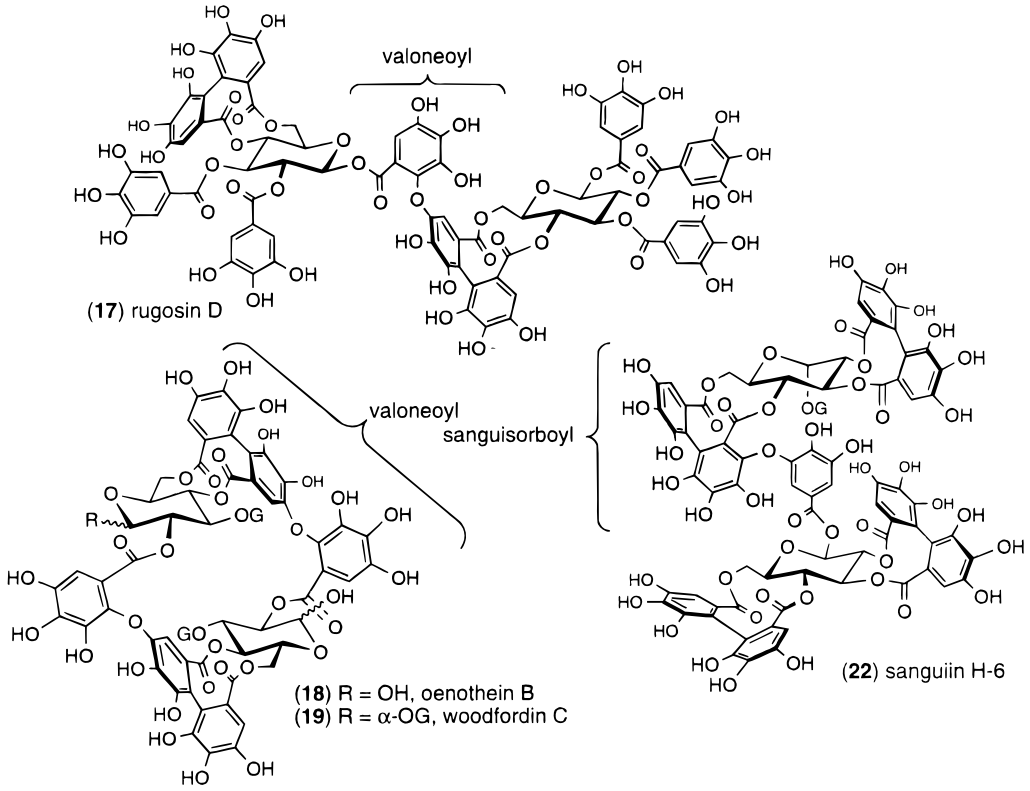
a: valoneoyl ester (cf. **17** and **18**/**19**)
b: tergalloyl ester[24,5f,g]
c: macaranoyl ester[5g]
d: sanguisorboyl ester (cf. **22**)
a + a "trimer": woodfordinoyl ester[25]
a + b dimer: euphorbinoyl ester[4a,5h,26]

example, the formation of the sanguisorboyl unit involves coupling between C(5) of a HHDP moiety and the C(3)-phenol of a galloyl moiety and is evident in sanguin H-6 (**22**).[5c,e,23] Participation of a C(3)-phenol of a HHDP moiety in coupling processes leads to the tergalloyl unit of, *inter alia*, eucalbanin C.[24] This diaryl ether bond type also occurs in concert with the valoneoyl-type diaryl ether species to give rise to the tetragalloyl euphorbinoyl linking unit of the euphorbins C/D.[4a, 26]

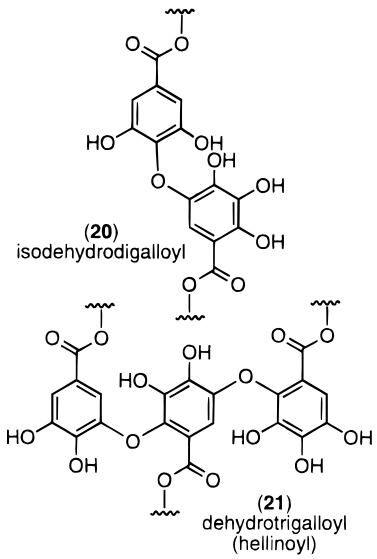
3. Further Modifications

Further structural variation, in addition to the aforementioned array of oxidative C−C and C−O coupling processes, characterizes several complex ellagitannin subclasses. In particular, subsequent biochemical transformations of either the HHDP unit or the anomeric carbon afford entry into the so-called "dehydrohexahydroxydiphenoyl" (DHHDP, **24**) and C-glycosidic ellagitannins, respectively. Of particular note is the apparently facile reactivity of an axial HHDP unit emanated at the 2,4-positions of the glucose core. Indeed, this biaryl group has never been observed as such in ellagitannin natural products, for it invariably experiences further *in vivo* modifications notably leading to the DHHDP ester

Scheme 6



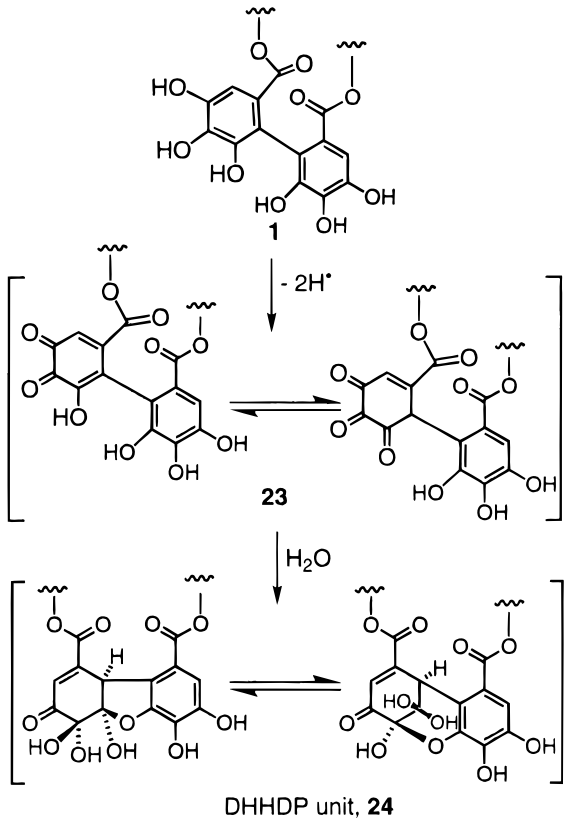
Scheme 7



group **24** (Scheme 8). This more highly oxidized ellagitannin structural entity is also found bridging the glucose 3,6-, 4,6-, and β-1,3-positions.[3a,5i,27] Schmidt suggested that this acyl unit originates in the dehydrogenation of an initially formed HHDP group (**1**) to furnish a quinonoid cyclohexenetrione (**23**) which is subsequently stabilized by hydration of one of the ketone carbonyls[27b,c,28] (Scheme 8).

Okuda[4d,14,29] later proposed that intramolecular hemiketalization in aqueous media gives rise to the equilibrium isomeric mixture depicted in Scheme 8, and exemplified in geraniin (**12**) and carpinusin (**13**) wherein the cyclohexenetrione acyl moiety is attached to the 4-position of glucose (Scheme 9). It is worth noting that chemical hydrogenation of **12**

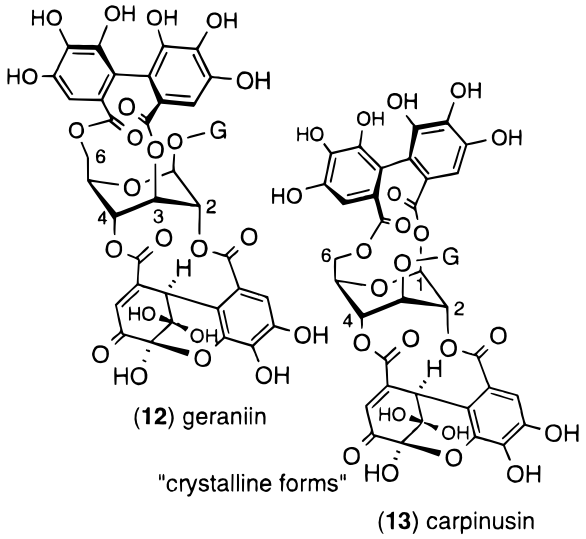
Scheme 8



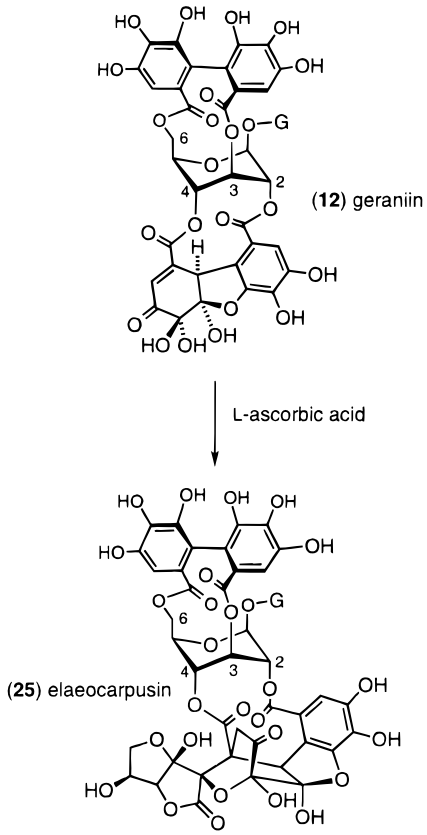
furnishes its 2,4-(*R*)-HHDP-containing putative biogenetic precursor which is readily hydrolyzed to give corilagin (**11**) (Scheme 3).[12a]

The 2,4-HHDP esters are also postulated to be unobserved intermediates in the biogenesis of elaeocarpusinoyl-bearing ellagitannins. These complex

Scheme 9



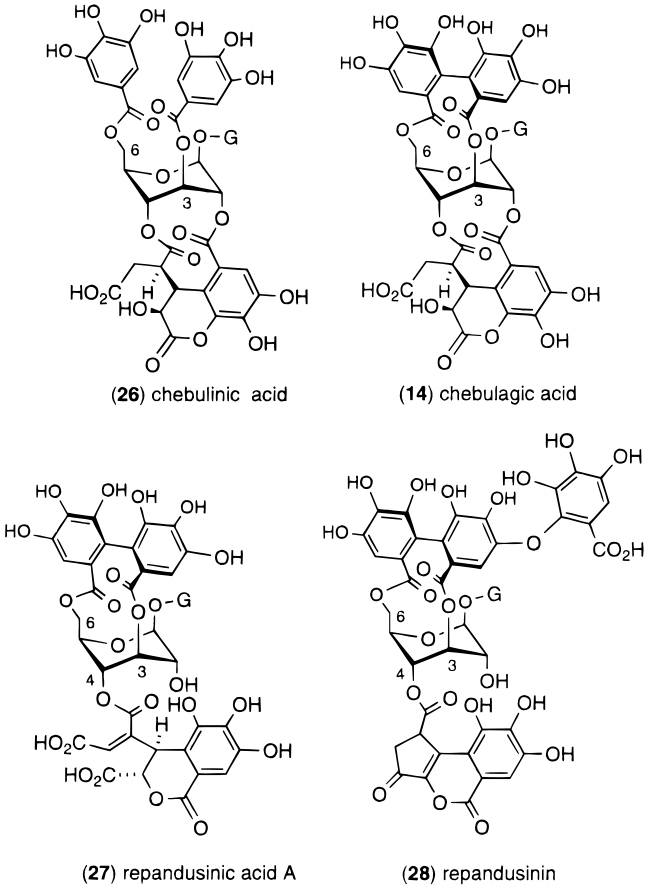
Scheme 10



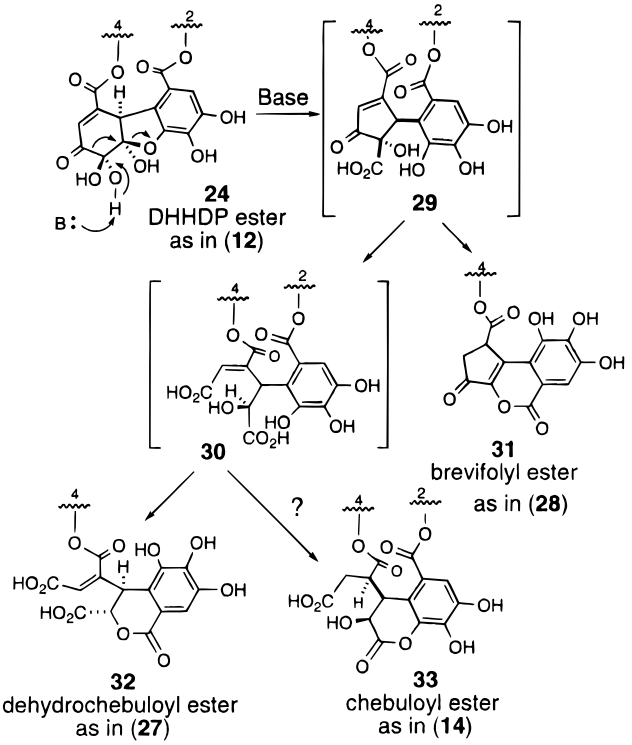
attachments could arise from reaction of L-ascorbic acid with 2,4-DHHDP esters. Okuda's "biomimetic" synthesis of elaeocarpusin (**25**)[5b,j,k] from ascorbic acid and geraniin (60% conversion) provides strong evidence for this possibility (Scheme 10),[30] although an alternative but complementary scenario utilizing dehydroascorbic acid as an oxidizing cosubstrate of an enzymically mediated conversion of 2,4-HHDP units into 2,4-DHHDP units, via elaeocarpusinoyls, has been investigated.[5j,l]

Another noteworthy structural modification of the galloyl-derived biphenyl functionality at the 2,4-positions of glucopyranose derivatives is contained within ellagitannins bearing dehydrochebuloyl (**32**)

Scheme 11

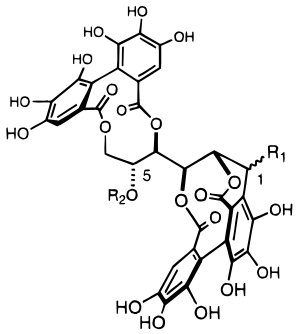


Scheme 12

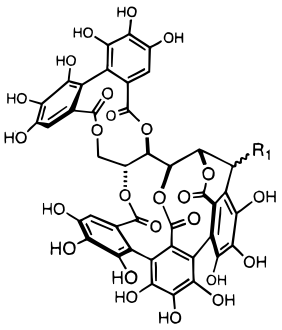


or chebuloyl (**33**) ester groups (Schemes 11 and 12). Typical examples of this subfamily are the crystalline chebulinic and chebulagic acids (**26** and **14**),[3g,13b−c,15,31] and repandusinic acid A (**27**),[5m] which features a dehydrochebuloyl group at the 4-position of β-1-galloyl-3,6-(*R*)-(hexahydroxydiphenoyl)-D-glucose

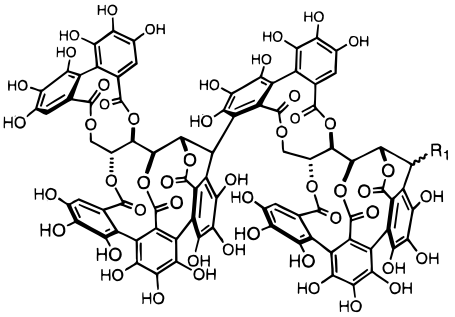
Scheme 13



(**33**) R_1 = β-OH, R_2 = G, stachyurin
(**37**) R_1 = β-OH, R_2 = H, 5-desgalloyl stachyurin
(**34**) R_1 = α-OH, R_2 = G, casuarinin
(**38**) R_1 = α-OH, R_2 = H, casuariin



(**35**) R_1 = β-OH, vescalagin
(**36**) R_1 = α-OH, castalagin



(**39**) R_1 = β-OH, roburin A
(**40**) R_1 = α-OH, roburin D

(Scheme 11). The structural relationship between chebulic acyl and hexahydroxydiphenic acyl groups was first recognized by Schmidt, who suggested that *in vivo* hydrolytic cleavage of one aromatic ring of a presumed 2,4-HHDP bearing precursor might provide the biogenetic link to the chebuloyl esters.[2,3g] Interestingly, geraniin (**12**) is converted into **27** in 17% yield upon brief treatment with aqueous sodium hydroxide (Scheme 12).[5n,32] The formation of chebuloyl (**33**) moieties through the intermediacy of naturally occurring 2,4-DHHDP ester groups could also have some biosynthetic relevance (Scheme 12).

The DHHDP ester group of **12** was alternatively contracted to a brevifolincarboxyl group (**31**) attached at the glucose 4-position (cf. section II.B), in 33% yield upon treatment with triethylamine in acetonitrile (Scheme 12).[5n,32] This brevifolyl ester group is found, *inter alia*, in the ellagitannins repandusinin (**28**)[5m] (Schemes 11 and 12) and heterophylliin E.[33]

Further structural variation is evident among the C-glycosidic ellagitannin metabolites wherein the glucose core exists in its open-chain form. Key representatives of this subclass include the epimeric monomeric species stachyurin (**33**)/casuarinin (**34**), and vescalagin (**35**)/castalagin (**36**) (Scheme 13).[5o,34] The presence of the 2,3-(*S*)- and 4,6-(*S*)-HHDP units conceivably relates them biogenetically to pedunculagin (**9**) and/or casuarictin/potentillin (**7**/**8**) with which they generally co-occur in plants.[3a] Evidence supporting this putative origin of C-glycosides can be found in the work of Tanaka, in which **9** was converted to the known ellagitannins 5-desgalloylstachyurin (**37**)[5p,q] and casuariin (**38**)[34a−c] in 34% and 6% yield, respectively, upon moderate heating under slightly basic conditions.[5r] Roburins A/D (**39**/**40**)[35] are examples of C-glycosidic dimers composed of two vescalagin/castalagin (**35**/**36**) moieties. Of particular note for biomimetic approaches to these compounds is the TFA-mediated conversion of **35** to **39**,[36] which likely involves the intermediacy of a vescalagin-derived benzylic carbocation. Such C-1 cationic species have also been suggested as transient intermediates in the generation of flavan-3-ol- and lyxose-subsituted C-glycosidic ellagitannins.[3a,5s−v,37]

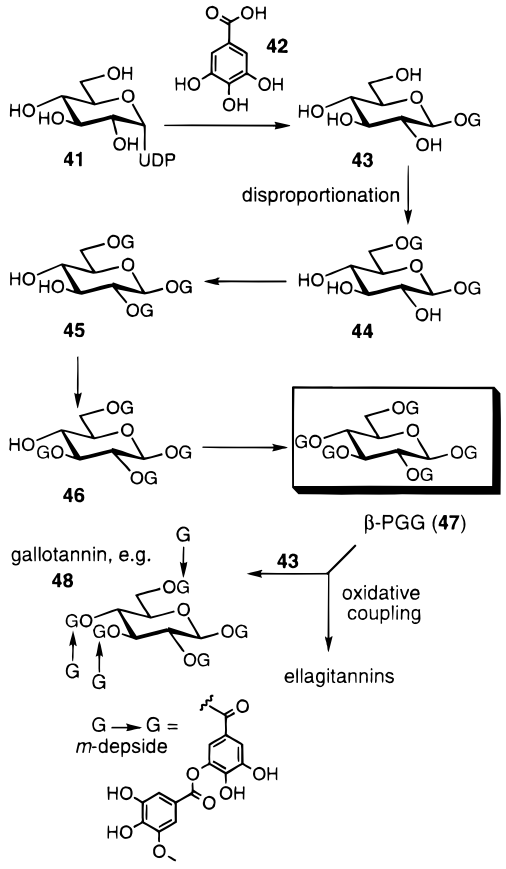
Despite these seemingly endless structural variations among ellagitannin natural products, it must be recognized that the major challenge in their total syntheses resides in the ability to generate galloyl-derived biphenyl moieties in a stereoselective fashion at different locations on the glucose core. A discussion of the biosynthetic pathway(s) for assembly of the key ellagitannin precursors becomes relevant since it may provide valuable clues for developing successful biomimetic routes to access ellagitannins by total chemical synthesis.

