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Asymmetric Allylic Alkylation, an Enabling Methodology

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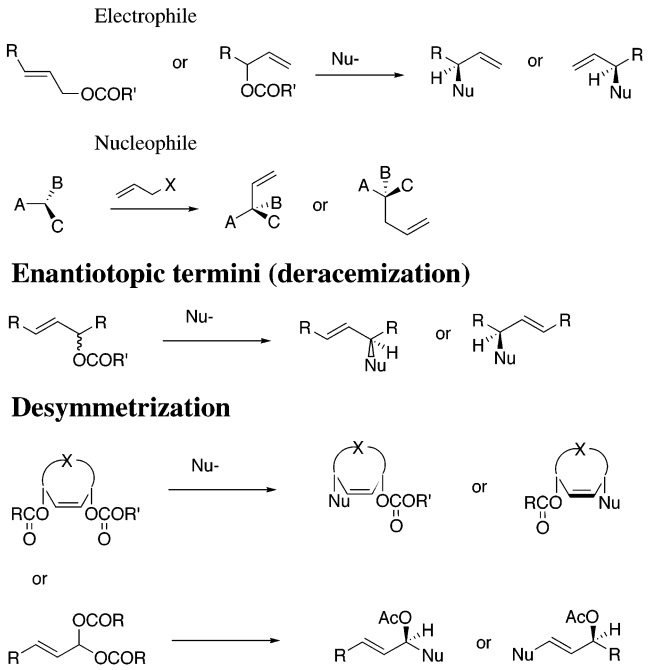
The diversity of mechanisms for enantiodiscrimination and of bond types that can be formed make Pd-catalyzed asymmetric allylic alkylation a powerful key step for simplification of synthetic strategy to complex molecular targets. Using a wide range of different classes of compounds including alkaloids, polyhydrofurans, nucleosides and carbanucleosides, cyclohexitols and cyclopentitols, chromanes, cyclopentanoids, amino acids, barbiturates, etc., novel synthetic strategies emerge that provide short efficient asymmetric syntheses.

Chemistry distinguishes itself from the other disciplines in approaching scientific questions by its ability to design structure for function unfettered by what is available. A key enabling aspect of this freedom is the effectiveness of synthetic methodology to solve problems of selectivity, a feature that is particularly noted when dealing with biological problems. Providing efficient synthesis to complex molecules requires minimizing the number of steps, any side reactions, and purification protocols. Among the most challenging issues is obtaining enantiomerically pure compounds for which asymmetric catalysis constitutes a core competency.

Among asymmetric bond forming reactions, the metal-catalyzed asymmetric allylic alkylation (AAA) is unique for several reasons.[1] First, it has numerous mechanisms for enantiodiscrimination, not one (see Scheme 1). The most common enantiodiscriminating mechanism for asymmetric hydrogenation, epoxidation, and dihydroxylation, i.e., differentiating prochiral faces of a π-unsaturation, also applies here. However, unlike hydrogenation and oxidation, both reacting partners, i.e., the electrophile and nucleophile, may be prochiral wherein stereochemistry can be induced at either or both. Deracemizing allylic alcohols via *meso*-type π-allylmetal intermediates involves enantiodiscrimination by preferential attack at one of the two enantiotopic termini. In addition, *meso*-diester substrates create chiral nonracemic products by differential ionization of prochiral leaving groups.

Second, an AAA reaction may form many different kinds of bonds with the same catalyst, not just one. Whereas the electrophile typically involves carbon, the nucleophilic center may be H, N, O, S, C, etc., a fact providing access to C−H, C−N, C−O, C−S, C−C, etc. bonds in the same type of reaction. Third, depending upon the metal and the nucleophile, the reaction may proceed by a net inversion or a net retention mechanism (see Scheme 2). The reaction typically involves a metal-promoted ionization followed by a nucleophilic addition. The nature of each these steps ultimately determines the overall stereochemical event. If the process has an odd number of inversions (or retentions), the overall process is inversion. On the other hand, a net retention can result from either a double inversion or a double retention path. While palladium involves a net retention via a double inversion mechanism with "soft" nucleophiles and a net inversion path with "hard" nucleophiles,[2] many other metals also catalyze allylic alkylation, e.g., Rh,[3] Ru,[4] Ir,[5] Mo,[6] W,[7] and Cu,[8] which may involve different stereochemical courses. For example, Mo-catalyzed asymmetric allylic alkylation involves a net retention of stereochem-