B. Biosynthesis

1. β-PGG and the Gallotannins

The ultimate products of metabolism of gallic acid (**42**), ellagitannins and gallotannins, emanate from galloylation of D-glucopyranose.[3] This acylation process, whose enzymology has been almost completely elucidated by Gross,[38] commences with the produc-

Scheme 14



tion of β-glucogallin (**43**, β-1-galloyl-D-glucose) from UDP-glucose (**41**) and free gallic acid (**42**). This monogalloylated species then serves as a primary, but not exclusive, galloyl group donor/acceptor in a series of transgalloylation steps successively leading to β-1,6-digalloyl-D-glucose (**44**), β-1,2,6-trigalloyl-D-glucose (**45**), β-1,2,3,6-tetragalloyl-D-glucose, (**46**) and finally, β-1,2,3,4,6-pentagalloyl-D-glucose (**47**, β-PGG) (Scheme 14). The metabolite β-PGG (**47**) is considered to be the common precursor of both ellagitannins and gallotannins.[3a,c,g,39] The presence of **47** in *Quercus robur* tissue culture, but the absence of further elaborated galloyl and HHDP esters (which are metabolized by the fully differentiated plant), provide some circumstantial evidence supporting this proposal.[3d,9a,40] Gallotannins would result from attachment of additional galloyl groups to the free phenolic hydroxyls of the β-PGG molecule (**47**), resulting in meta-depsidic bonds (Scheme 14). Gallotannin extracts, such as Chinese gallotannin (**48**, tannic acid) depicted in Scheme 14, are usually composed of mixtures of related species differing from one another by the frequency, location, and length of the chains of these depsidically linked galloyl ester groups.[3a,c,g,5w,x,38b,41]

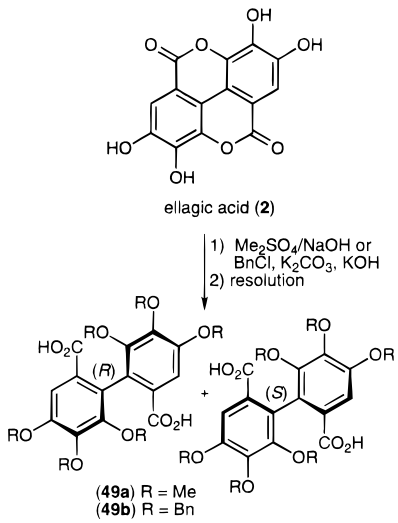
2. The Ellagitannins: The Schmidt–Haslam Hypothesis

Although the enzymology of the biosynthesis of monomeric ellagitannins still remains a mystery, Schmidt and Mayer's proposal,[2] which states that HHDP moieties descend from oxidative C−C coupling transformations of appropriately juxtaposed galloyl groups on the β-PGG molecule, constitutes the basis of current dogma in ellagitannin chemistry. This hypothesis offers (1) a logical and highly hierarchical picture of the construction of ellagitannins, while emphasizing the putative role of β-PGG as the keystone molecule, and, more importantly for the sake of synthesis endeavors, (2) a rationale for the apparent stereochemical outcome of HHDP formation (*vide infra*). If the scenario implied by 1 is correct, ellagitannins with unacylated glucose hydroxyls would result from hydrolysis of fully galloylated monomers or oligomers within the plant cell, with concommitant release of either gallic acid (**42**) or ellagic acid (**2**). It is, however, possible that hydrolysis may also occur *post mortem*. This unfortunate ambiguity raises concerns when identifying isolates as *bona fide* natural products.[3a]

Schmidt *et al.* obtained the optically active hexahydroxydiphenic acid derivatives **49a**/**b** via resolution of their racemates which were generated by hydrolysis/methylation (or benzylation) of ellagic acid (**2**) (Scheme 15).[42]

These early workers also demonstrated, on the basis of the results from hydrolysis of methylated HHDP esters which furnished the hexamethoxydiphenic acid in its native atropisomeric form, that the 3,6-HHDP unit of corilagin (**11**) exists in the dextrorotary form (*R* configuration)[14b] and that the 2,3- and 4,6-HHDP units of pedunculagin (**9**) are levorotatory forms (*S* configuration).[11b,43] These assignments have been confirmed by CD spectroscopy[44] and generalized to most 2,3-, 4,6-, and 3,6-HHDP containing molecules.[3a,9a,12a] Cercidinins A/B,

Scheme 15



cuspinin,[5y] platycaryanin D,[5f] and nupharin A[5z] are exceptions to this generalization. The 1,6-HHDP ester groups invariably exist in an *S* atropisomeric form.[3a]

Haslam then postulated that the apparent diastereoselectivity of biphenyl bond formation is simply dictated by the geometrical constraints imposed by the glucopyranose ring.[3g,9a,12a] It then follows that enzymic intervention would not be an absolute requirement for achieving stereochemical control. It is worth noting that conceptually related cases of stereochemical induction can be found in the "biomimetic" conversion of polyolefins into polycyclic terpenoids whose ring fusion geometry is, following the Stork−Eschenmoser postulate,[45] induced by the double-bond geometry of the olefin and the conformation adopted by the polyene chain during cationic cyclization.[46] In the ellagitannin series, the successful "biomimetic" diastereoselective bigalloyl coupling transformations discussed in section II provide the first demonstrations of the validity of the Schmidt−Haslam hypothesis.

C. Biological Activity

1. Traditional Uses

The defining chemical attribute of ellagitannins and gallotannins is their ability to engage in noncovalent (and possibly covalent) recognition/modification of biological macromolecules, such as proteins and polysaccharides.[3c,47] This property of polyphenolic substances, termed astringency, underlies their utilization in traditional tannage of animal hides, a process during which tannin molecules from vegetable extracts interact with the amino acid side chains in amorphous regions of the fibrillar skin protein collagen to produce nonputrescible leathers.[3c] Complexation between polyphenols and mucousal glycoproteins is also believed to cause the characteristic astringent taste of polyphenol-containing foodstuffs and plant-derived beverages.[3c] The various curative and palliative effects of certain traditional herbal medicines principally depend upon their ellagitannin/gallotannin composition.[48] The continuing search for new pharmaceutical agents has recently

placed polyphenol-rich folk medicines in the spotlight and has fueled many research endeavors aimed at elucidating the structure of biologially active ellagitannins. The molecular mechanism(s) which govern polyphenol−protein interactions have not yet been unraveled, but some interesting observations have been made on the differences in molecular recognition processes of ellagitannins and gallotannins.[3c,47l,o,49]

2. Gallotannins

Numerous experimental inquiries revealed the ability of gallotannins to recognize and bind with varying affinities to almost all proteins examined, including bovine serum albumin, gelatin, caseins, β-glucosidase, hemoglobin, amylase, lipase, and peptidases.[3c,47] Model studies, conducted with a series of tri- to pentagalloylated D-glucoses (Scheme 14) and bovine serum albumin as a test case protein, indicated gallotannin−protein effective dissociation constants to be typically in the millimolar range.[47l] This type of association is likely a consequence of reversible complexation governed by hydrogen bonding and hydrophobic interactions between gallotannin phenolic moieties and surface protein functionalities. The highest affinities are observed for conformationally flexible, proline-rich proteins.[47a,b,l,m,48a] A collorary to this conformational dependence on binding is that the more rigid HHDP-bearing ellagitannins appear to be less prone to participate in protein surface binding.[47l,o,49] This generalized protein recognition capability of gallotannins raised some concerns about their significance and functional role in the plant,[3e,50] but it seems logical to envisage the gallotannins as participants in the plant chemical defense against pathogenic microbes and herbivores. The development of astringent taste, the limitation of dietary protein accessibility, and the inhibition of digestive enzymes are commonly cited consequences of protein damage by complexation/precipitation with gallotannins, and demonstrate the antinutritional effects of these polyphenols.[3e,47e−h,50a,b,51,52]

3. Ellagitannins

The proliferation of structural complexity in the ellagitannin family of higher plant secondary metabolites is at first puzzling when considering their functional role in the plant. An intriguing, although biochemically simplistic rationale can be drawn from the apparent faculty of the plant's metabolic machinery to generate libraries of analogs from which key molecules could be selected to engage in highly specific interactions with, *inter alia*, target enzymes. Unlike the conformationally flexible gallotannins, which are more likely to accomodate the varying terrain on protein surfaces, ellagitannins are much less successful at protein surface recognition.[47l,o,49] However, their more rigid structures, borne out of biphenyl bond formation, may provide them with a well-defined three-dimensional scaffold capable of presenting an array of potential H-bonding loci and hydrophobic residues to a target protein. This preorganization might then enhance the opportunity for precise recognition processes, which may or may not, of course, be of any benefit to the plant.

In fact, ellagitannins are believed to be the principal active substances of several tannin-containing plants used in folk medicine.[48] High levels of anticancer and antiviral activity have been observed for pure isolated ellagitannins. Their apparent efficacy with disease-associated target proteins typically falls into the micromolar to nanomolar range. For example, several ellagitannins exhibit remarkable inhibitory activity against promising anticancer targets such as the DNA topoisomerases. Tellimagrandin II (**3b**), pedunculagin (**9**), geraniin (**12**), chebulagic/chebulinic acid (**14**/**26**), elaeocarpusin (**25**), vescalagin/castalagin (**35**/**36**), and the dimer sanguiin H-6 (**22**) are all inhibitors of human DNA topoisomerase II function *in vitro*, having IC_{100} values of 200−500 nM, and are 100- to 250-fold more potent than the clinically useful topoisomerase II poison etoposide (VP-16).[53] Chebulagic acid (**14**) is the most potent anti-topoisomerase I agent yet reported, showing 10- to 50-fold more activity than camptothecin (and derivatives) in inhibiting DNA relaxation.[54] Geraniin (**12**), chebulagic acid (**14**), vescalagin/castalagin (**35**/**36**), and the lyxose-substituted C-glycoside grandinin[5o,s] display selective cytotoxicity against human solid tumor cell lines with EC_{50} values ranging from 0.09 to 0.84 μM against RPMI-7951 melanoma cells.[55]

Remarkable *host*-mediated antitumor activities are displayed by some dimeric ellagitannins. Coriariin A (**15**), agrimoniin (**16**), rugosin D (**17**), oenothein B (**18**), and woodfordin C (**19**) all exhibit strong tumoricidal activity at 5−10 mg/kg in mice inoculated with sarcoma-180 cells.[20a,56] Agrimonin (**16**) and oenothein B (**18**) also shows strong antitumor effects against MM2 ascites-type and solid-type tumors. A single dose of 10−30 mg/kg of **16** or **18** caused almost complete rejection of the tumor in mice inoculated with MM2 cells.[57] Current *in vitro* studies on the molecular basis for these antitumor activities support a mechanism in which these dimers stimulate the release of interleukin-1β from mouse adherent peritoneal exudate cells and from human peripheral blood mononuclear cells in a dose-dependent manner.[57c,58a] Agrimoniin (**16**) also has been demonstrated to increase the activity of natural killer cells in mice.[58b] It would thus appear that the aforementioned dimeric ellagitannins are not directly cytotoxic, but rather act as immunomodulatory agents to enhance the host immune defense system.[57b,58] It is worth mentioning that the agrimoniin-rich plant *Agrimonia pilosa* Ledeb has been used in China for the treatment of cancer in humans.[59]

Antiviral activities among the ellagitannins have also been reported.[48f,g,i,60] For example, tellimagrandin I (**3a**), geraniin (**12**), the dimers coriariin A (**15**), rugosin D (**17**), and oenothein B (**18**) inhibit replication of *Herpes simplex* virus *in vitro* by blocking viral adsorption to cultured cells with EC_{50} ranging from 20 to 100 nM and $CC_{50} > 16$ μM.[48g,60b] Tellimagrandin I (**3a**) and pedunculagin (**9**) inhibit reverse transcriptase activity in mouse leukemia virus-infected cells with EC_{50}'s of 50 and 130 nM, respectively.[61] Coriariin A (**15**), agrimoniin (**16**), oenothein B (**18**) and the tetramer trapanin B are potent inhibitors of HIV replication *in vitro*.[48f,g,i] Trapanin B inhibits HTLV-IIIB adsorption to MT-4 cells with $EC_{50} = 0.86$ μM, while $CC_{50} = 12.5$ μM. Preliminary

data suggest that both inhibition of virus adsorption to the cells and inhibition of HIV reverse transcriptase activity are involved in this antiviral effect.[48g]

D. Problems for Synthesis

The challenges for organic synthesis posed by the ellagitannins center on achieving selectivity amidst all of the potential structural diversity that these species offer. Issues of chemoselectivity, regioselectivity, and stereoselectivity pervade any consideration of the modes of galloyl coupling that form the crux of any synthesis effort. Thus, efficiency in synthesis design and brevity in synthesis execution will only attend those strategies which address these overriding selectivity issues head on.

A hierarchy of problems associated with assembly of these modular plant metabolites can be identified. Paramount is the development of an efficient means to join galloyl moieties on the same glucose core to form the HHDP unit which defines these natural products. This carbon−carbon bond-forming reaction must satisfactorily address both the stereochemical and the regiochemical demands of biaryl synthesis. Thus, selection of a desired pair of galloyl groups for coupling in a pergalloylated glucose substrate when several combinations are possible places a premium on developing efficient means to differentiate between the regioisomeric galloyl groups. In addition, control of atropisomer formation between galloyl rings destined to be united represents a transformation (i.e., asymmetric synthesis of biaryls) which remains at the forefront of current art in organic synthesis.

Carbon−oxygen bond formation between intermolecularly disposed galloyl rings defines the next task in ellagitannin synthesis. In this transformation as in the C−C coupling case, control of the regiochemistry of bond formation is required for success (cf. Scheme 5). The electron-rich nature of the aromatic rings involved and the sterically crowded environment surrounding the coupling sites place these substrates beyond the high-yielding regimes of current diaryl ether synthesis methodology. Therefore, development of new phenol *O*-arylation chemistry is indicated.

The last issue of selectivity that is confronted in ellagitannin synthesis involves acylation chemistry at the anomeric carbon of the glucopyranose ring. Preparation of either the α- or the *β*-stereochemistry at C(1) upon demand, irrespective of the functionality at C(2), would in principle allow access to any ellagitannin structure. Preliminary results suggest that there is nothing inherently complicating with these particular glucose derivatives, and so application of standard anomeric hydroxyl acylation chemistry to ellagitannin precursors may suffice.

Implicit in the development of chemistry for imposing selectivity on polyhydroxylated molecules is the positive and the negative roles that protecting groups play in achieving success. Thus, the trade-off between control of reaction site on the one hand and inefficiency in synthesis on the other is apparent. Judicious choice of these necessary inconveniences will be critical for favoring the former result while minimizing the penalty incurred in the latter circumstance. The value of appropriate protecting groups becomes all the more obvious when manipulation of the end products are considered. The well-documented difficulties associated with purification and isolation of the perhydroxylated natural products[44a] themselves highlights the absolute necessity of preparing a readily purifiable penultimate synthetic precursor which, upon simple deprotection, will deliver ellagitannin product free of impurities. Thus, the protecting groups not only must modulate the reactivity of the attached phenolic rings but also must provide "handles" compatible with delicate chromatographic purification at the end of the synthesis.

The ellagitannins provide a novel and underexplored testing ground for organic synthesis. As in any new area, challenges will lead to opportunities, and unexpected observations can presage development of new chemistry. Details of the initial forays into this fascinating area of chemistry are described below, and it is clear that many interesting problems remain, as yet, beyond the horizon.

II. Strategies and Results

A. C−C Bond Formation via Galloyl Ester Coupling

1. Strategy

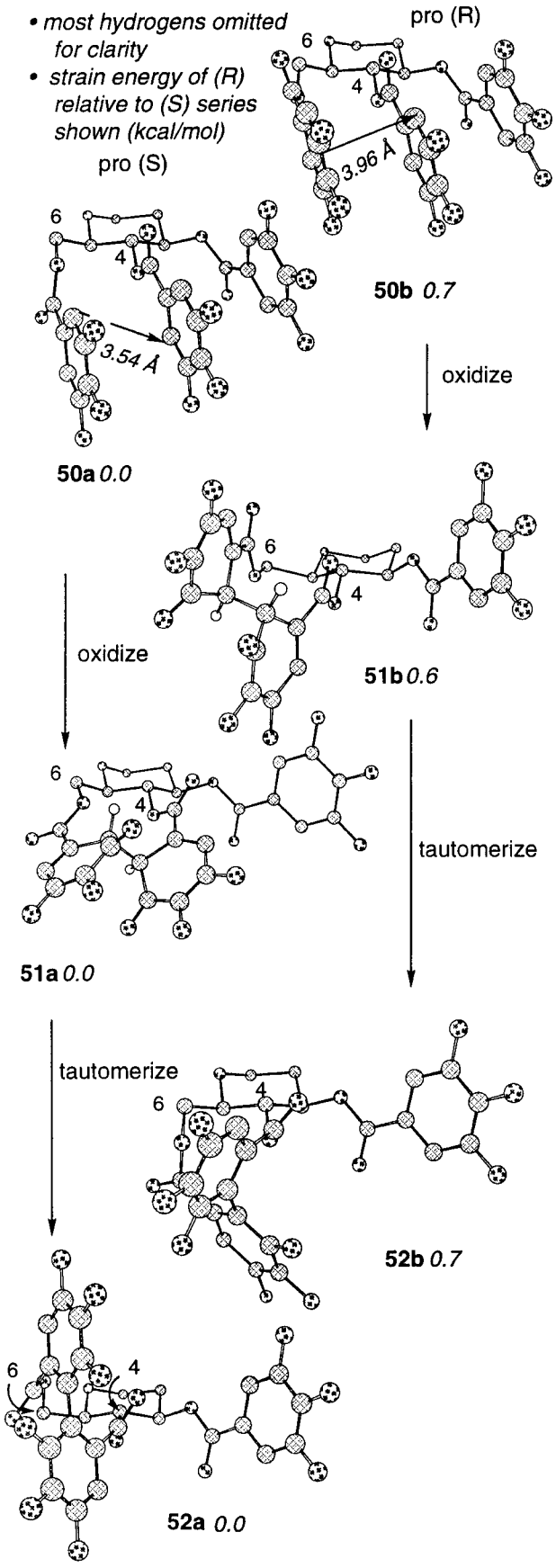
Successful construction of a glucose-attached HHDP unit requires effective solutions to two key problems: (1) coupling of two galloyl esters with preservation of the ester linkages to the glucose core, and (2) rigorous stereochemical control of bond formation (atropdiastereoselectivity). The early recognition of the role that ellagitannins played in human commerce led to numerous structural/synthesis studies of specific members of this natural product class. Galloyl coupling was appreciated at the outset of these studies, and the original reports on oxidative galloyl coupling employing either gallic acid itself (1868)[62a] or ethyl gallate (1871)[62b] afforded the C−C-coupled species ellagic acid (**2**) long before the details of its structure were secured.[62c] Unfortunately, this auspicious beginning did not presage facile entry into the glucose bearing HHDP unit characteristic of the ellagitannins, as numerous subsequent galloyl oxidative coupling investigations over the succeeding 100 years consistently furnished either ellagic acid or benzotropolone derivatives with only occasional (and low yielding) glimpses of nonlactonized product[9a,38b,62] In particular, recent studies by Mayer on oxidation of galloylated glucose derivatives with horseradish peroxidase/H_2O_2 as a presumably "biomimetic" oxidant led only to ellagic acid and not to a glucose-attached HHDP unit as hoped.[62j] This final, conspicuous failure at HHDP synthesis emphasized the seeming inevitability of ester hydrolysis upon attempted coupling of fully unprotected galloyl esters *in vitro* and reinforced the notion that modulation of the reactivity of the galloyl moiety (and the coupled product) by judicious introduction of appropriate protecting/activating groups on the phenolic hydroxyls was a *sine qua non* for successful HHDP synthesis. Toward this end, several different ver-

sions of protected galloyl esters were screened for their resistance to ester cleavage upon (or subsequent to) oxidative coupling; these results are detailed below (section II.A.2).

The second critical strategic issue raised by the conversion of glucose-bound galloyl esters to an HHDP unit is the stereochemistry of bond formation. The speculation by Schmidt and Haslam (*vide supra*) on the biosynthetic basis for generating the atropisomer featured in the natural products provides a framework to explore the chemical particulars of bond formation. Specifically, the Schmidt−Haslam hypothesis does not address the atomic level details by which the postulated conformational preferences of the glucose-bound galloyls are translated into stereochemical imperatives. Absent hard structural data (e.g., X-ray) on the coupling precursors, molecular mechanics (MM)-based analyses of galloyl juxtaposition in these species constitutes the next best (only?) means to access this information.[63] Thus, MM-based searches of conformational space for model precursors to HHDP units at the 4,6-, 2,3-, and 4,6- when the 2- and 3-positions already bear an HHDP unit were pursued in an effort to illuminate this issue.

Examination of the trigalloylated substrate **50**, the coupled dione intermediates **51a/b**, and the final model HHDP-containing products **52a/b** by this technique afforded families of low-energy conformations for each compound that only differed by rotation about the aryl-OH linkages (phenolic hydrogens not shown). The lowest energy species for each series which appeared to give divergent stereochemical results are shown in Scheme 16 along with their relative (*R*-to-*S*) strain energies. The hexahydroxy trigalloylated precursor **50** appears to exist in two low-energy conformers **50a** and **50b** which differ by only 0.7 kcal/mol in strain energy. Conformer **50a** has a relatively "clockwise" tilt of the galloyl units in the rendition shown, and if C−C bond formation ensues between the closest pair of intergalloyl carbon atoms, the dione **51a** would result and the ultimate stereochemistry (atropisomer) is now set. Simple tautomerization of **51a** leads unambiguously to the (*S*)-HHDP-containing product **52a**. Similarly, the alternative starting conformer **50b** has a "counterclockwise" tilt of the galloyl rings which aligns a different (diastereotopic) pair of carbons as nearest neighbors. Proximity-induced bond formation upon oxidation of **50b** would furnish dione **51b** and then the (*R*)-HHDP ellagitannin model **52b**. These calculations suggest that the modest energy difference which attends substrate conformers **50a**/**50b** is sustained as starting materials proceed to diastereomeric products (**50a** → **52a**; **50b** → **52b**). Different modes of galloyl coupling, such as "straight across" the inter-ring gap rather than along the "diagonals" shown, leads to dione intermediates which are at least 0.6 kcal/mol higher in strain energy than the diones **51a/b**. This alternative coupling geometry is not considered further in the first generation analysis presented here. Thus, the essence of this calculational study distills down to identification of two structural features as the key control elements in linking conformational preference with stereochemical outcome: (1) a preferred "clockwise" tilt of galloyl rings, and (2) bond formation between the most proximal carbon−carbon pair. These results suggest that a biomimetic approach to galloyl coupling which

Scheme 16



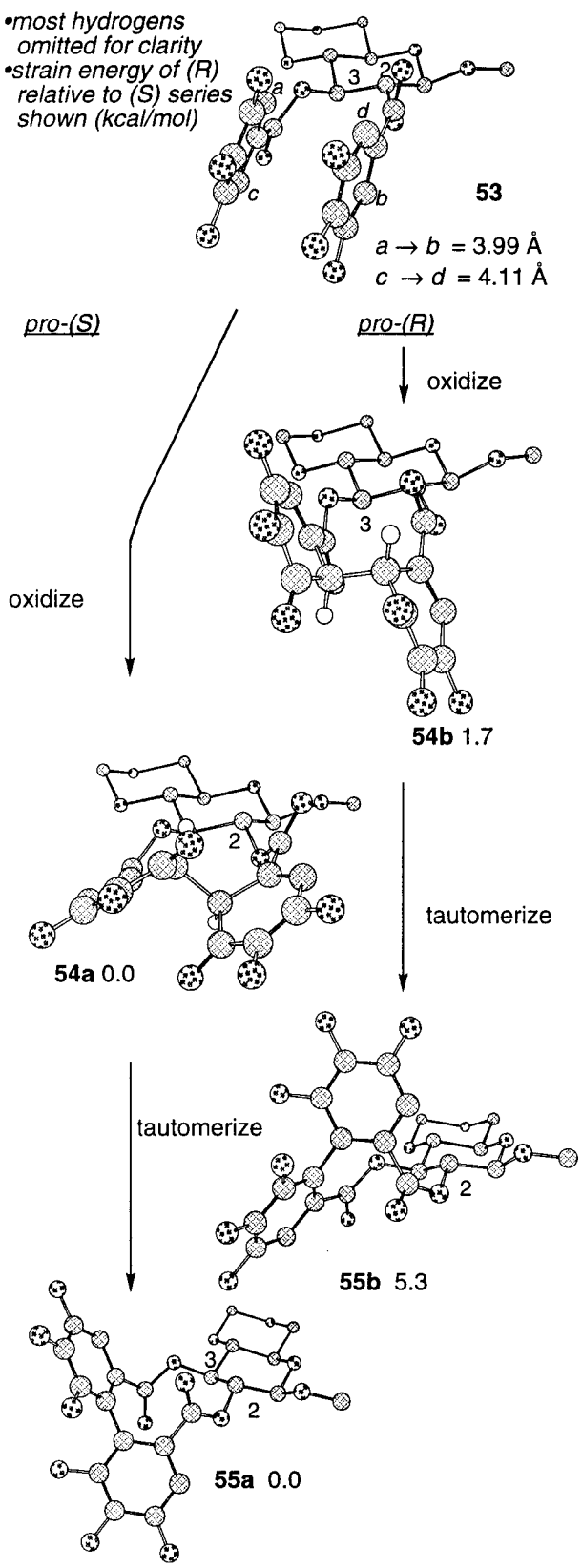
takes advantage of existing conformational biases is a sound strategy for effecting stereoselective HHDP formation at the 4- and 6-positions of glucose.

A similar analysis was applied to the coupling preferences of galloyl groups attached to the 2- and 3-positions of a glucose derivative that has a methylene acetal spanning O(4)/O(6) and an anomeric β-methyl ether, (Scheme 17). In this instance, no species which featured O(2)- and O(3)-galloyl groups with a "counterclockwise" tilt could be identified within 2 kcal/mol of the "global" minimum "clockwise" tilted conformer **53**. In contrast to the 4,6-coupled series, however, the *pro-S* carbon pairing was only marginally closer than the alternative *pro-R* combination of inter-ring atoms (3.99 Å vs 4.11 Å, respectively). The energetic difference between the *pro-S* and the *pro-R* channels become manifest at the next stage of the transformation, where approximately 1.7 kcal/mol of additional strain energy attends the *pro-R* coupled species **54b** when compared with its *pro-S* diastereomer **54a**. This differential strain energy is amplified upon going to the (*S*)-HHDP and (*R*)-HHDP containing products **55a** and **55b**, respectively. Thus, these calculations suggest that the preference for 2,3-coupled (*S*)-HHDP product becomes apparent along the reaction coordinate as ground state **53** proceeds to the diastereomeric transition states that precede formation of **54a** and **54b**. This stereochemical preference is in accord with the vast majority of the naturally occurring 2,3-HHDP containing ellagitannins.

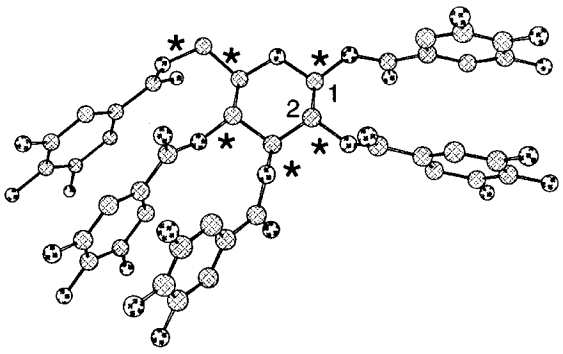
The biosynthetic sequencing of 2,3- and 4,6-galloyl coupling that precedes *in vivo* assembly of ellagitannins such as pedunculagin (**9**) is unknown. Interestingly, however, exploration of the conformational space about the rotatable bonds in the presumed biosynthetic precursor β-pentagalloylglucose (**47**) did not permit identification of a single low-energy species among the >100 discrete minima located within 2.5 kcal/mol of the "global" minimum structure **56** which had galloyl rings extending from positions 2 and 3 juxtaposed for cyclization. Rather, the galloyl ring at O(2) aligned comfortably with the galloyl ring at the anomeric position, while the O(4) and O(6) galloyl esters adopted the adjacent arrangement with a *pro-S* tilt (cf. **50a**) in the low-energy conformations of **47**. In contrast, a similar analysis of the 4,6-coupled derivative of β-pentagalloylglucose (**47**) [e.g., tellimagrandin II (**3b**)] led to the intriguing observation that the O(2)/O(3) aligned species **57** was equienergetic with the O(2)/O(1) alternative. Thus, these calculations tolerate an interpetation wherein appropriate alignment for coupling of the O(2)/O(3) galloyls is energetically accessible only when the O(4)/O(6) galloyls have already been coupled. From this perspective, ellagitannins such as pterocaryanin C (**4**) (2,3-coupled; 4,6-uncoupled) might then require enzymic intervention to enforce proximity of the O(2)/O(3) galloyls. Conversely, pterocaryanin C (**4**) might not be a product of the primary metabolism of β-pentagalloylglucose, but rather originate through galloylation at O(4) and O(6) of a 2,3-HHDP containing molecule.

Protecting group manipulations in the course of a total synthesis effort directed toward pedunculagin

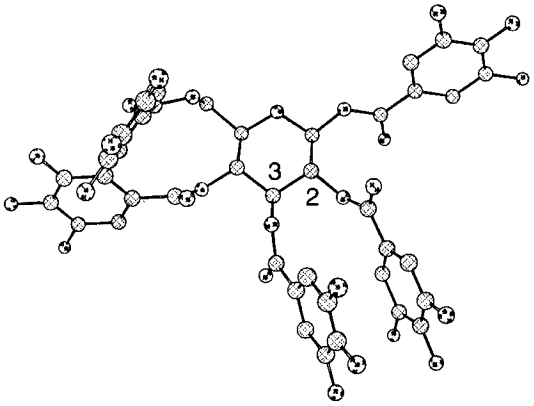
Scheme 17



(**9**) can be minimized if the 2,3-HHDP unit is installed first, followed by 4,6-galloyl coupling to deliver the fully coupled glucose core (*vide infra*). Whether the comfortable *pro-S* alignment of the 4- and 6-galloyl groups described earlier (Scheme 16) will be perturbed by the rigidifying influence of a resident 2,3-HHDP unit remains an unresolved issue. A conformational study of an appropriate model system



56 "global" minimum energy conformer of β-pentagalloylglucose **47** (5000 step search about bonds marked with an *). Hydrogens omitted for clarity.



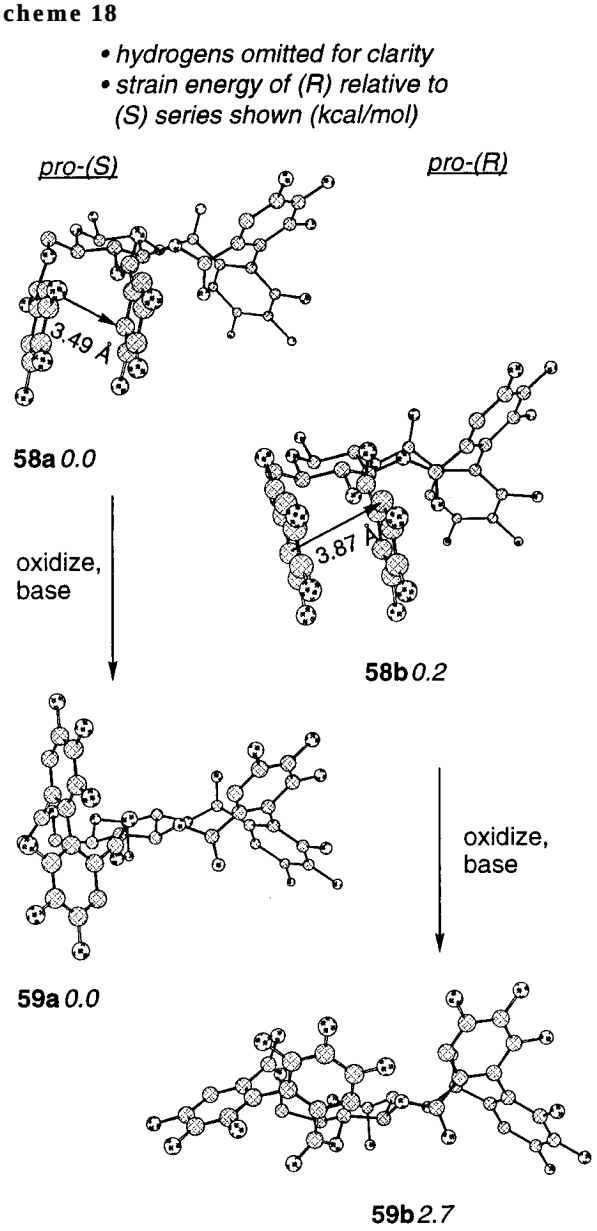
57 "global" minimum energy conformation of tellimagrandin II (**3b**). Hydrogens omitted for clarity.

58 (Scheme 18) helps allay these concerns. The desired *pro-S* clockwise tilt of the galloyl appendages in **58a** stands only 0.2 kcal/mol more favorably disposed than the *pro-R* counterclockwise alternative **58b** when an HHDP unit is already in place at the 2,3-positions of the pyranose core. However, in analogy with the prior computational study described in Scheme 17, the preference for the *S* reaction manifold is increased as these *pro-S* and *pro-R* substrates proceed on to coupled products **59a** and **59b**. In this instance as well, the calculated outcome of coupling is consistent with the biosynthetic observations and help buttress a biomimetic synthesis strategy which relies on the substrate's natural conformational preferences to deliver product with the desired biaryl stereochemistry.

2. Model System Studies[64]

The long history of frustrated HHDP synthesis attempts underscores the minimal tolerance that this transformation is likely to display to variation in reaction/reagent conditions. Incremental optimization studies based on earlier work lacked both a starting point and a direction to pursue, and hence did not appear to be a productive first line of inquiry. Rather, an Edisonian approach was adopted, wherein a family of six related digalloyl substrates **61a**−**f** of varying oxidation potential was crossed with a slate of common phenolic (and aromatic ether) oxidants,

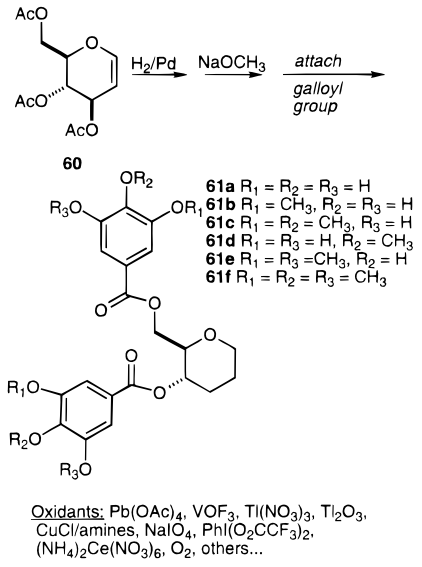
Scheme 18



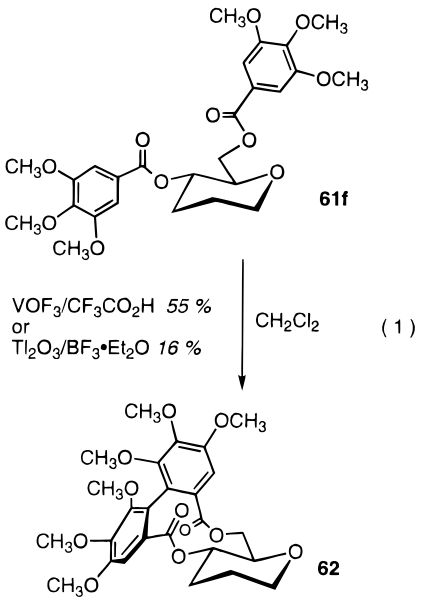
(Scheme 19). "Hits" in the resulting matrix of experiments could then serve as starting points for further optimization studies. Thus, the 4,6-digalloylated model substrates were readily prepared from D-glucal triacetate (**60**) and the appropriately protected galloyl species. These differentially methylated substrates were expected to display varying oxidation potentials as a function of number and position of methyl ether, in accord with much precedent.[65] The reagents chosen included reputed one-electron and two-electron oxidants, although the mechanistic details which underlie the actual sequence of electron and proton transfers remain obscure in most cases.

Ultimately, successful coupling was achieved with just two digalloylated substrates (**61c** and **61f**) and three oxidants ($Pb(OAc)_4$, VOF_3, Tl_2O_3) (eqs 1 and 2). Both of the potent aryl ether oxidants VOF_3 and Tl_2O_3 mediated the oxidative cyclization of the fully methylated precursor **61f** to furnish a permethylated version of the 4,6-coupled HHDP unit in **62**. Unfortunately, incompatibility with sensitive functionality eventually doomed these couplings. The highly acidic

Scheme 19

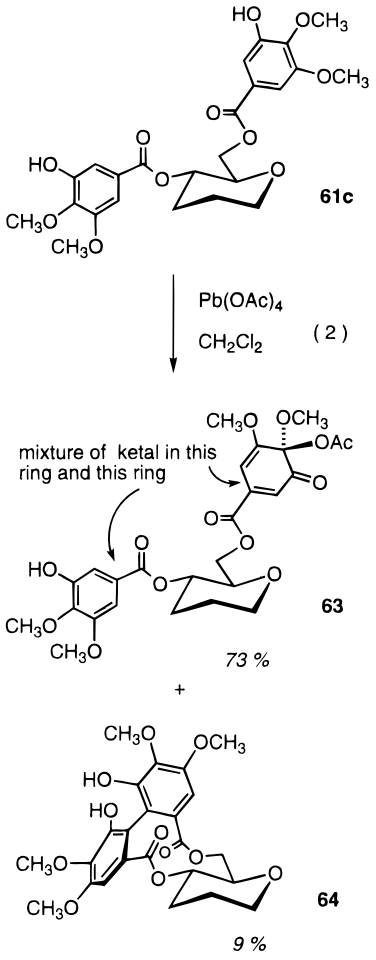


medium required for these oxidations proved to be an insurmountable liability in subsequent studies,



where a perbenzylated analog of **61f** rapidly succumbed and no oxidative cyclization products could be identified. Other phenol protecting groups (*i*-Pr, *p*-nitrobenzyl) were equally compromised. Demethylation studies with **62** were met with degradation of the HHDP unit, and so this promising approach was reluctantly abandoned as unsuitable for application to the more delicate substrates required for natural products synthesis.

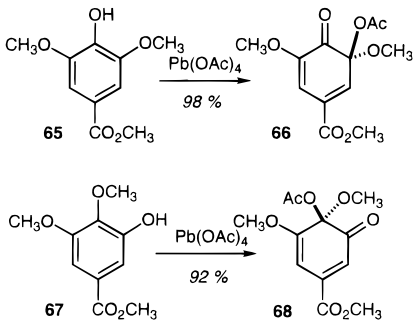
A more promising approach evolved from combination of the unsymmetrically methylated digalloyl substrate **61c** and $Pb(OAc)_4$, (eq 2). Thus, two types of products resulted from this pairing: an orthoquinone ketal mixture **63** in majority, and the HHDP-containing tetramethylated bicycle **64** as a minor component of the reaction. The mildness of the conditions ($T = -25$ °C → 0 °C, pyridine tolerated) suggested that this reaction was a viable candidate for yield optimization studies and could perhaps serve as the basis of a general strategy for ellagitannin synthesis.



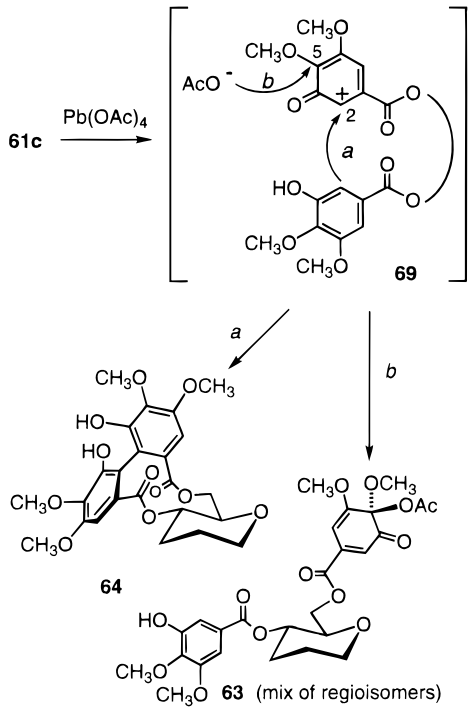
It is critical to note that *all* HHDP-containing coupling products produced in these preliminary studies (i.e., **62**, **64**) were formed as strictly the *S* atropisomers as indicated by CD spectroscopy. No evidence, even as minor (<5%) components, for any "leakage" to the *R* manifold could be obtained. Thus, the predictions of the Schmidt−Haslam hypothesis as well as the subsequent MM-based analysis were borne out in these relatively simple cases. That **64** was formed as a single regioisomer is interesting but of no immediate consequence in synthesis.

Concurrent oxidation studies with simple galloyl monophenols and $Pb(OAc)_4$ (Scheme 20) revealed some of the scope of this oxidation reaction. Thus, nearly quantitative conversion of either the symmetrical monophenol **65** or its unsymmetrical counterpart **67** to orthoquinone monoketals **66** and **68**, respectively, was accomplished by Pb(IV) oxidation. Quinone ketal **66** is thermally stable, while the dienone **68** dimerizes via $[4\pi + 2\pi]$ cycloaddition upon warming in methanol.[64b] Both compounds are competent electrophiles, and this characteristic will be used to advantage in subsequent galloyl coupling chemistry (*vide infra*). It is interesting to note that no biaryl products attend formation of either **66** or **68**. One interpretation of this observation is that exposure of **65** or **67** to $Pb(OAc)_4$ generates a reactive electrophilic intermediate which traps nucleophiles in solution. Apparently, acetate (from $Pb(OAc)_4$) is superior to unreacted phenol in this regard, and this intermolecular competition is claimed by the former nucleophile.

Scheme 20

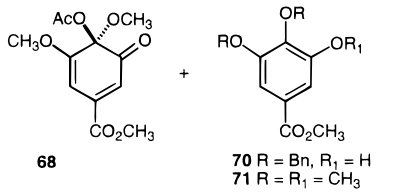


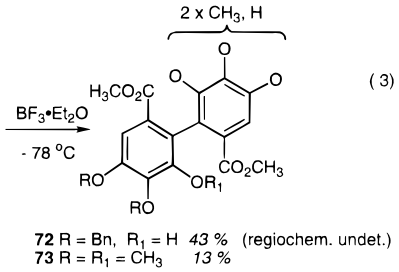
Scheme 21

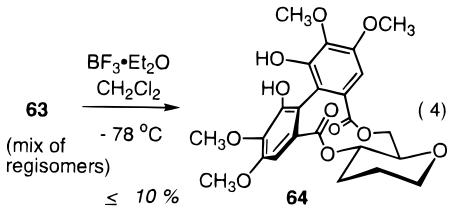


The postulated mechanistic basis for formation of the quinone monoketals **66/68** and HHDP-containing product **64** from **61c** with $Pb(OAc)_4$ served as an entrée into optimization studies (Scheme 21). Prior studies by Norman[66] suggest that exposure of a phenol to $Pb(OAc)_4$ leads to a cyclohexadienonyl cation following formal loss of two electrons and a proton. In the case of interest here, treatment of **61c** with $Pb(OAc)_4$ might then furnish a reactive electrophilic intermediate which serves, at the very least, as the functional equivalent of cation **69**. This electrophilic species can then partition between the two available nucleophiles, acetate and adjacent phenol. Clearly, the competition is won in this example by acetate (path *b*), but the small amount of the path *a* intramolecular trapping product **64** offers hope that minor adjustments in the energetics of the dual pathways might invert the product ratio and favor path *a*.