SCHEME 1. Mechanisms of Enantiodiscrimination



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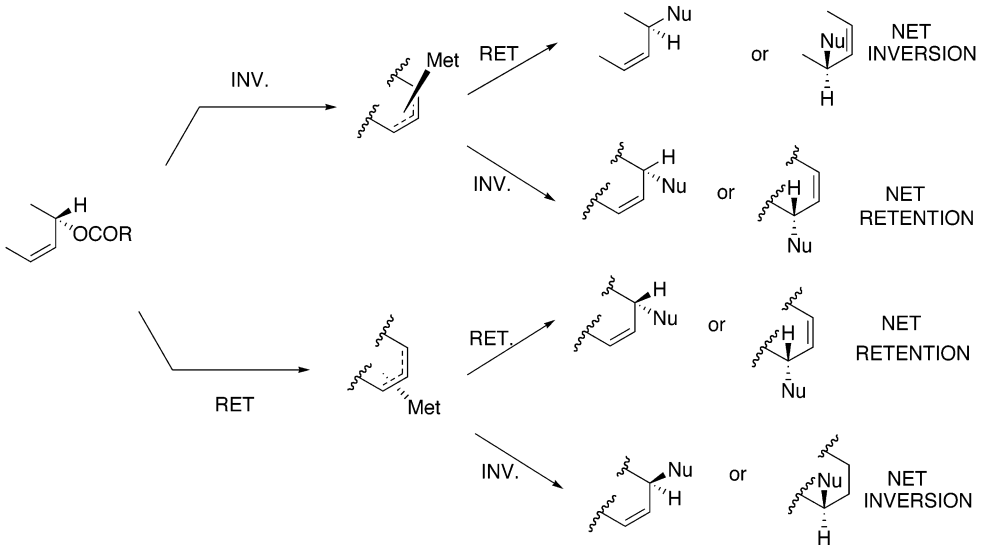
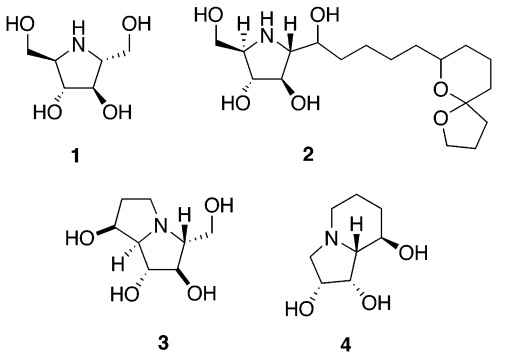
SCHEME 2. Overall Stereochemistry