Evidence in support of this mechanistic proposal can be found in the transformations cited in eqs 3 and 4. Thus, treatment of the orthoquinone monoketal **68** and phenol **70** or permethyl ether **71** with Lewis acid furnishes the biaryl products **72** and **73**, respectively, presumably through regeneration of a cyclohexadienonyl cation resembling **69**. Unfortunately, only trace amounts of the HHDP-containing product **64** could be detected in the complex reaction mixture which resulted from treatment of the model glucose-derived orthoquinone monoketal substrate mixture **63** with $BF_3{\cdot}Et_2O$.

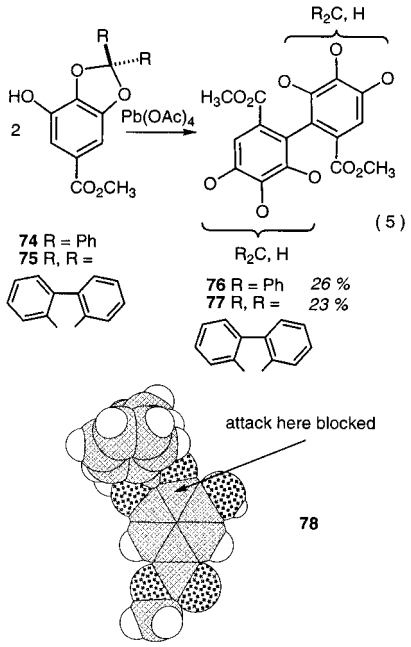






Two distinct approaches for favoring path *a* over path *b* could be envisioned on the basis of this mechanistic model. One approach involved oxidation of **61c** with a Pb(IV) salt which contained a much less nucleophilic counterion than acetate. Scouting experiments with $Pb(OBz)_4$ or $Pb(OTFA)_4$ and bisphenol substrate **61c** did not, however, lend encouragement to this strategy. Lead tetrakis(trifluoroacetate) rapidly destroyed the substrate while $Pb(OBz)_4$ delivered a mixture of the orthoquinone monoketals analogous to **63** and a bisorthoquinone monoketal. In neither case could any HHDP-containing product be detected.

The second approach, which relied on *steric* effects to control partitioning of the electrophilic intermediate, ultimately proved more successful. Attachment of the aryl nucleophile to this intermediate occurs at the hydrogen-bearing carbon C(2) and hence is subject to only modest steric effects. In contrast, acetate only seems to attach at the methoxyl-bearing carbon C(5) for reasons not fully elucidated. While methoxy is not a particularly imposing steric abutment, the methyl appendage can be replaced by a larger fragment that may retard acetate capture at this carbon. This line of inquiry was pursued with the simple diphenyl ketal and fluorenyl ketal-containing methyl gallates **74** and **75**, respectively (eq 5). The steric impediment to acetate addition at C(5) can be appreciated by examination of the MM-derived depiction **78** of the diphenyl ketal substrate **74**. Both substrates **74** and **75** afforded modest yields of *C−C-coupled* products uncontaminated by any trace of orthoquinone monoketals upon $Pb(OAc)_4$



mediated oxidation! This observation stands in sharp contrast to the related oxidations of the *methoxy*-substituted galloyl esters **65** and **67**, where only the orthoquinone monoketals were produced. In each case, the biaryl product was formed as an inseparable 1:1 mixture of regioisomers.

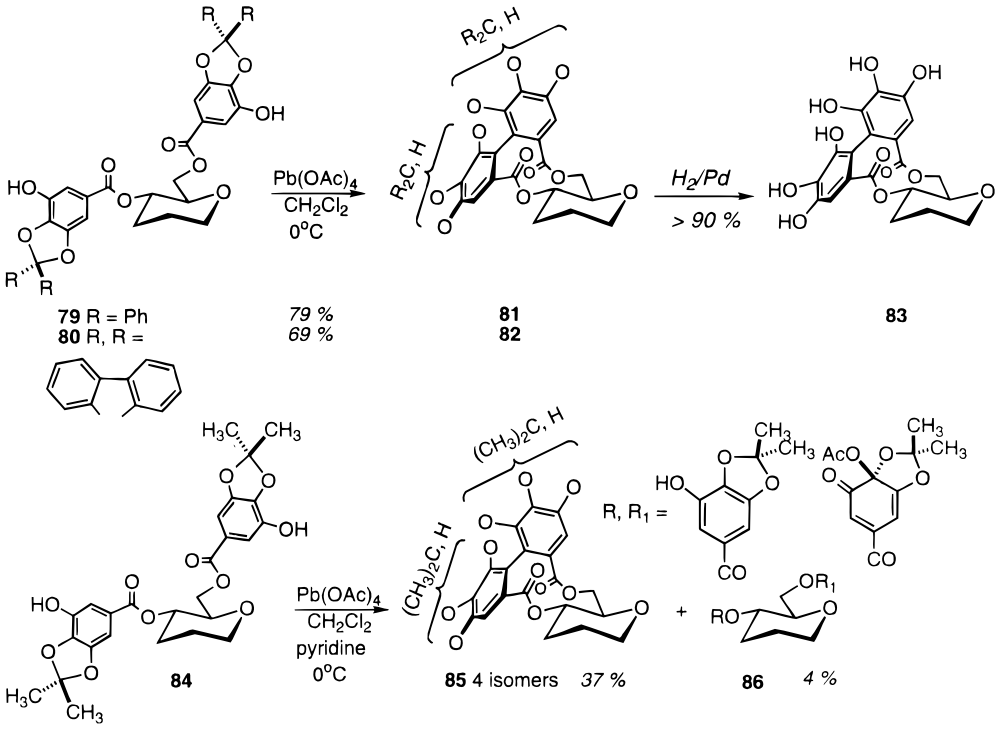
Extension of this protecting group chemistry to the digalloylated glucose model substrate furnished the first glimpse of unqualified success in the area of HHDP synthesis, (Scheme 22). Both the diphenyl ketal species **79** and the fluorenyl ketal analog **80** generated *only* HHDP-containing products **81** and **82**, respectively, upon $Pb(OAc)_4$-mediated oxidative cyclization. The yields were uniformly high and no degradation to ellagic acid derivatives was detected.

The diphenyl ketal substrate **79** provided HHDP product **81** as a 2:1.6:1.5:1.0 mixture of isomers. Separation and independent conversion (by hydrogenolysis) of each isomer into the same (*S*)-hexahydroxybiaryl product **83** confirmed that (1) these isomers differed in regiochemistry only, and (2) each isomer had the (*S*)-HHDP stereochemistry. Similarly, the fluorenyl ketal species **80** afforded a 1.6:1.3:1.0 product mixture **82** upon oxidation which also converged on the same product, (*S*)-**83**, following treatment with H_2/Pd. Thus, the high level of diastereoselectivity which attended the initial efforts was maintained in the more complicated (and more relevant for synthesis!) examples. The obvious advantages of simplicity and high yield upon protecting group removal vis-à-vis the methoxy system is a not insignificant feature of this chemistry, given the difficulty which often attends chromatographic purification of the fully hydroxylated ellagitannins themselves.[3c,44a]

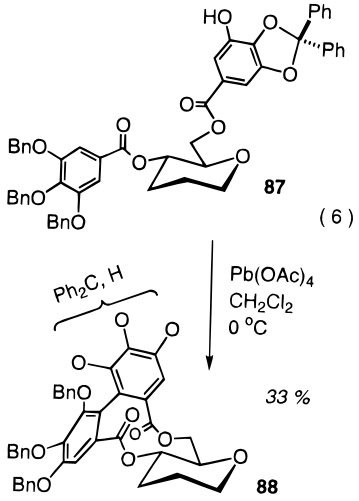
Parallel studies with the acetonide-protected galloyl groups in substrate **84** were mechanistically revealing although not particularly compelling in terms of ellagitannin synthesis.[67a] Exposure of diacetonide **84** to $Pb(OAc)_4$ under standard conditions furnished a 37% yield of HHDP containing coupling products **85** as a mixture of four isomers which were not further characterized. In addition, a 4% yield of orthoquinone monoketal product **86** was isolated, in distinct contrast to the oxidations with the more sterically "protected" substrates **79** and **80**. Thus, it is plausible that the smaller size of the acetonide moiety allows some path *b* leakage upon electrophile capture, while this reaction channel is completely suppressed with the larger aryl ketal groups.

Additional exploration of the scope of this Pb(IV)-mediated oxidative cyclization revealed that the nucleophilic aryl component need not be a phenol.[67a]

Scheme 22



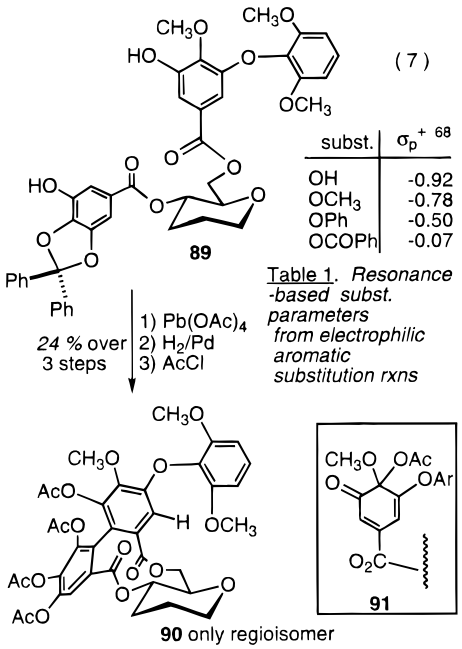
Treatment of the monophenol/perbenzyl ether substrate **87** with $Pb(OAc)_4$ at 0 °C produced the HHDP-containing product **88** in modest yield as a single (unassigned) isomer (eq 6). In this example, oxida-



(6)

tion is localized at the phenol-bearing ring. Unfortunately, the benzyl ether substituents on the adjacent nucleophilic aryl ring do not appear to enhance the prospects for cyclization beyond that observed with the presumably more nucleophilic phenol (e.g. **79** in Scheme 22).

The chemoselective delivery of the oxidative charge to the O(6)-galloyl ring in substrate **87** was unambiguously controlled by choice of substituents on the aryl rings. However, more subtle electronic factors can be equally effective in determining the site of initial ring oxidation in a bisphenol substrate **89** (eq 7).[67a] In principle, either phenolic ring in **89** could



(7)

subst.	σ_p^+ [68]
OH	-0.92
OCH_3	-0.78
OPh	-0.50
OCOPh	-0.07

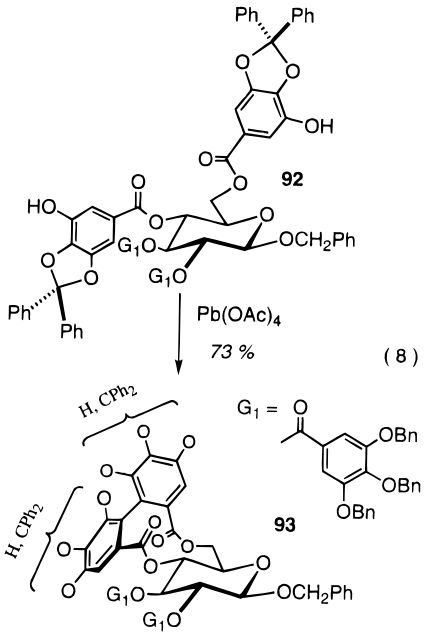
Table 1. *Resonance -based subst. parameters from electrophilic aromatic substitution rxns*

be oxidized by $Pb(OAc)_4$. In practice, however, $Pb(OAc)_4$ apparently can exploit the differences in electron demand between an aryl and an alkyl ether, and only oxidation at the alkyl ether (diphenyl ketal)-substituted ring is supported by the observed result. This latter conclusion is based upon the expectation that if oxidation of the *aryl* ether-substituted ring had occurred, acetate-trapping products of the type **91** would be obtained. No evidence for this orthoquinone monoketal was detected. In any event, oxidation of the O(4) galloyl ring in this substrate, followed by trapping of the resultant electrophilic intermediate by the O(6) nucleophilic galloyl ring, provides a complementary approach (compared to the reverse sequence, eq 6) to HHDP synthesis at the 4,6 positions of glucose. The aryl ether-substituted product **90** bears some resemblance to *valoneoyl* containing ellagitannins (cf **17**−**19**), and so this example serves as a cognate model system which demonstrates that *regioselective* galloyl coupling at the 4,6 locus, as is required for synthesis of members of this subgroup of ellagitannins, is feasible.

3. C–C Bond Formation with Fully Functionalized Substrates

The successful $Pb(OAc)_4$-mediated oxidative coupling of phenolic galloyl units esterified to positions O(4) and O(6) of a glucose core model system sets the stage for more advanced studies of galloyl coupling within fully functionalized glucose substrates as a prelude to excursions in natural products synthesis. These studies address issues of functional group tolerance/compatibility and probe the stereochemical fidelity of the coupling reaction in a more complex molecular environment. In particular, 2,3-galloyl coupling as well as the more familiar 4,6-HHDP synthesis will be tested.

The prospects for successful coupling between phenolic galloyl esters bound to O(4) and O(6) of a genuine D-glucose substrate were explored with the β-benzyl glucoside **92** (eq 8). This substrate has only

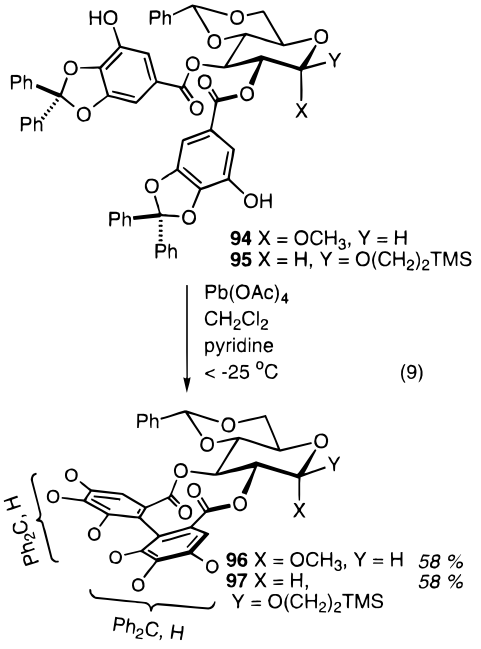


(8)

two galloyl units which can participate in Pb(IV)-mediated oxidation, but it remained to be seen whether the nucleophilic galloyl unit at O(3) might

compete with the O(6) ring for an electrophilic intermediate attached to O(4), should it be generated (cf. **69**). Furthermore, the potential for oxidation at the anomeric center cannot be dismissed. It was gratifying to observe that oxidation of substrate **92** produced the desired 4,6-coupled product **93** free of any recognizable byproducts. This product was formed as a mixture of four isomers by analogy with the coupling of the model system **79**, but subsequent reductive removal of the protecting groups verified that all (regio)isomers had the expected (*S*)-HHDP stereochemistry. This cyclization is part of a synthesis of tellimagrandin I (**3a**),[69] and substrate preparation and transformations of **93** will be described in section II.D.1.

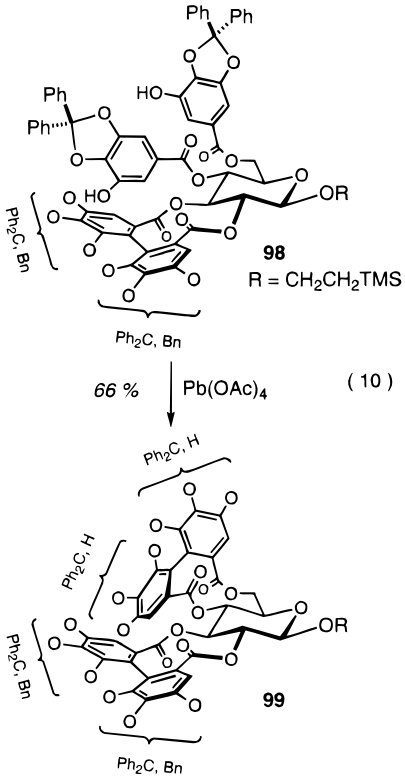
The applicability of this galloyl oxidative cyclization protocol to the preparation of (*S*)-HHDP units at the 2- and 3-positions of glucose had yet to be demonstrated. Thus, it was unclear at the outset that acceptable cyclization yields could be obtained in this series. These concerns proved to be largely unfounded, however, as moderate yields of the 2,3-coupled products **96** and **97** could be obtained by exposure of the appropriate substrates **94** and **95**, respectively, to exactingly optimized oxidative cyclization conditions (eq 9).[70] Much more careful



attention to reaction temperature and concentration was required to achieve even this level of success compared with the more tolerant 4,6-coupling reaction.

The α-methyl glucoside cyclized product **96** was formed as a mixture of three isomers which were chromatographically separable. Spectroscopic (CD) and chemical (H_2/Pd) studies similar to those described with the 4,6-coupled case **79** led to the inescapable conclusion that these species were regioisomers of each other, all having the desired *S* stereochemistry. An entirely analogous reaction course was followed with the *β*-(trimethylsilyl)ethyl glucoside **95**, which afforded cyclized product **97** as a mixture of three regioisomeric HHDP-containing species. All isomers exhibited the *S* stereochemistry in the HHDP unit. It is worth noting that, at least for these 2,3 coupling examples, the stereochemistry at C(1) does not appear to exert any meaningful influence on the reaction course at nearby C(2)/C(3).

Access to the next level of ellagitannin structural complexity requires successful galloyl coupling at both the glucopyranose 4,6- and 2,3-positions. Given the rather more modest yield that attended 2,3-coupling, it seemed prudent to challenge the less demanding 4,6-coupling reaction with a rigidifying 2,3-HHDP unit already in place. In the reverse sequence, the diminished flexibility of a 4,6-HHDP unit might make 2,3-coupling intolerably difficult, the calculations with **57** notwithstanding. This strategy was probed with the substrate **98** which was derived from the coupling product **97** already in hand.[67b] Treatment of this digalloylated species with $Pb(OAc)_4$ under standard conditions smoothly afforded the 2,3;4,6-coupled ellagitannin-like product **99** as a mixture of both 2,3- and 4,6-regioisomers. Simple hydrogenolysis removed all of the phenolic protecting groups and furnished a dodecahydroxylated compound as a *single isomer*. That this species had the 2,3-*S*;4,6-*S* stereochemistry was demonstrated by comparison of its ^1H NMR spectra with that of the related natural product pedunculagin (**9**). Thus, the high expectations set by the prior 4,6-coupling studies have been met in this more challenging example without any untoward complications caused by the attached 2,3-(*S*)-HHDP unit.



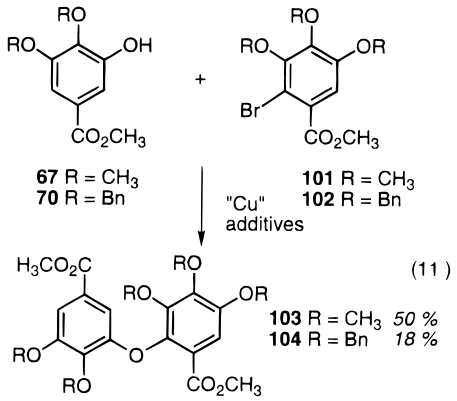
The successful coupling of galloyl groups at both the 4,6- and 2,3-positions of glucose with complete stereochemical control provides a ringing endorse-

ment for the Schmidt−Haslam biosynthetic hypothesis. Furthermore, continuing reliance on MM-based conformational analysis for rationalizing/predicting the stereochemical outcome of coupling in other galloylated glucose permutations appears for the time being to be justified. Nevertheless, the validity of a hypothesis cannot be ascertained by merely accumulating corroborative evidence, and many challenges to this model await. In particular, synthesis studies directed toward the areas of (1) 2,4- or 3,6-galloyl coupling where both (*S*)- *and* (*R*)-HHDP containing (or derived) naturally occurring ellagitannins are known,[3a,5z] and (2) 2,3-coupling to furnish the unusual *R* atropisomer found in the natural products cercidinins A/B, cuspinin and platycaryanin D,[5y,5f] will provide stringent tests of this strategy for imparting stereochemical control.

B. C–O Bond Formation upon Galloyl Coupling

1. Strategy

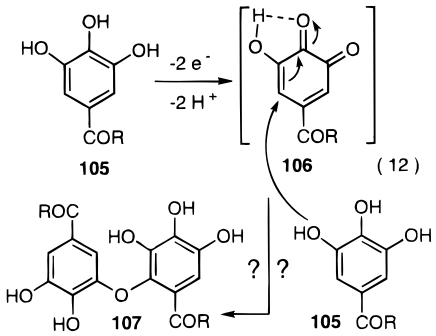
The formation of a diaryl ether linkage upon combination of two galloyl units defines the central challenge in synthesizing dimeric ellagitannins containing dehydrodigalloyl [e.g., agrimoniin (**16**)] or valoneoyl (e.g., **17**−**19**) units. As a general problem in organic synthesis, this type of target has usually been addressed via some version of the Ullmann reaction or through nucleophilic aromatic substitution.[71] The latter process requires substituent patterns which are not directly applicable to the galloyl class of substrates and so the utility of that particular C−O bond-forming scheme has yet to be demonstrated. On the other hand, a galloyl Ullmann coupling process was first examined by Mayer[62f] and more recently exploited by Nishioka *et al.* with moderate success to prepare the digalloyl ether **103** as part of the structural elucidation of macaranin B.[72] However, similar reaction with the more synthetically useful perbenzylated systems **70**/**102** provided aryl ether product **104** with even less efficiency.[67c] Optimization studies were not able to materially improve this process, and so recourse to alternative approaches seemed warranted.



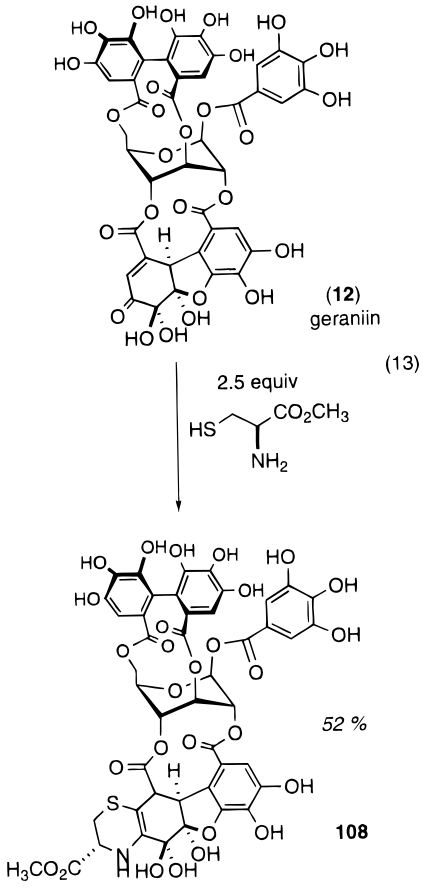
(11)

The successful biomimetic strategy for galloyl C−C coupling described earlier raised the possibility that a similar line of inquiry might be exploited profitably to secure C−O coupling as well. Speculation about the biosynthetic course of C−O galloyl coupling has centered on the nature of the reactive intermediate (phenoxy radical or electrophilic cyclohexadienonyl cation) that might precede C−O bond formation. Haslam and Cai argue by analogy with the earlier studies of Waters[73] that phenoxy radicals may in fact precede C−O bond formation, while the intermediacy of more highly oxidized species (i.e. cyclohexadienonyl cations) favors C−C bond formation.[3a] However, subjecting the various digalloylated substrates **61** or their simple methyl ester analogs to a variety of putative one-electron oxidants (cf. Scheme 19) did not lead to identification of any digalloyl ether products. Thus, data which support this intriguing hypothesis remain to be collected.

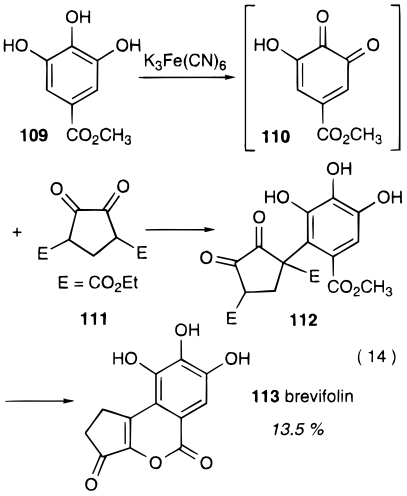
An alternative scenario for the genesis of the digalloyl ether subunit, which builds upon some well-known two-electron oxidation chemistry of catechols, can be envisioned.[74] Specifically, oxidation of the galloyl species **105** can afford an *orthoquinone* intermediate, which in turn might capture the nucleophilic phenol residue of a second galloyl partner, (eq 12). Orthoquinones have been posited as reactive intermediates in a broad range of biological milieus, where invariably their potent electrophilicity marks them as prime coupling partners for endogenous nucleophiles.[75] Phenolic nucleophiles have not yet demonstrated competence in this capacity, however.



In fact, oxidation of glucose-bound HHDP units to orthoquinones underlies the current biosynthetic hypothesis for generation of complex tannins of the dehydroellagitannin family, including geraniin (**12**), carpinusin (**13**), elaeocarpusin (**25**), and euphorbin C, among others (cf. section I.A.3). These orthoquinone species are invariably isolated in hydrated form and as internal hemiketals. Nonaka *et al.* have shown that the residual electrophilicity inherent in these masked orthoquinones is sufficient to permit capture of thiol nucleophiles such as cysteine methyl ester (eq 13),[76] a result which may bear on the plausibility of ellagitannin-mediated covalent modification of proteins *in vivo.* Furthermore, a biomimetic synthesis of the natural product brevifolin (**113**) from methyl gallate (**109**) and the keto ester **111** has been reported by Wanzlick (eq 14).[77] This transformation presumably proceeds via addition of the nucleophilic β-keto ester enolate formed from **111** to an intermediate galloyl-derived orthoquinone **110**, followed by further manipulation of the ester moieties in **112** to ultimately deliver **113**. Thus, these examples leave open the promise that galloyl-derived orthoquinones are both accessible (at least in protected form) and may participate as electrophilic

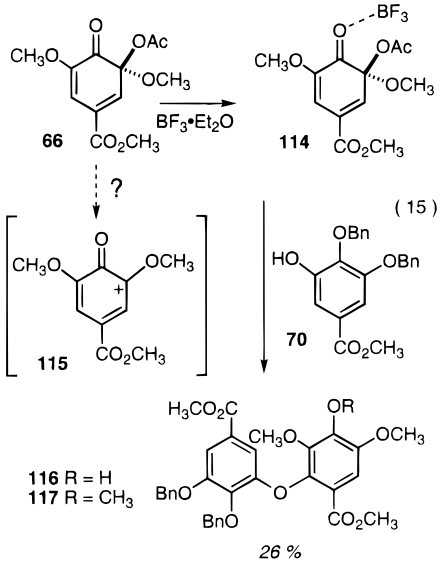


partners in bond forming processes relevant to diaryl ether synthesis.



2. Orthoquinone Monoketals as Electrophiles: C–O Coupling

The difficulties anticipated with formation, isolation, and manipulation of galloyl-derived orthoquinones themselves suggested that exploring the chemistry of the related orthoquinone monoketals **66** and **68** already in hand might provide a more tractable first generation approach to C−O coupling. The "para" ketal **68** does, in fact, react as a functional equivalent of cyclohexadienonyl cation **69** upon Lewis acid activation, and the C−C-bonded galloyl dimers **72/73** are formed in moderate yield (eq 3). In contrast, the "meta" ketal **66** might give a cation **115** which would not be as sterically accessible to nucleophiles as the cation derived from **68**, and hence may be a less competent electrophile (eq 15). A second

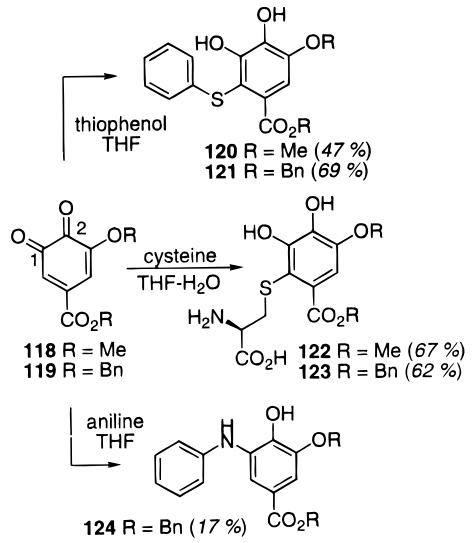


reaction channel may then be available to **66** which is relevant to C−O bond formation. The Lewis acid may plausibly activate the enone portion of orthoquinone monoketal **66** for nucleophilic (e.g. phenol) attack by analogy with the acid-catalyzed addition of alcohols to enones.[78] In this instance, the reactive intermediate **114** arguably resembles an "internal acid" activated orthoquinone species **106** that may play a role in biosynthesis. In any event, treatment of a mixture of orthoquinone monoketal **66** and phenolic galloyl ester **70** with $BF_3{\cdot}Et_2O$ did in fact lead to formation of the C−O-coupled digalloyl ether **116** (characterized as its trimethyl ether **117**) to the exclusion of any identifiable C−C coupling products.[67a] Unfortunately, further optimization studies have not yet elevated the yield of **116** beyond the rather modest Ullmann coupling range. Nevertheless, this demonstration of feasibility prompted a more extensive inquiry into the chemistry of the galloyl orthoquinones themselves.

3. Galloyl Orthoquinones: Exploratory Chemistry

The reactivity profile of galloyl-derived orthoquinones merits further discussion in view of their possible participation in both C−C and C−O coupling processes related to the construction of ellagitannins, and the established electrophilicity of orthoquinone hemiketals (i.e. in DHHDP ester groups, **24**) and ketals mentioned above. Protected versions of galloyl-derived orthoquinones, such as **118** and **119** are readily synthesized and undergo more or less successful addition reactions with heteroatomic nucleophiles (Scheme 23).[79] Nucleophilic thiols, such as thiophenol and cysteine, efficiently trap **118** and **119** in a conjugate fashion to give the rearomatized adducts **120**/**121** and **122**/**123**, respectively. Attempts at capturing orthoquinones **118** and **119** with aliphatic primary amines, including lysine, invariably met with failure, whereas aniline afforded the monoanilino adduct **124** in 17% from condensation at the quinonoid C-1 carbonyl carbon.

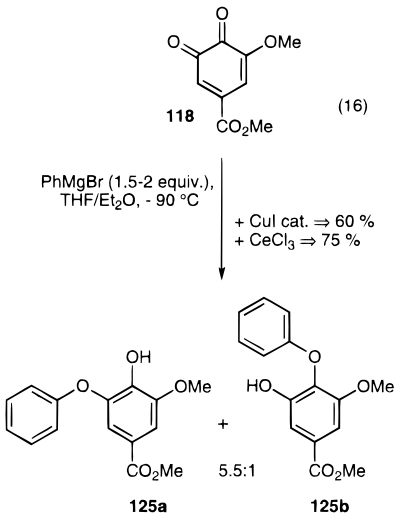
Scheme 23



The efficient capture of galloyl-derived orthoquinones by the amino acid cysteine, as opposed to lysine, underscores the distinctive role that cystyl residues may play in gallotannin- and ellagitannin-mediated covalent modification of proteins, a process which could conceivably underlie certain biological activities of these hydrolyzable tannins (cf. section I.C).

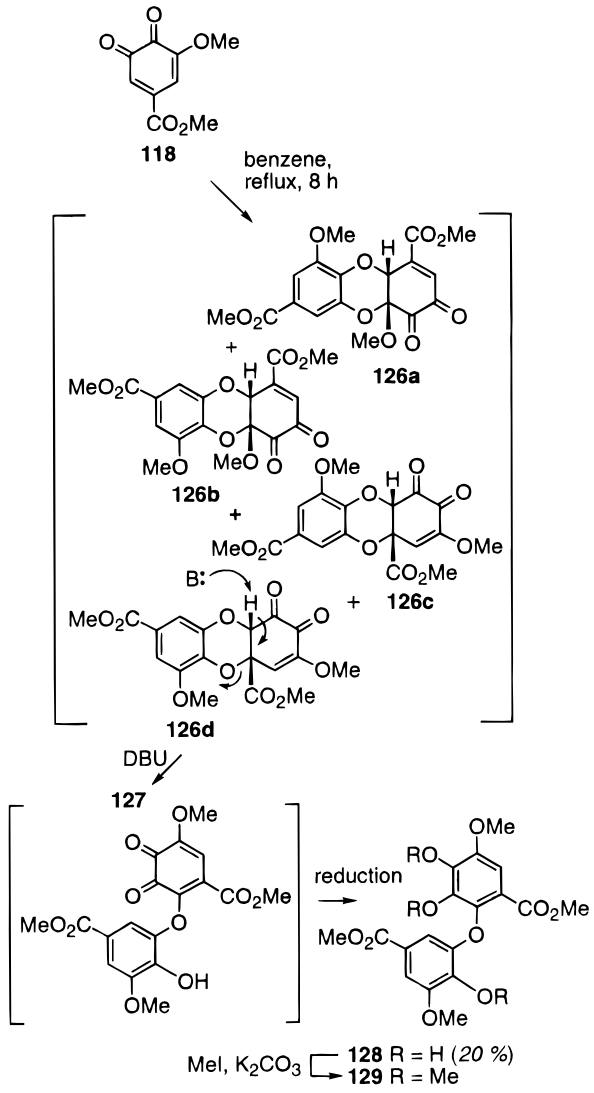
In contrast to the orthoquinone monoketal **66**, orthoquinones **118** and **119** did not display sufficient selectivity in conjugate addition with phenols to furnish diaryl ether species. Attempted addition of simple phenol or galloyl-derived phenols under either acidic or basic catalysis invariably led to complex product mixtures.

Further exploration of the reactivity profile of these quinones unveiled their propensity to undergo oxophilic addition of aryl-bearing organometallic reagents at their quinonoid carbonyls.[80] For example, addition of PhMgBr to **118** at −90 °C in the presence of CuI afforded the regioisomeric diaryl ethers **125a** and **125b** in a 5.5:1 ratio and 60% yield (eq 16). This yield was increased to 75% by utilizing the Grignard reagent in concert with the oxophilic additive $CeCl_3$.[79] The results of this model study provide some encouragement for the implementation of this methodology to the synthesis of ellagitannin diaryl ethers.



A characteristic reaction of orthoquinones utilizes their ability to function either as dienes (and heterodienes) or dienophiles in [4π + 2π] cycloadditions.[81] For example, Critchlow reported the dehydrogenation of 4,6-di-*tert*-butylpyrogallol to dibenzodioxin dimers, a reaction which presumably involves an orthoquinone intermediate as both the dienophile and the heterodiene of a Diels−Alder-like cycloaddition.[81c] In a similar fashion, the galloyl orthoquinone **118** smoothly undergoes a thermally induced hetero-Diels−Alder dimerization reaction to furnish a 3:2:1 regioisomeric mixture of three out of the four possible cycloadducts. Their structures are tentatively ascribed to (three of) the four α,β-diketones **126a**−**d** (Scheme 24). Degradation upon solvent removal prevented their separation and respective structural assignment, but direct treatment of the mixture with the nonnucleophilic base DBU afforded the diaryl ether **128**, as the major product in 20% yield. Its formation is rationalized in terms of base-mediated opening of the internal dioxane ring of **126d** to the orthoquinone **127**, followed by *in situ* reduction (Scheme 24). Structural confirmation of **128** was accomplished by methylation, which gave the known permethylated dehydrodigalloyl ester **129** (cf. section II.B.1).[62f,72] Further optimization of this hetero-

Scheme 24



Diels−Alder reaction will be required to assess its full potential in ellagitannin diaryl ether synthesis.

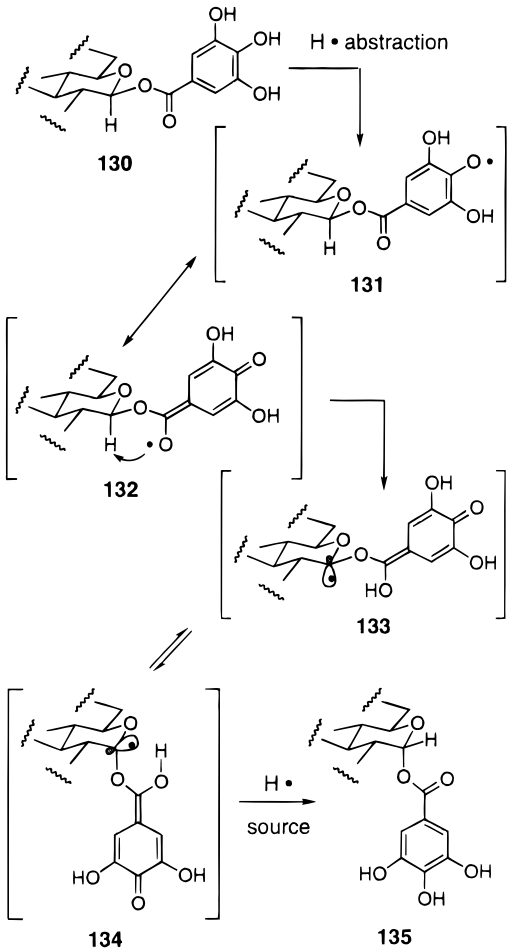
C. Anomeric Acylation Studies

1. Background and Strategy

The stereochemical patterns observed at the anomeric center of 1-galloylated ellagitannins are no less diverse than any of the other stereochemical issues embodied by these structures. Thus, monomeric ellagitannins which feature the β (equatorial) disposition of a galloyl ester at C(1) include both 2,3-galloyl-coupled [e.g., casuarictin (**7**)] and 2,3-galloyl-uncoupled [e.g., tellimagrandin II (**3b**)] species. Similarly, the anomeric α (axial) galloyl stereochemistry is displayed in both 2,3-coupled [potentillin (**8**)] and uncoupled [woodfordin C (**19**)] naturally occurring ellagitannins. Further coupling permutations at the 4 and 6 positions render any attempt to discern stereochemical trends at C(1) as a function of structural details at C(2)−C(6) extremely unpromising.

The biosynthetic origins of the α-stereoisomers remain rather mysterious as the presumed metabolic precursor of the ellagitannins, the pentagalloyl species **47**, has β-stereochemistry at C(1). Haslam has postulated that a radical-mediated epimerization of the β- to the α-galloyl disposition may underlie the genesis of the latter species (Scheme 25).[3a] However, no evidence which bears on this intriguing hypothesis has surfaced; furthermore, any analysis of this proposal must confront the vast body of evidence which unequivocally documents the difficulty of 1,4-hydrogen abstractions by oxygen radical (e.g., **132** → **133**) compared with the much more facile (and available in this instance) 1,5-abstraction alternative.[82] In any event, the lack of experimental guidance on this topic dictates that this radical proposal, as well as any other conceivable hetereolytic (i.e., C−O scission) mechanism, cannot reasonably be expected to serve as the foundation for a biomimetic strategy for stereochemical control at C(1).

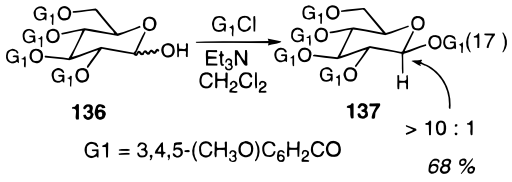
Scheme 25

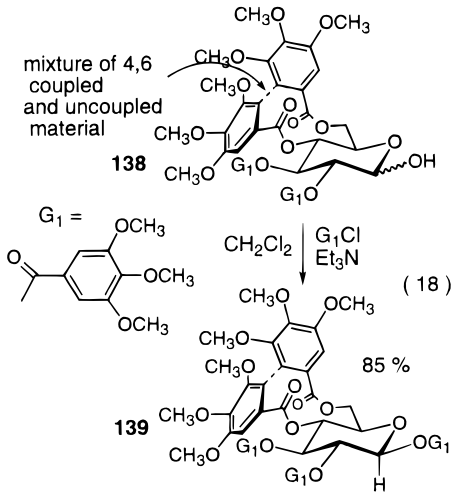


The critical role that anomeric stereochemistry plays in the structural elaboration of 1-acyl saccharides has ensured that a great deal of effort has been devoted to developing reaction/reagent conditions which favor formation of either the C(1) α- or the C(1) β-acylated carbohydrate product upon demand.[83] Tapping into this literature affords various protocols which might be applicable, at least in principle, to the ellagitannin system. At present, two of the four possible ellagitannin target structures have been accessed, at least in germane model systems (eqs 17 and 18).

2. β-Specific Acylation

Acylation of 2,3,4,6-tetrakis(3,4,5-*O*-methylgalloyl)-glucose (**136**) with the galloyl chloride 3,4,5-$(CH_3O)C_6H_2COCl$ under a variety of base/solvent conditions revealed that strict β-stereochemistry at C(1) attended only reaction with triethylamine in CH_2Cl_2 (eq 18).[83f] The high selectivity of this transformation could be exported to the 4,6-galloyl-coupled series where per-*O*-methyl tellimagrandin II (**139**) could be prepared from the anomeric hydroxyl precursor **138**. These results are relevant to the synthesis effort directed toward the β-C(1) galloyl bearing ellagitannin sanguiin H-5 (**6**) discussed below.