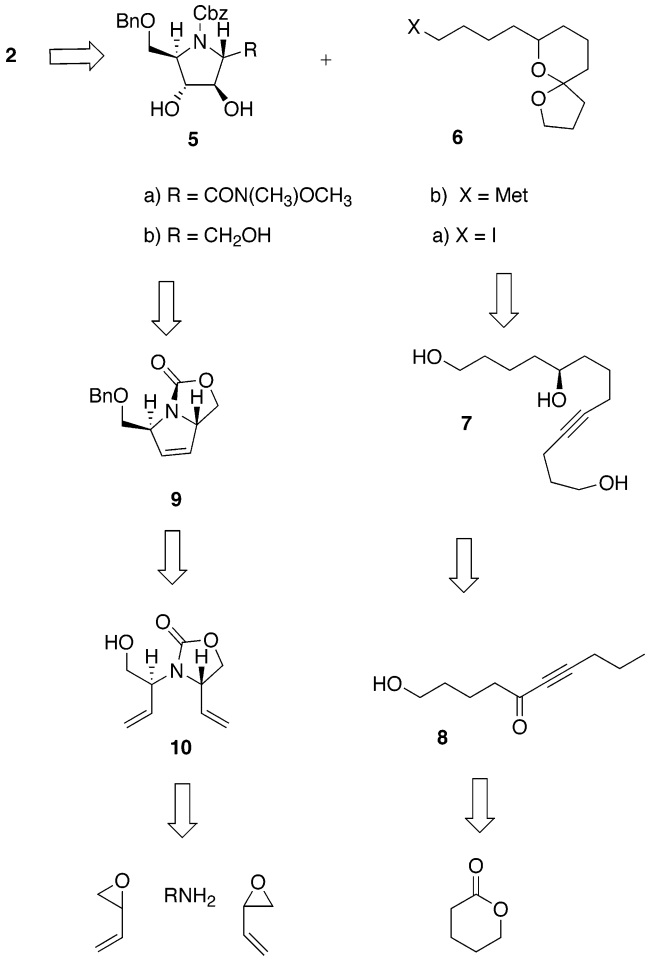


istry but by a double retention pathway.[6] From the perspective of asymmetric allylic alkylations, our work has focused on Pd and Mo. The great flexibility offered by this methodology provides opportunities to simplify complex synthesis across many types of bioactive compounds. In addition, the intrinsic presence of a carbon−carbon double bond provides great flexibility for further structural modifications. In this perspective, we examine how this methodology provides effective strategic approaches for an immense array of bioactive targets.

Pyrrolidine-Based Alkaloids. The pyrrolidine alkaloids attracted attention because of their ability to mimic the transition state of hydrolysis during carbohydrate processing. This fundamental biochemical process makes such glycosidase inhibitors potentially applicable as antiviral, antibacterial, antimetastatic, or antidiabetic agents provided that high glycosidase selectivity can be achieved. While simple pyrrolidines represented by (2*R*,5*R*)-dihydroxymethyl-(3*R*,4*R*)-dihydroxy-pyrrolidine (DMDP, **1**)[9] function as potent α- and *β*-glucosidase and *β*-galactosidase inhibitors, the potentially more interesting compounds because of prospects for enhanced selectivity are more structurally elaborate. One such family is the broussonetines,[10] which consists of about 30 members illustrated by broussonetine G (**2**), one of the more complicated members.[10b] The bicyclic pyrrolizidine alkaloids, represented by one of the first to be identified, australine (**3**), retain potency with enhanced selectivity. A similar behavior derives from incorporating a six-membered



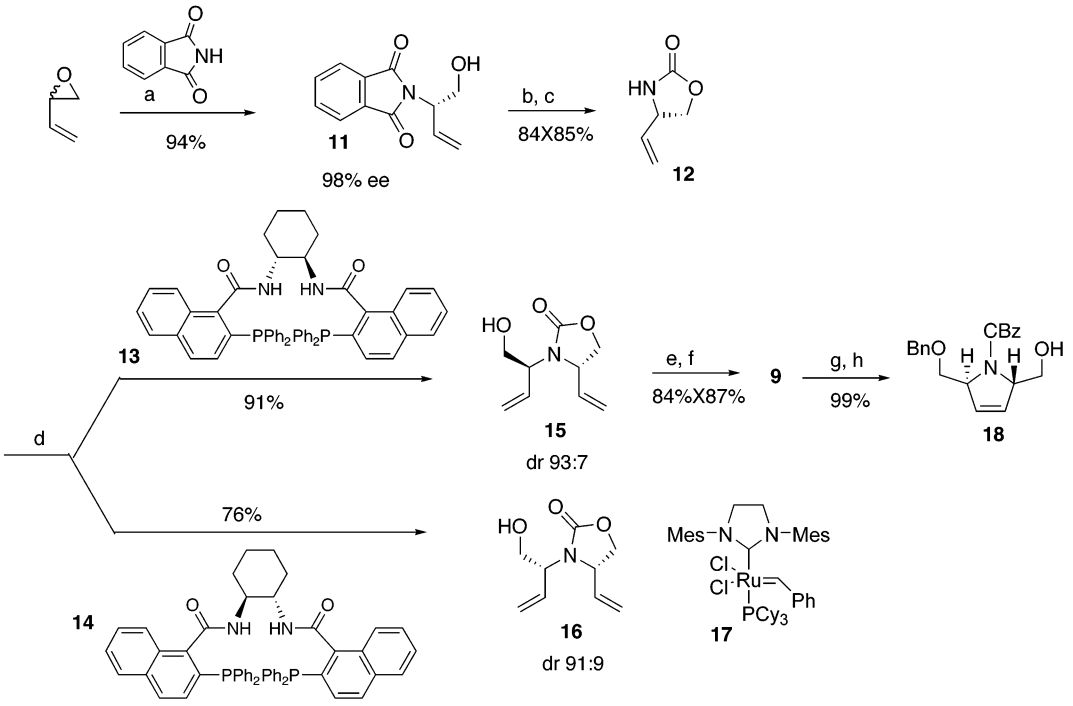
SCHEME 3. Retrosynthetic Analysis of a Pyrrolidine Alkaloid



ring as in the indolizidine swainsonine **4**. Indeed, it has been evaluated clinically as a possible anticancer agent.