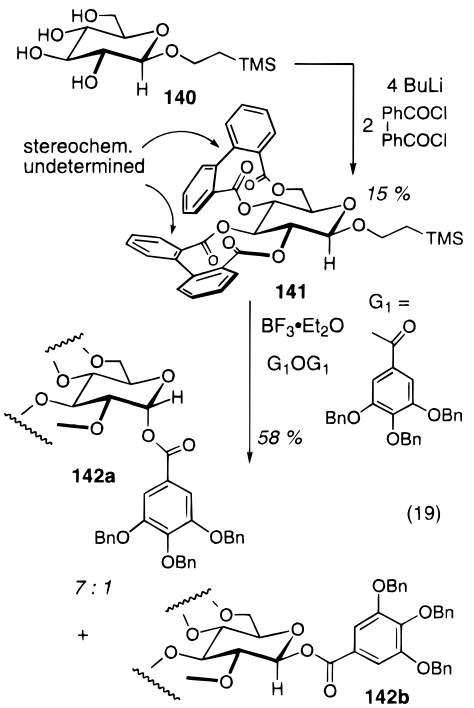




3. α-Selective Acylation

The second galloylated glucose attachment pattern accessed through model system chemistry is the α-1-

galloyl-2,3-HHDP-glucopyranose motif characteristic of, *inter alia*, potentillin (**8**) (eq 19). Direct acylation



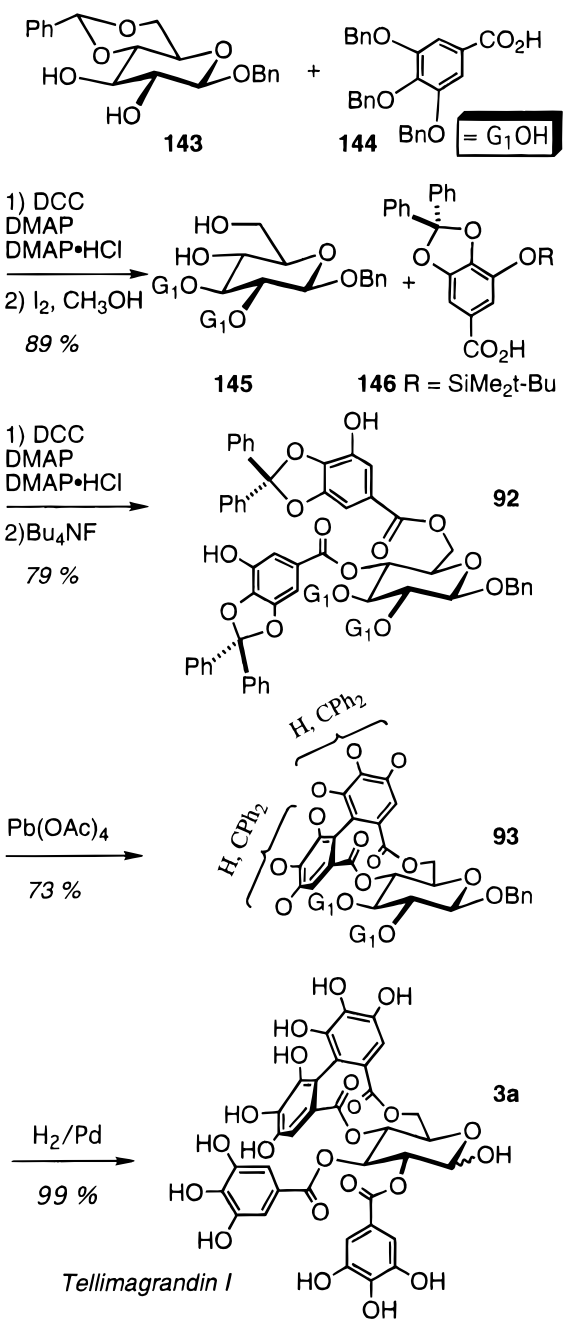
of tetrol **140** with biphenoyl chloride led to modest yields of the bis biaryl ellagitannin model compound **141** as a single (undefined) stereoisomer. Application of Magnusson's Lewis acid-mediated anomeric acylation protocol[83b] to this silylethyl ether furnished the expected C(1) galloyl ester **142a/b** with a strong bias (7:1) toward the α-C(1) stereochemistry. The Magnusson procedure is reported to favor the *β*-acyl disposition with substrates bearing simple acylated (e.g., tetraacetoxy) glucose cores. The role that the rigidifying biaryl units play in this reversal of stereochemical selectivity has yet to be defined, but it is plausible that these units are not appropriately positioned to direct *β*-glycosylation through anchimeric assistance. Subsequent control experiments indicated that the anomeric stereochemistry in **142a** does not equilibrate under the acidic reaction conditions. These results become significant within the context of agrimoniin synthesis, a long-term goal for this program.

D. Total Syntheses

1. Tellimagrandin I[69]

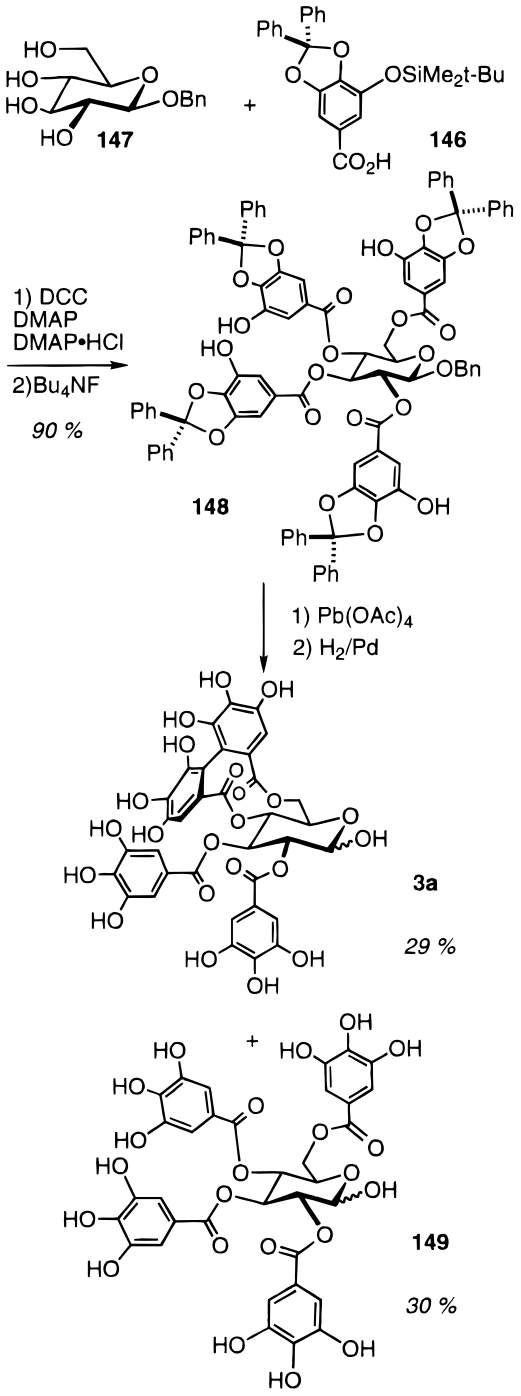
The total chemical synthesis of the simple 4,6-HHDP-containing ellagitannin tellimagrandin I (**3a**) represents the culmination of the methodology development work described earlier. The issue of regioselectivity upon galloyl coupling (4,6-coupled; 2,3-uncoupled galloyl groups) was addressed in a conservative manner in this initial foray into ellagitannin total synthesis. Thus, a substrate **92** was prepared which featured $Pb(OAc)_4$-sensitive galloyl groups only at positions O(4) and O(6)—the O(2) and O(3) galloyl groups were fully protected with benzyl ethers and completely inert (control experiments) to the Pb(IV) oxidant (Scheme 26). Synthesis of **92**

Scheme 26



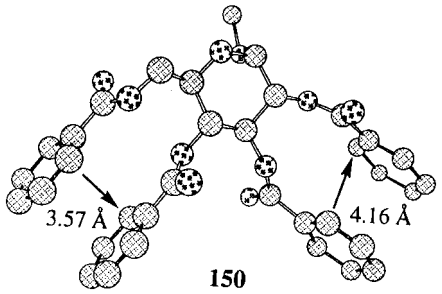
commenced with the known 4,6-benzylidene acetal **143**[84] and relied on Keck's modification[85] of Steglich esterification to attach the appropriate galloyl groups to the glucose core. As described earlier, oxidative cyclization of the tetragalloyl substrate **92** afforded the 4,6-coupled product **93** in good yield and with complete stereochemical control, but as an inconsequential mixture of four regioisomers. Hydrogenolysis of all 11 benzylic ether linkages in this mixture of isomers liberated tellimagrandin I (**3a**) in 99% yield as a pure mixture of α/*β* anomers which was indistinguishable from the natural material. The importance of employing a predictable and "clean" transformation as the ultimate step in ellagitannin chemical synthesis became apparent when limited solubility and susceptibility to adventitious air oxidation made manipulation of the tan solid **3a** problematical.

Scheme 27



A second more concise but regiochemically less secure approach to the synthesis of tellimagrandin I was imagined as well.[69] In this alternative strategy, a glucose substrate **148** (Scheme 27) adorned with four oxidation sensitive phenolic galloyl groups is used to probe the question of whether some inherent preference for regioselective galloyl pairing, in addition to the stereochemical preference elucidated earlier, could be detected. Surprisingly, only a *single* galloyl coupled product (29%) emerged upon treatment of **148** with 1 equiv of $Pb(OAc)_4$ followed by hydrogenolytic removal of all of the protecting groups. This product proved identical in all respects to a sample of tellimagrandin I prepared as depicted in Scheme 26. In addition to the coupled species **3a**, an equal amount of 2,3,4,6-tetragalloylglucose **149** was formed, presumably via simple deprotection of residual substrate **148** which had survived exposure to $Pb(OAc)_4$. Varying the reaction time or equivalents of Pb(IV) oxidant did not materially improve the yield or **3a**/**149** ratio. In addition, resubmission of the crude coupling mixture to a further charge of oxidant did not increase production of (the protected form of) **3a**. Rather, under all of these modifications, further reaction transpired to provide complicated and as yet uncharacterized mixtures of compounds. It is possible that a 4,6;2,3-bis-coupled product related to pedunculagin (**9**) is contained within this mixture, but this point awaits further study. Nevertheless, the brevity of this synthesis (five steps from glucose) is a testament to the power of a biomimetic approach to controlling coupling selectivity within the context of tellimagrandin synthesis.

An *a posteriori* rationalization for the remarkable coupling regioselectivity exhibited by tetragalloyl substrate **148** can be extracted from an MM conformational analysis of a model system related to it. A search of conformational space about all exocyclic rotatable bonds of α-methyl glucose tetrabenzoate furnished approximately 50 low-energy species within 1.5 kcal/mol of the "global" minimum structure **150**. Structure **150** features a "clockwise" *pro-S* tilt in each of the 4,6- and the 2,3-galloyl pairs. The lowest energy alternative "tiltomer" which unambiguously displays a "counterclockwise" *pro-R* disposition of galloyl groups resides approximately 0.7 kcal/mol higher in energy than **150**. An examination of the



150

distances between the nearest inter-ring carbon atoms in both the 4,6- and 2,3-galloyl pairs reveals that a simple proximity argument might suffice to rationalize the observed regioselectivity. The *pro-S* pair of carbons within the 4,6-digalloyl unit span a 3.57 Å gap, while the alternative *pro-S* carbon pair within the 2,3-galloyl grouping is over 0.5 Å more distant. Thus, the nearest neighbors may plausibly react more rapidly.

The mechanism by which this proximity translates into preferential reactivity remains the subject of speculation. It is not beyond the realm of possibility that anchimeric assistance plays a defining role in connecting proximity with reactivity. In this wholly conjectural scenario, the π-electrons in the spatially aligned and closest packed galloyl rings might suffer HOMO−HOMO mixing and generate a new higher molecular HOMO which would in turn be more susceptible to oxidation. In short, those rings which are closer together would be more easily oxidized. Physical evidence which addresses either the conformational or the stereoelectronic hypotheses described above remains to be generated.

2. Sanguiin H-5[70]

Sanguiin H-5 (**6**) ratchets up the degree of difficulty in ellagitannin synthesis a notch as this structure embodies two features (2,3-galloyl coupling *and* an anomeric galloyl group) absent in tellimagrandin I. Thus, the total synthesis of sanguiin H-5 (**6**) requires (1) successful execution of the more demanding 2,3-galloyl ester coupling in a complex molecular environment, and (2) selective protection/deprotection at the anomeric position to enable installation of the β-galloyl linkage.

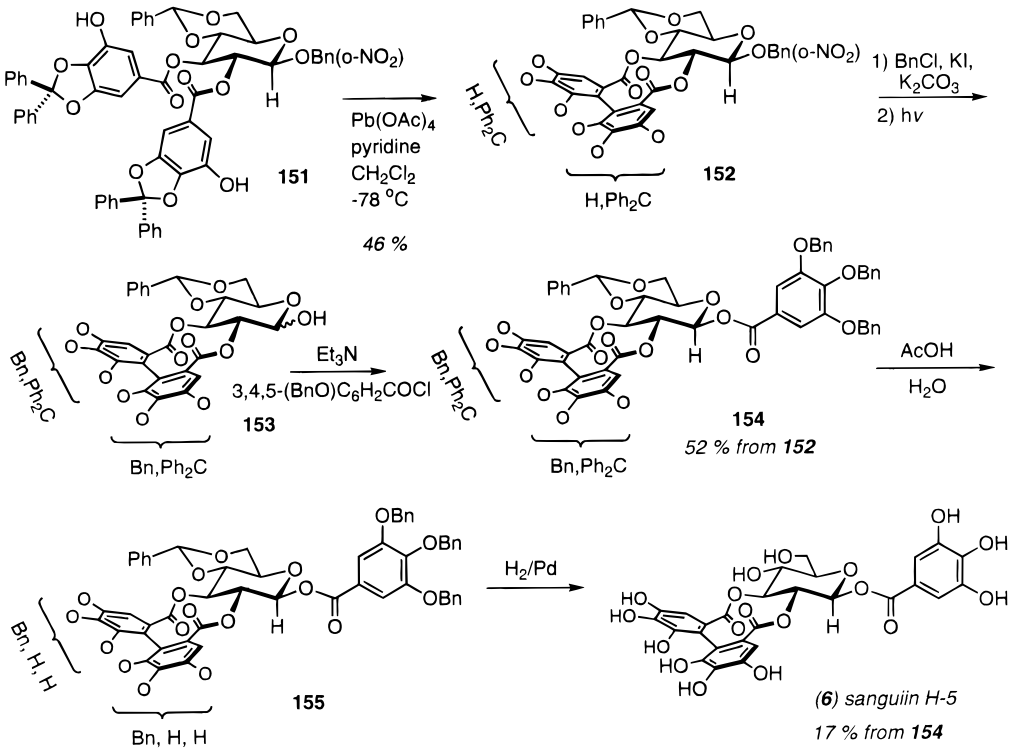
Precedent for the first of these operations (2,3-galloyl coupling) seemed secure given the results of the model studies discussed earlier. The photochemically labile *o*-nitrobenzyl ether anomeric protecting group was eventually chosen after several false starts with other unsuitable prospects. This group permitted facile and selective anomeric deprotection under conditions which preserved the integrity of the remaining functionality. However, the effect of the electron-deficient character of this species (compared with the methyl or 2-trimethylsilylethyl ethers **94** and **95**) on the efficiency of the coupling chemistry at the adjacent C(2)/C(3) positions of the glucose core remained an open question.

The synthesis of sanguiin H-5 (**6**) begins from the known β-*o*-nitrobenzyl glucoside, itself available from α-1-bromoglucose tetraacetate in two steps. Protection of the O(4) and O(6) positions of this tetrol as a benzylidene acetal and then attachment of phenolic galloyl units at O(2) and O(3) follows earlier work and affords the oxidative cyclization precursor **151** in good yield, (Scheme 28). In the key step of the synthesis, exposure of bisphenol **151** to $Pb(OAc)_4$ in CH_2Cl_2/pyridine at −78 °C furnished the 2,3-HHDP-containing product **152** in as much as 46% yield as a mixture of three isomers. Significant effort was directed toward optimizing the yield of this transformation with respect to concentration, temperature, and additives. This relatively modest yield (46%) does not compare favorably with the yields obtained (~58%) when coupling 2,3-galloyl groups on substrates with more electron-rich anomeric protecting groups (cf. **94** and **95**). Thus, the concerns regarding the potential for inductive deactivation with the *o*-nitrobenzyl group mentioned earlier may, in fact, have been realized. Spectroscopic (CD) studies on the separated isomers and eventual conversion of all of these species to natural sanguiin H-5 (**6**) confirmed that these compounds were all regioisomers with respect to the diphenyl ketal's position. Strict adherence to the stereochemical paradigm elucidated earlier was observed as each compound contained only the (*S*)-HHDP atropisomer at C(2)/C(3). At this point, the free phenolic hydroxyls were benzylated in anticipation of manipulations at the anomeric center to give a mixture of regioisomeric ethers. Irradiation of this mixture provided the free anomeric hydroxyl-containing pyranose **153**, which was immediately acylated with tri-*O*-benzylgalloyl chloride under conditions previously identified as being strongly β-selective.

In fact, only a single epimer at C(1) could be seen, the β-glucoside **154**.

Simple hydrogenolytic deprotection was now the only transformation that stood between the sanguiin H-5 precursor **154** and acquisition of the natural product. Quite surprisingly, exhaustive exploration of hydrogenolysis conditions (metal, solvent, H_2 pressure, additives) with substrate **154** did not afford any encouraging results, despite the earlier success of this process. At best, all protecting groups but one (or two) diphenyl ketal moieties could be excised by this approach. It is possible that access to the catalyst

Scheme 28



surface (or metal center in homogeneous variants) is precluded on steric grounds for the refractory diphenyl ketal moieties, but culpability may lie elsewhere as well. In any event, an alternative route to deprotection which exploited the diphenyl ketal's acid liability eventually proved serviceable. Treatment of the regioisomer mixture **154** with aqueous acetic acid led to a diphenyl ketal-free tetraphenol **155** which was subjected without further purification to hydrogenolytic deprotection of the remaining benzylic ether linkages. This two-step procedure afforded sanguiin H-5 (**6**) in 17% overall yield from **154** following cleanup by preparative reverse-phase chromatography. The sample of sanguiin H-5 so obtained exhibited spectral data indistinguishable from that reported for the natural material.[5c]

3. Toward Pedunculagin[67b]

The lessons learned in the tellimagrandin 1 and sanguiin H-5 syntheses can be applied to the total synthesis of the more complex target pedunculagin (**9**) (Scheme 29). Prior studies ascertained the feasibility of achieving 2,3;4,6-galloyl coupling (eq 10), but that system featured an anomeric protecting group [β-(trimethylsilyl)ethyl] relevant to agrimoniin but not to pedunculagin synthesis. In the work in progress described below, a simple benzyl ether at C(1) suffices, as the final target possesses only an anomeric hydroxyl group.

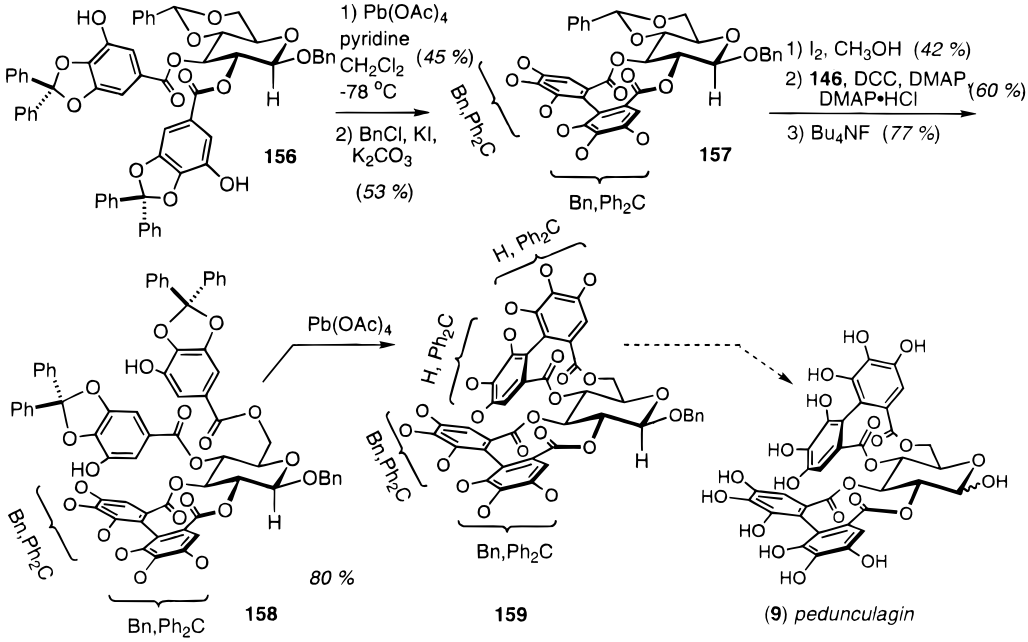
The precursor to 2,3-digalloyl coupling **156** was prepared from diol **143** and acid **146** through chemistry analogous to that described for sanguiin H-5, in accord with a strategy which dictates formation of the more difficult 2,3-HHDP unit first and construction of the more accommodating 4,6-HHDP moiety last (*vide supra*). Oxidative cyclization of the phenolic galloyl substrate **156** mediated by $Pb(OAc)_4$ furnished the expected (*S*)-HHDP-containing products as a mixture of inconsequential regioisomers in 45% yield. This rather modest yield is more in line with that observed using the relatively more electron-deficient *o*-nitrobenzyl ether at C(1) (cf. **151** → **152**) and can probably benefit from further optimization studies. The free phenolic hydroxyls in these crude cyclization products were benzylated only with surprising difficulty to furnish the fully protected intermediate **157**, which was treated with I_2/CH_3OH to cleave the 4,6-protecting group and deliver a diol in preparation for assembly of the 4,6-HHDP unit. Attachment of the familiar protected galloyl unit **146** to both O(4) and O(6) of the intermediate 4,6-diol provided the next cyclization substrate **158** following desilylation with fluoride. In a transformation reminiscent of the model study **98** → **99**, diphenol **158** smoothly cyclized under Pb(IV) oxidation to afford the desired 2,3;4,6-bis-coupled pedunculagin precursor **159** as a mixture of many (uncharacterized) isomers. Removal of all of the protecting groups in this crude mixture of presumed regioisomeric coupling products to deliver pedunculagin (**9**) remains to be accomplished.

4. Ellagitannins via Convergent Coupling of Glucose Diols with Preformed HHDP Units

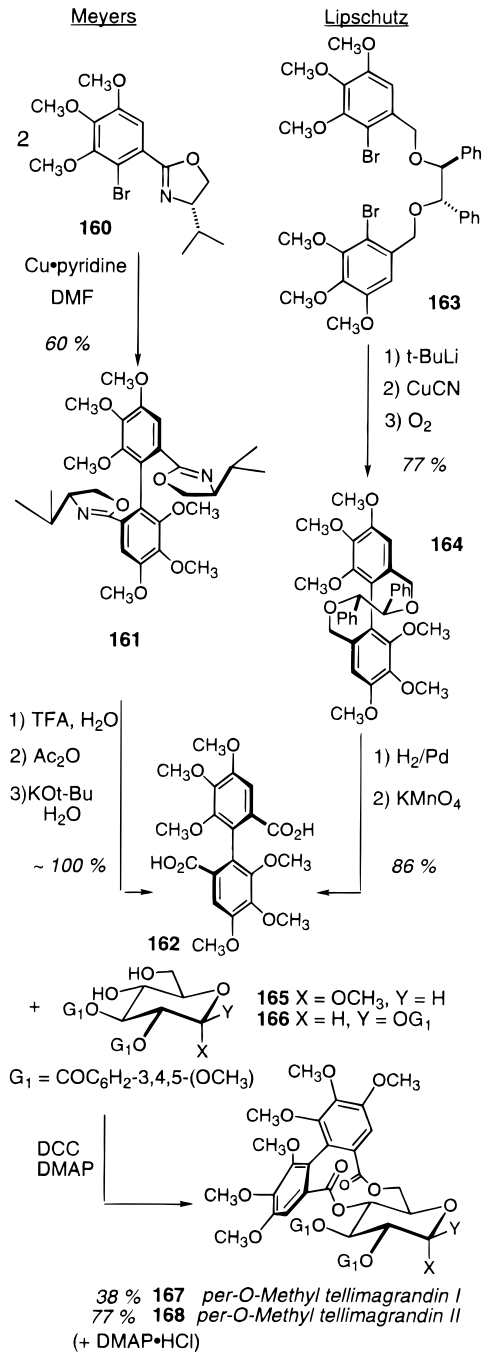
An alternative to the biomimetic oxidative cyclization strategy for ellagitannin synthesis developed herein has been pursued by Meyers[86] and, independently, Lipshutz.[87] This approach to ellagitannin assembly is modular in nature and features the convergent union of glucose diols **165**/**166** with a fully formed, chiral HHDP unit **162** (Scheme 30).

The crux of both the Colorado State and Santa Barbara syntheses of permethylated versions of tellimagrandins I and II is the enantioselective preparation of the (*S*)-HHDP unit via *reductive* coupling of appropriately activated galloyl precursors **160**/**163** that bear chiral auxiliaries. The Colorado State approach utilizes an oxazoline auxiliary in an Ullmann-type coupling (**160** → **161**) which proceeds in good yield and with high diastereomeric excess. Careful auxiliary hydrolysis then affords the key (*S*)-diacid **162**. The related cuprate-mediated coupling

Scheme 29



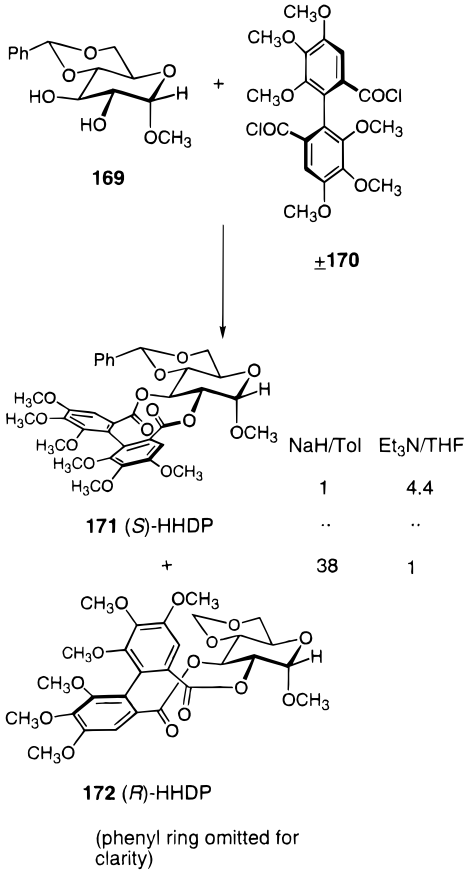
Scheme 30



of the chiral bis galloyl derivative **163** favored by Lipshutz *et al.* is equally efficient and selective for the (*S*)-biphenyl unit **164**. Two facile steps delivers the same (*S*)-diacid **162**. At this point, both approaches mesh and attachment of the chiral (*S*)-HHDP fragment **162** to the per-*O*-methylgalloylated glucose cores **165** (Meyers) or **166** (Lipshutz) furnishes the tellimagrandin I and II derivatives **167** and **168**, respectively, in modest to good yields.

The high level of reagent-based stereochemical control demonstrated by the reductive couplings **160** → **161** and **163** → **164** is a notable accomplishment which stands in contrast to the substrate-based control of HHDP stereochemistry central to the oxidative cyclization strategy. Nevertheless, actual acquisition of a naturally occurring ellagitannin still awaits successful exhaustive deprotection of the permethylated acylation products **167** or **168**.

Scheme 31



Itoh and Chika have extended this theme of sugar/HHDP coupling to assembly of both 2,3-(*R*)- and (*S*)-HHDP-containing glucose derivatives **171**/**172** (Scheme 31).[88] The critical element of this strategy which distinguishes it from the chemistry discussed above is the use of a racemic HHDP moiety (±)-**170** with the chiral sugar diol **169**. Varying degrees of kinetic resolution of the HHDP unit are observed as a function of solvent and base. The best selectivity for the *R* (unnatural) HHDP-containing species **172** is obtained with NaH/toluene, while triethylamine/THF is most advantageous for forming the *S* diastereomer **171**. The basis for the selectivity observed remains obscure at present. Nevertheless, the ready availability of the starting components **169** and **170** and the simplicity of the transformations auger well for utilization of this strategy in ellagitannin synthesis.

III. Future Directions

The ellagitannin family of hydrolyzable tannins presents many challenges and opportunities for organic chemistry. The structural diversity of these secondary plant metabolites, the extent of which was only hinted at in this review, ensures that the elucidation of biosynthetic connectivities will be an ongoing concern for the foreseeable future. In fact, given the *functional* similarity (i.e., broad spectrum protein association) of the hydrolyzable tannins, the profusion of molecular architectures which all plausibly emanate from a single, simple precursor is yet

another example of nature gainfully employing a "combinatorial library" approach to solving problems in molecular recognition. Extracting structure/function "generalities" from all of this diversity remains a major challenge in understanding the functional as well as ecological role of these compounds in plants.

Organic synthesis is, and will continue to be, a central tool in aiding the study of these secondary metabolites. Pure samples of natural materials and/or rationally designed analogs will be required to probe the issues raised above and the related questions that attend the exquisitely selective recognition of specific biological receptors by certain medicinally active ellagitannins. The challenges for synthesis are many, and the preliminary results described in this review only serve as a foundation for approaching the next generation of structurally complex targets that include the more biologically potent species. The presumably biomimetic strategy adopted for HHDP synthesis offers advantages in economy and efficiency, but its scope is as yet untested. The relationship between polygalloyl substrate conformation and oxidative cyclization stereochemistry is not fully understood, and "anomalous" outcomes might be anticipated (*vide supra*). In addition, synthetic access to the oxygen-bridged dimeric (and multimeric) ellagitannins will require fundamental improvements in diaryl ether synthesis methodology. Thus, as advances in synthesis enable advances in structure/binding studies, a richer understanding of the function of the ellagitannins and gallotannins in their various milieus will come into focus.

IV. Acknowledgments

We thank the NIH (GM 35727) and the NSF (IBN 94-07308) for financial support, and all of our coworkers referenced below for their critical contributions to this work.

V. References

(1) (1) (a) Fischer, E. *Untersuchungen über Depside und Gerbstoffe (Studies on Depsides and Tannins)*; Springer Verlag: Berlin, 1919. (b) Freudenberg, K. *Chem. Ber.* **1919**, *52*, 1238.
(2) (a) Schmidt, O. T. *Fortschr. Chem. Org. Naturst.* **1956**, *13*, 70. (b) Schmidt, O. T.; Mayer, W. *Angew. Chem.* **1956**, *68*, 103.
(3) (a) Haslam, E.; Cai, Y. *Nat. Prod. Rep.* **1994**, 41. (b) Haslam, E. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; p 169. (c) Haslam, E. *Plants polyphenols - Vegetable tannins revisited*; Cambridge University Press: Cambridge, 1989. (d) Haslam, E. In *Natural Products of Woody Plants*; Rowe, J. W., Ed.; Springer-Verlag: Berlin-Heidelberg-New York, 1989; Vol. 1, p 399. (e) Haslam, E. *J. Chem. Ecol.* **1988**, *14*, 1789. (f) Haslam, E. *Rec. Adv. Phytochem.* **1986**, *20*, 163. (g) Haslam, E. *Prog. Chem. Org. Nat. Prod.* **1982**, *41*, 1.
(4) (a) Okuda, T.; Yoshida, T.; Hatano, T. *Phytochemistry* **1993**, *32*, 507. (b) Yoshida, T.; Hatano, T.; Kuwajima, T.; Okuda, T. *Heterocycles* **1992**, *33*, 463. (c) Okuda, T.; Yoshida, T.; Hatano, T. *Heterocycles* **1990**, *30*, 1195. (d) Okuda, T.; Yoshida, T.; Mori, K.; Hatano, T. *Heterocycles* **1981**, *15*, 1323.
(5) (a) Nonaka, G.-I.; Harada, M.; Nishioka, I. *Chem. Pharm. Bull.* **1980**, *28*, 685. (b) Saijo, R.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1989**, *37*, 2063. (c) Tanaka, T.; Nonaka, G.-I.; Nishioka, I. *J. Chem. Res. (S)* **1985**, 176. (d) Nonaka, G.-I.; Akazawa, M.; Nishioka, I. *Heterocycles* **1992**, *33*, 597. (e) Nonaka, G.-I.; Tanaka, T.; Nita, M.; Nishioka, I. *Chem. Pharm. Bull.* **1982**, *30*, 2255. (f) Tanaka, T.; Kirihara, S.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1993**, *41*, 1708. (g) Lin, J.-H.; Ishimatsu, M.; Takashi, T.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1990**, *38*, 1844. (h) Lin, J.-H.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I.; Chen, I.-S. *Chem. Pharm. Bull.* **1990**, *38*, 2162. (i) Lee, S.-H.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1991**, *39*, 630. (j) Tanaka, T.; Nonaka, G. I.; Nishioka, I.; Miyahara, K.; Kawasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 369. (k) Lin, J.-H.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I.; Chen, I.-S. *Chem. Pharm. Bull.* **1990**, *38*, 2162. (l) Nonaka, G.-I.; Morimoto, S.; Nishioka, I. *Chem. Pharm. Bull.* **1986**, *34*, 941. (m) Saijo, R.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1989**, *37*, 2624. (n) Tanaka, T.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1990**, *38*, 2424. (o) Nonaka, G.-I.; Sakai, T.; Tanaka, T.; Mihashi, K.; Nishioka, I. *Chem. Pharm. Bull.* **1990**, *38*, 2151. (p) Lee, S.-H.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I. *Phytochemistry* **1990**, *29*, 3621. (q) Xu, Y.-M.; T., S.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1991**, *39*, 639. (r) Tanaka, T.; Kirihara, S.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1993**, *41*, 1708. (s) Nonaka, G.-I.; Ishimaru, K.; Azuma, R.; Ishimatsu, M.; Nishioka, I. *Chem. Pharm. Bull.* **1989**, *37*, 2071. (t) Nonaka, G.-I.; Nishimura, H.; Nishioka, I. *J. Chem. Soc., Perkin Trans. 1* **1985**, 163. (u) Ishimaru, K.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1987**, *35*, 602. (v) Lin, T.-C.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I.; Young, T.-J. *Chem. Pharm. Bull.* **1991**, *39*, 1144. (w) Nishizawa, M.; Yamagishi, T.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1980**, *28*, 2850. (x) Nishizawa, M.; Yamagishi, T.; Nonaka, G.-I.; Nishioka, I. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2963. (y) Nonaka, G.-I.; Ishimatsu, M.; Ageta, M.; Nishioka, I. *Chem. Pharm. Bull.* **1989**, *37*, 50. (z) Ishimatsu, M.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I.; Nishizawa, M.; Yamagishi, T. *Chem. Pharm. Bull.* **1989**, *37*, 129.
(6) Wilkins, C. K.; Bohm, B. A. *Phytochemistry* **1976**, *15*, 211.
(7) Yoshida, T.; Ohwashi, W.; Haba, K.; Ohbayashi, H.; Ishihara, K.; Okano, Y.; Shingu, T.; Okuda, T. *Chem. Pharm. Bull.* **1991**, *39*, 2264.
(8) Yoshida, T.; Okuda, T.; Memom, M. U.; Shingu, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 315.
(9) (a) Gupta, R. K.; Al-Shafi, S. M. K.; Layden, K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2525. (b) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1765. (c) Okuda, T.; Yoshida, T.; Ashida, M. *Heterocycles* **1981**, *16*, 1681.
(10) (a) Okuda, T.; Yoshida, T.; Kuwahara, M.; Memon, M. U.; Shingu, T. *J. Chem. Soc., Chem. Commun.* **1982**, 163. (b) Okuda, T.; Yoshida, T.; Kuwahara, M.; Memon, M. U.; Shingu, T. *Chem. Pharm. Bull.* **1984**, *32*, 2165.
(11) (a) Jurd, L. *J. Am. Chem. Soc.* **1958**, *80*, 2249. (b) Schmidt, O. T.; Würtele, L.; Harréus, A. *Liebigs Ann. Chem.* **1965**, *690*, 150. (c) Seikel, M. K.; Hillis, W. E. *Phytochemistry* **1970**, *9*, 1115.
(12) (a) Haddock, E. A.; Gupta, R. K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2535. (b) Hatano, T.; Hattori, S.; Ikeda, Y.; Shingu, T.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 1902. (c) Self, R.; Eagles, J.; Galletti, G. C.; Mueller-Harvey, I.; Hartley, R. D.; Lea, A. G. H.; Magnolato, D.; Richli, U.; Gujer, R.; Haslam, E. *Biomed. Environ. Mass Spectrom.* **1986**, *13*, 449.
(13) (a) Schmidt, O. T.; Schmidt, D. M.; Herok, J. *Liebigs Ann. Chem.* **1954**, *587*, 67. (b) Schmidt, O. T.; Blinn, F.; Lademann, R. *Liebigs Ann. Chem.* **1952**, *576*, 75. (c) Schmidt, O. T.; Schmidt, D. M. *Liebigs Ann. Chem.* **1952**, *578*, 31.
(14) (a) Okuda, T.; Yoshida, T.; Hatano, T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 9. (b) Okuda, T.; Yoshida, T.; Hatano, T. *Tetrahedron Lett* **1980**, *21*, 2561. (c) Okuda, T.; Nayeshiro, H.; Seno, K. *Tetrahedron Lett.* **1977**, 4421. (d) Okuda, T.; Yoshida, T.; Nayeshiro, H. *Chem. Pharm. Bull.* **1977**, *25*, 1862. (e) Okuda, T.; Yoshida, T.; Nayeshiro, H. *Tetrahedron Lett.* **1976**, 3721.
(15) (a) Schmidt, O. T.; Blinn, F. *Naturwissenschaften* **1951**, *38*, 72. (b) Schmidt, O. T.; Schulz, J.; Fiesser, H. *Liebigs Ann. Chem.* **1967**, *706*, 187. (c) Yoshida, T.; Fujii, R.; Okuda, T. *Chem. Pharm. Bull.* **1980**, *28*, 3713. (d) Yoshida, T.; Okuda, T.; Koga, T.; Toh, N. *Chem. Pharm. Bull.* **1982**, *30*, 2655.
(16) Hatano, T.; Hattori, S.; Okuda, T. *Chem. Pharm. Bull.* **1986**, *34*, 4092.
(17) (a) Schmidt, O. T.; Komarek, E. *Liebigs Ann. Chem.* **1955**, *591*, 156. (b) Schmidt, O. T.; Grünewald, H. H. *Liebigs Ann. Chem.* **1957**, *603*, 183. (c) Schmidt, O. T.; Komarek, E.; Rentél, H. *Liebigs Ann. Chem.* **1957**, *602*, 50.
(18) (a) Okuda, T.; Hatano, T.; Ogawa, N. *Chem. Pharm. Bull.* **1982**, *30*, 4234. (b) Hatano, T.; Okonogi, A.; Okuda, T. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; p 195. (c) Yoshida, T.; Namba, O.; Chen, L.; Liu, Y.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 3296. (d) Hatano, T.; Ogawa, N.; Shingu, T.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 3341. (e) Hatano, T.; Ogawa, N.; Yasuhara, T.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 3308.
(19) (a) Hatano, T.; Yashuhara, T.; Matsuda, M.; Yazaki, K.; Yoshida, T.; Okuda, T. *Chem. Pharm. Bull.* **1989**, *37*, 2269. (b) Hatano, T.; Yashuhara, T.; Matsuda, M.; Yazaki, K.; Yoshida, T.; Okuda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2735.
(20) (a) Yoshida, T.; Chou, T.; Nitta, A.; Miyamoto, K.-I.; Koshiura, R.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 1211. (b) Kadota, S.; Takamori, Y.; Kikuchi, T.; Motegi, A.; Ekimoto, H. *Tetrahedron Lett.* **1990**, *31*, 393. (c) Kadota, S.; Takamori, Y.; Nyein Nyein, K.; Kikuchi, T.; Tanaka, K.; Ekimoto, H. *Chem. Pharm.*

Bull. **1990**, *38*, 2687. (d) Yoshida, T.; Chou, T.; Nitta, A.; Okuda, T. *Heterocycles* **1989**, *29*, 2267.
(21) Hatano, T.; Okonogi, A.; Yazaki, K.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 2707.
(22) (a) Yoshida, T.; Ahmed, A. F.; Memon, M. U.; Okuda, T. *Phytochemistry* **1993**, *33*, 197. (b) Yoshida, T.; Hatano, T.; Ahmed, F. A.; Okonogi, A.; Okuda, T. *Tetrahedron* **1991**, *47*, 3575. (c) Yoshida, T.; Ahmed, A. F.; Memon, M. U.; Okuda, T. *Chem. Pharm. Bull.* **1991**, *39*, 2849.
(23) Yoshida, T.; Feng, W.-S.; Okuda, T. *Chem. Pharm. Bull.* **1992**, *40*, 1997.
(24) Yoshida, T.; Maruyama, T.; Nitta, A.; Okuda, T. *Chem. Pharm. Bull.* **1992**, *40*, 1750.
(25) (a) Yoshida, T.; Chou, T.; Matsuda, M.; Yasuhara, T.; Yazaki, K.; Hatano, T.; Nitta, A.; Okuda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1157. (b) Yoshida, T.; Chou, T.; Nitta, A.; Okuda, T. *Chem. Pharm. Bull.* **1992**, *40*, 2023. (c) Yoshida, T.; Tanei, S.; Liu, Y.-Z.; Yuan, K.; Ji, C.-R.; Okuda, T. *Phytochemistry* **1993**, *32*, 1287.
(26) Yoshida, T.; Namba, O.; Chen, L.; Okuda, T. *Chem. Pharm. Bull.* **1990**, *38*, 86.
(27) (a) Yazaki, K.; Hatano, T.; Okuda, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2289. (b) Schmidt, O. T.; Schanz, R.; Wurmb, R; Eckert, R. *Liebigs Ann. Chem.* **1967**, *706*, 131. (c) Schmidt, O. T.; Schanz, R.; Wurmb, R.; Groebke, W. *Liebigs Ann. Chem.* **1967**, *706*, 154. (d) Yoshida, T.; Arioka, H.; Fujita, T.; Chen, X.-M.; Okuda, T. *Phytochemistry* **1994**, *37*, 863.
(28) Schmidt, O. T.; Wieder, G. *Liebigs Ann. Chem.* **1967**, *706*, 198.
(29) Okuda, T.; Hatano, T.; Nitta, H.; Fujii, R. *Tetrahedron Lett.* **1980**, *21*, 4361.
(30) Okuda, T.; Yoshida, T.; Hatano, T.; Ikeda, Y.; Shingu, T.; Inoue, T. *Chem. Pharm. Bull.* **1986**, *34*, 4075.
(31) (a) Haslam, E.; Uddin, M. *J. Chem. Soc. (C)* **1967**, 2381. (b) Haworth, R. D.; De Silva, L. B. *J. Chem. Soc.* **1951**, 3511. (c) Freudenberg, K. *Chem. Ber.* **1919**, *52*, 1238.
(32) Schmidt, O. T.; Wurmb, R.; Schulz, J. *Liebigs Ann. Chem.* **1967**, *706*, 180.
(33) Yoshida, T.; Jin, Z.-X.; Okuda, T. *Chem. Pharm. Bull.* **1991**, *39*, 49.
(34) (a) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1765. (b) Okuda, T.; Yoshida, T.; Yazaki, K.; Ashida, M. *Chem. Pharm. Bull.* **1982**, *30*, 766. (c) Okuda, T.; Yoshida, T.; Hatano, T.; Yazaki, K.; Ashida, M. *Phytochemistry* **1982**, *21*, 2871. (d) Mayer, W.; Gabler, W.; Riester, A.; Korger, H. *Liebigs Ann. Chem.* **1967**, *707*, 177. (e) Mayer, W.; Seitz, H.; Jochims, J. C. *Liebigs Ann. Chem.* **1969**, *721*, 186. (f) Mayer, W.; Seitz, H.; Jochims, J. C.; Schauerte, K.; Schilling, G. *Liebigs Ann. Chem.* **1971**, *751*, 60.
(35) (a) Hervé du Penhoat, C. L. M.; Michon, V. M. F.; Ohassan, A.; Peng, S.; Scalbert, A.; Gage, D. *Phytochemistry* **1991**, *30*, 329. (b) Hervé du Penhoat, C. L. M.; Michon, V. M. F.; Peng, S.; Viriot, C.; Scalbert, A.; Gage, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1653.
(36) Viriot, C.; Scalbert, A.; Hervé du Penhoat, C. L. M.; Michon, V. M. F.; Moutounet, M. *Phytochemistry* **1994**, *36*, 1253.
(37) Han, L.; Hatano, T.; Yoshida, T.; Okuda, T. *Chem. Pharm. Bull.* **1994**, *42*, 1399.
(38) (a) Gross, G. In *Plant Cell Wall Polymers - Biogenesis and Biodegradation*; Lewis, N. G., Paice, M. G., Eds.; ACS Symposium Series 399; American Chemical Society: Washington, DC, 1989; p 108. (b) Gross, G. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; p 43.
(39) Haslam, E. *Nat. Prod. Rep.* **1986**, 217.
(40) Haddock, E. A.; Gupta, R. K.; Al-Shafi, S. M. K.; Layden, K.; Haslam, E.; Magnolato, D. *Phytochemistry* **1982**, *21*, 1049.
(41) (a) Haslam, E. *J. Chem. Soc. (C)* **1967**, 1734. (b) Haddock, E. A.; Gupta, R. K.; Al-Shafi, S. M. K.; Haslam, E.; Magnolato, D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2515.
(42) (a) Schmidt, O. T.; Demmler, K. *Liebigs Ann. Chem.* **1952**, *576*, 85. (b) Schmidt, O. T.; Voigt, H.; Puff, W.; Köster, R. *Liebigs Ann. Chem.* **1954**, *586*, 165. (c) Schmidt, O. T.; Demmler, K. *Liebigs Ann. Chem.* **1954**, *586*, 179.
(43) (a) Schmidt, O. T.; Schmidt, D. M.; Herok, J. *Liebigs Ann. Chem.* **1954**, *587*, 67. (b) Schmidt, O. T.; Blinn, F. *Naturwissenschaften* **1951**, *38*, 72.
(44) (a) Okuda, T.; Yoshida, T.; Hatano, T. *J. Nat. Prod.* **1989**, *52*, 1. (b) Okuda, T.; Yoshida, T.; Hatano, T.; Koga, T.; Toh, N.; Kuriyama, K. *Tetrahedron Lett.* **1982**, *23*, 3937. (c) Okuda, T.; Yoshida, T.; Hatano, T.; Koga, T.; Toh, N.; Kuriyama, K. *Tetrahedron Lett.* **1982**, *23*, 3941.
(45) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
(46) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, Part B, p 341.
(47) (a) Murray, N. J.; Williamson, M. P.; Lilley, T. H.; Haslam, E. *Eur. J. Biochem.* **1994**, *219*, 923. (b) Luck, G.; Liao, H.; Murray, N. J.; Grimmer, H. R.; Warminsky, E. E.; Williamson, M. P.; Lilley, T. H.; Haslam, E. *Phytochemistry* **1994**, *37*, 357. (c) Hagerman, A. E. In *Phenolic Compounds in Food and Their Effects on Health, I*; Ho, C.-T., Lee, C. Y., Huang, M. T., Eds.; ACS Symposium Series 506; American Chemical Society: Washington, DC, 1992; p 236. (d) Hagerman, A. E.; Butler, L. G. *J. Agric. Food Chem.* **1980**, *28*, 944. (e) Goldstein, J. L.; Swain, T. *Phytochemistry* **1965**, *4*, 185. (f) Kumar, R.; Singh, M. *J. Agric. Food Chem.* **1984**, *32*, 447. (g) Mole, S.; Waterman, P. G. *Phytochemistry* **1987**, *26*, 99. (h) Butler, L. G.; Riedl, D. J.; Lebryk, D. G.; Blytt, H. J. *JAOCS* **1984**, *61*, 916. (i) Ozawa, T.; Lilley, T.; Haslam, E. *Phytochemistry* **1987**, *26*, 2937. (j) Okuda, T.; Mori, K.; Hatano, T. *Chem. Pharm. Bull.* **1985**, *33*, 1424. (k) Takechi, M.; Tanaka, Y. *Phytochemistry* **1987**, *26*, 95. (l) McManus, J. P.; Davis, K. G.; Beart, J. E.; Gaffney, S. H.; Lilley, T. H.; Haslam, E. *J. Chem Soc., Perkin Trans. 2* **1985**, 1429. (m) Calderon, P.; Van Buren, J.; Robinson, W. B. *J. Agric. Food Chem.* **1968**, *16*, 479. (n) Spencer, C. M.; Cai, Y.; Martin, R.; Gaffney, S. H.; Goulding, P. N.; Magnolato, D.; Lilley, T. H.; Haslam, E. *Phytochemistry* **1988**, *27*, 2397. (o) Haslam, E.; Lilley, T. H.; Warminski, E.; Liao, H.; Cai, Y.; Martin, R.; Gaffney, S. H.; Goulding, P. N.; Luck, G. In *Phenolic Compounds in Food and their Effects on Health, I*; Ho, C.-T., Lee, C. Y., Huang, M. T., Eds.; ACS Symposium Series 506; American Chemical Society: Washington, DC, 1992; p 8.
(48) (a) Haslam, E.; Lilley, T. H.; Cai, Y.; Martin, R.; Magnolato, D. *Planta Med.* **1989**, *55*, 1. (b) Nishizawa, K.; Najata, I.; Kishida, A.; Ayer, W. A.; Browne, L. M. *Phytochemistry* **1990**, *29*, 2491. (c) Kakiuchi, N.; Hattori, M.; Nishizawa, M.; Yamagishi, T.; Okuda, T.; Namba, T. *Chem. Pharm. Bull.* **1986**, *34*, 720. (d) Ivancheva, S.; Manolova, N.; Serkedjieva, J.; Dimov, V.; Ivanovska, N. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; p 717. (e) Serkedjieva, J.; Manolova, N. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; p 705. (f) Okuda, T.; Yoshida, T.; Hatano, T. *Planta Med.* **1989**, *55*, 117. (g) Okuda, T.; Yoshida, T.; Hatano, T. In *Phenolic Compounds in Food and their Effects on Health, II*; Huang, M.-T., Ho, C.-T., Lee, C. Y., Eds.; ACS Symposium Series 507; American Chemical Society: 1992; p 87. (h) Okuda, T.; Yoshida, T.; Hatano, T. In *Phenolic Compounds in Food and their Effects on Health, II*; Huang, M.-T., Ho, C.-T., Lee, C. Y., Eds.; ACS Symposium Series 507; American Chemical Society: Washington, DC, 1992; p 160. (i) Okuda, T.; Yoshida, T.; Hatano, T. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; p 539.
(49) Cai, Y.; Gaffney, S. H.; Lilley, T. H.; Magnolato, D.; Martin, R.; Spencer, C. M.; Haslam, E. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2197.
(50) (a) Zucker, W. V. *Am. Nat.* **1983**, *121*, 335. (b) Beart, J. E.; Lilley, T. H.; Haslam, E. *Phytochemistry* **1985**, *24*, 33. (c) Martin, J. S.; Martin, M. M.; Bernays, E. A. *J. Chem. Ecol.* **1987**, *13*, 605.
(51) Hagerman, A. E.; Buttler, L. G. In *Herbivores, Their Interaction with Secondary Metabolites*; Rosenthal, G. A., Berenhaum, M. R., Eds.; Academic Press: San Diego, 1991; Vol. 1; p 355.
(52) (a) Butler, L. G.; Rogler, J. C. In *Phenolic Compounds in Food and Their Effects on Health, I*; Ho, C.-T., Lee, C. Y., Huang, M. T., Eds.; ACS Symposium Series 506; American Chemical Society: Washington, DC, 1992; p 298. (b) Scalbert, A. *Phytochemistry* **1991**, *30*, 3875.
(53) (a) Kashiwada, Y.; Nonaka, G.-I.; Nishioka, I.; Lee, K. J.-H.; Bori, I.; Fukushima, Y.; Bastow, K. F.; Lee, K.-H. *J. Pharm. Sci.* **1993**, *82*, 487. (b) Bastow, K. F.; Bori, I.; Fukushima, Y.; Kashiwada, Y.; Tanaka, T.; Nonaka, G.-I.; Nishioka, I.; Lee, K.-H. *Planta Med.* **1993**, *59*, 240.
(54) Berry, D. E.; Mackenzie, L.; Shultis, E. A.; Chan, J. A. *J. Org. Chem.* **1992**, *57*, 420.
(55) Kashiwada, Y.; Nonaka, G.-I.; Nishioka, I.; Chang, J.-J.; Lee, K.-H. *J. Nat. Prod.* **1992**, *55*, 1033.
(56) Miyamoto, K.; Kishi, N.; Koshiura, R.; Yoshida, T.; Hatano, T.; Okuda, T. *Chem. Pharm. Bull.* **1987**, *35*, 814.
(57) (a) Miyamoto, K.; Koshiura, R.; Ikeya, Y.; Taguchi, H. *Chem. Pharm. Bull.* **1985**, *33*, 3977. (b) Miyamoto, K.; Kishi, N.; Koshiura, R. *Jpn. J. Pharmacol.* **1987**, *43*, 187. (c) Miyamato, K.-I.; Nomura, M.; Sasakura, M.; Matsui, E.; Koshiura, R.; Murayama, T.; Furukawa, T.; Hatano, T.; Yoshida, T.; Okuda, T. *Jpn. J. Cancer Res.* **1993**, *84*, 99.
(58) (a) Murayama, T.; Kishi, N.; Koshiura, R.; Tagaki, K.; Furukawa, T.; Miyamoto, K.-I. *Anticancer Res.* **1992**, *12*, 1471. (b) Miyamoto, K.-I.; Kishi, N.; Murayama, T.; Furukawa, T.; Koshiura, R. *Cancer Immunol. Immunother.* **1988**, *27*, 59.
(59) Sugi, M. In *Cancer Therapy in China Today*; Kondo, K., Ed.; Shizensha: Tokyo, 1977; p 95.
(60) (a) Takechi, M.; Tanaka, Y.; Takehara, M.; Nonaka, G.-I.; Nishioka, I. *Phytochemistry* **1985**, *24*, 2245. (b) Fukuchi, K.; Sagakami, H.; Okuda, T.; Hatano, T.; Tanuma, S.; Kitajima, K.; Inoue, Y.; Inoue, S.; Ichikawa, S.; Nomomiya, M.; Konno, K. *Antiviral Res.* **1989**, *11*, 285.
(61) Ogata, T.; Kato, A. (Tsumura and Co.) Jpn. Kokai Tokkyo Koho JP 04,264,026 [92,264,026].
(62) (a) Löwe, J. F. F. F. *Z. Chem.* **1868**, *4*, 603. (b) Ernst, F.; Zwenger, C. *Annalen* **1871**, *159*, 32. (c) Perkin, A. G.; Nierenstein, M. *J.*

Chem. Soc. **1905**, *87*, 1412. (d) Perkin, A. G. *J. Chem. Soc.* **1906**, *89*, 251. (e) Erdtman, H. *Svensk Kem. Tidskr.* **1935**, *47*, 223. (f) Mayer, W. *Annalen* **1952**, *578*, 34. (g) Hathway, D. E. *J. Chem. Soc.* **1957**, 519. (h) Jurd, L. *J. Am. Chem. Soc.* **1959**, *81*, 4606. (i) Pastuska, G. *Naturwissenschaften* **1961**, *48*, 457. (j) Mayer, W.; Hoffmann, E. H.; Lösch, N.; Wolf, H.; Wolter, B.; Schilling G. *Annalen* **1984**, 929. (k) Zeng, W.; Heur, Y.-H.; Kinstle, T. H.; Stoner, G. D. *Labelled Compd.* **1991**, *29*, 657. (l) Hathway, D. E. *Biochem. J.* **1957**, *67*, 445. (m) Flaig, W.; Haider, K. *Planta Med.* **1961**, *9*, 123. (n) Kamel, M. Y.; Saleh, N. A.; Ghazy, A. M. *Phytochemistry* **1977**, *16*, 521. (o) Pospisil, F.; Cvikrová, M.; Hrubcová, M. *Biochem. Plantar. (Praha)* **1983**, *25*, 373.

(63) Molecular mechanics calculations on all species described herein were performed on a Silicon Graphics Power Indigo 2XZ computer equipped with version 4.5 of macromodel (MM2* or MM3* force field). Conformational space was searched with either a 1000-step, a 2000-step, or a 5000 step mixed Monte Carlo/stochastic dynamics algorithm, depending upon the flexibility of the molecule. In each calculation, the minimum energy structure shown was found at least 10 times. In addition, several of the structures were tested for convergence by comparing the results obtained upon starting with significantly different input geometries. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. See also Still, W. C.; Guarnieri, F. *J. Comput. Chem.* **1994**, *15*, 1302.

(64) (a) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 1162. (b) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357.

(65) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1991**, *113*, 1736. (b) Mann, C. K.; Barnes, K. K. *Electrochemical Reactions in Nonaqueous Systems*; Marcel Dekker: New York, 1970.

(66) (a) Harrison, M. J.; Norman, R. O. C. *J. Chem. Soc. (C)* **1970**, 728. (b) For a different interpretation, see also: Bubb, W. A.; Sternhell, S. *Tetrahedron Lett.* **1970**, 4499.

(67) Unpublished results from Penn State: (a) K. S. Feldman. (b) R. S. Smith. (c) K. Sahasrabudhe.

(68) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. (b) Exner, O. In *Correlation Analysis in Chemistry*, Chapman, N. B., Shorter, J., Eds; Plenum Press: New York, 1978.

(69) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742.

(70) Feldman, K. S.; Sambandam, A. *J. Org. Soc.* **1995**, *60*, 8171.

(71) (a) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679. (b) Evans, D. A.; Ellman, J. A.; De Vries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912. (c) Pearson, A. J.; Bruhn, P. R. *J. Org. Chem.* **1991**, *56*, 7092. (d) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2304. (e) Schmittling, E. A.; Sawyer, J. S. *J. Org. Chem.* **1993**, *58*, 3229. (f) Beugelmans, R.; Singh, G. P.; Zhu, J. *Tetrahedron Lett.* **1993**, *34*, 7741. (g) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017.

(72) Lin, J.-H.; Ishimatsu, M.; Takashi, T.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1990**, *38*, 1844.

(73) Waters, W. A. *J. Chem. Soc. (B)* **1971**, 2026.

(74) (a) Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*; Wiley: New York, 1988; Vol. 2, Parts 1 and 2. (b) Kutyrev, A. A. *Tetrahedron* **1991**, *47*, 8043. (c) Peter, M. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 555. (d) Grundmann, C. In *Methoden der Organischen Chemie*, Mueller, E., Bayer, O., Eds.; Thieme: Stuttgart, 1979.

(75) (a) Hanzlik, R. P.; Harriman, S. P.; Frauenhoff, M. M. *Chem. Res. Toxicol.* **1994**, *7*, 177. (b) Nakano, H.; Tahara, S.; Iizuka, T.; Mizutani, J. *Agric. Biol. Chem.* **1987**, *51*, 549. (c) Matheis, G.; Whitaker, J. R. *J. Food Biochem.* **1984**, *8*, 137. (d) Pierpoint, W. S. In *Leaf Protein Concentrates*; Telek, L., Graham, H. D., Eds.; AVI: Westport, Connecticut, 1983; p 235. (e) Mason, H. S.; Peterson, E. W. *Biochem. Biophys. Acta* **1965**, *111*, 134. (f) Felton, G. W.; Duffey, S. S. *J. Chem. Ecol.* **1990**, *16*, 1221. (g) Sugumaran, M.; Dali, H.; Semensi V. *Arch. Insect Biochem. Physiol.* **1989**, *11*, 127. (h) Kalyanaraman, B.; Premovic, P. I.; Sealy, R. C. *J. Biol. Chem.* **1987**, *262*, 11080. (i) Salgues, M.; Cheynier, V.; Gunata, Z.; Wylde, R. *J. Food Sci.* **1986**, *51*, 1191.

(76) (a) Tanaka, T.; Fujisaki, H.; Nonaka, G.; Nishioka, I. *Heterocycles* **1992**, *33*, 375. (b) Tanaka, T.; Fujisaki, H.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1992**, *40*, 2937.

(77) Wanzlick, H.-W. *Chem. Ber.* **1959**, *92*, 3006.

(78) (a) Carless, H. A. J.; Swan, D. I.; Haywood, D. J. *Tetrahedron* **1993**, *49*, 1665. (b) Milas, N. A.; Sakal, E.; Plati, J. T.; Rivers, J. T.; Gladding, J. K.; Grossi, F. X.; Weiss, Z.; Campbell, M. A.; Wright, H. F. *J. Am. Chem. Soc.* **1948**, *70*, 1597.

(79) Quideau, S.; Feldman, K. S.; Appel, H. M. *J. Org. Chem.* **1995**, *60*, 4982.

(80) (a) Blomberg, C. *Bull. Soc. Chim. Fr.* **1972**, 2143. (b) Beak, P.; Yamamoto, J.; Upton, C. J. *J. Org. Chem.* **1975**, *40*, 3052. (c) Wege, D. *Aust. J. Chem.* **1971**, *24*, 1531

(81) (a) Finley, K. T. In *The Chemistry of the Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; Vol. 2, Part 1, p 537. (b) Grundmann, C. In *Methoden der Organischen Chemie (Houben-Weyl)*; Müller, E., Bayers, O., Eds.; Thieme: Stuttgart, 1979; Bd. VII/3b. (c) Critchlow, A.; Haslam, E.; Haworth, R. D.; Tinker, P. B.; Waldron, N. M. *Tetrahedron* **1967**, *23*, 2829. (d) Horspool, W. M.; Tedder, J. M.; Din, Z. U. *J. Chem. Soc. (C)* **1968**, 1597. (e) Horspool, W. M.; Tedder, J. M.; Din, Z. U. *J. Chem. Soc. (C)* **1969**, 1692. (f) Horspool, W. M.; Tedder, J. M.; Din, Z. U. *J. Chem. Soc. (C)* **1969**, 1694. (g) Horspool, W. M.; Smith, P.; Tedder, J. M. *J. Chem. Soc. (C)* **1971**, 1638. (h) Ansell, M. F.; Leslie, V. J. *J. Chem. Soc. (C)* **1971**, 1423. (i) Ansell, M. F.; Bignold, A. J.; Gosden, A. F.; Leslie, V. J.; Murray, R. A. *J. Chem. Soc. (C)* **1971**, 1414. (j) Ansell, M. F.; Gosden, A. F.; Leslie, V. J.; Murray, R. A. *J. Chem. Soc. (C)* **1971**, 1401. (k) Allmann, R.; Debaerdemaeker, T.; Friedrichsen, W.; Jürgens, H. J.; Betz, M. *Tetrahedron* **1976**, *32*, 147. (l) Friedrichsen, W.; Schröer, W.-D.; Schmidt, R. *Liebigs Ann. Chem.* **1976**, *32*, 793. (m) Bazan, A. C.; Edwards, J. M.; Weiss, U. *Tetrahedron* **1978**, *34*, 3005. (n) Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995. (o) Haiza, M.; Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 5008. (p) Lee, J.; Shan Mei, H.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 5013. (q) Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1991**, *47*, 5857. (r) Chiba, K.; Tada, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2485. (s) Nair, V.; Kumar, S.; Williard, P. G. *Tetrahedron Lett.* **1995**, *36*, 1605.

(82) (a) Dorigo, A. E.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 1650. (b) Green, M. M.; Boyle, B. A.; Vairamani, M.; Mukhopadhyay, T.; Saunders, W. H., Jr.; Bowen, P.; Allinger, N. L. *J. Am. Chem. Soc.* **1986**, *108*, 2381.

(83) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212 and references cited therein. (b) Jansson, K.; Ahlfors, S.; Frejd, T.; Kihlberg, J.; Magnusson, G.; Dahmén, J.; Noori, G.; Stenvall, K. *J. Org. Chem.* **1988**, *53*, 5629. (c) Kobayashi, M.; Shimadate, T. *Chem. Pharm. Bull.* **1986**, *34*, 4069. (d) Wood, H. B., Jr.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1956,** *78*, 207. (e) Soltes, E. J.; Timell, T. E. *Carbohydr. Res.* **1965**, *1*, 176. (f) Bols, M.; Hansen, H. C. *Acta Chem. Scand.* **1993**, *47*, 818.

(84) Sen, A. K.; Banerji, N. *Indian J. Chem.* **1989**, *28B*, 818.

(85) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(86) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577.

(87) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567.

(88) Itoh, T.; Chika, J.-i. *J. Org. Chem.* **1995**, *60*, 4968.

CR940716A