Broussonetine G also offered the challenge of establishing the stereochemistry of the side chain, and this was chosen as the prime target.[11] The retrosynthetic analysis separates the target into the cyclic core **5** and a functionalized side chain **6** (Scheme 3). By so doing, all

SCHEME 4. Synthesis of Dihydropyrrole 9[a]



[a] (a) 0.4 mol % $[\eta^3C_3H_5PdCl]_2$, 1.2 mol % ligand **13**, Na_2CO_3, CH_2Cl_2, rt. (b) $(H_2NCH_2)_2$, C_2H_5OH, reflux. (c) $(CCl_3O)_2CO$, $NaHCO_3$, $PhCH_3$, H_2O, 0 °C. (d) 0.25 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 0.75 mol % ligand **13** or **14**, DBU, CH_2Cl_2, rt. (e) NaH, $PhCH_2Br$, $(C_4H_9)_4NI$, THF, rt. (f) 1.2 mol % Grubb's II **17**, CH_2Cl_2, rt. (e) NaH, $PhCH_2Br$, $(C_4H_9)_4NI$, reflux. (h) Cbz-Cl, $NaHCO_3$, Na_2CO_3, H_2O, 0 °C−rt.

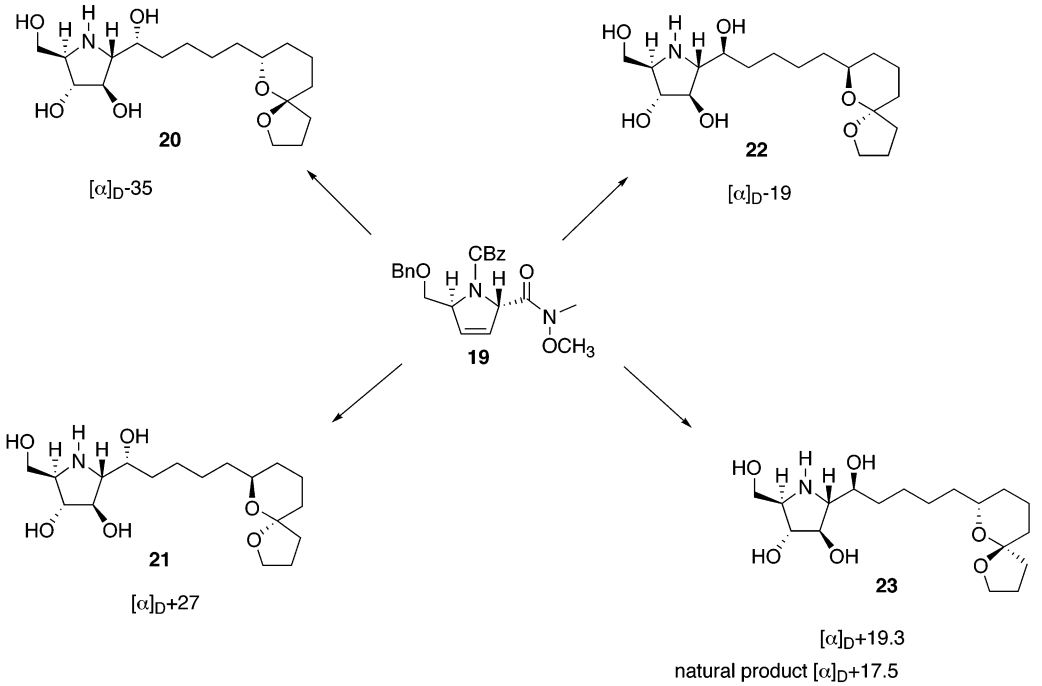


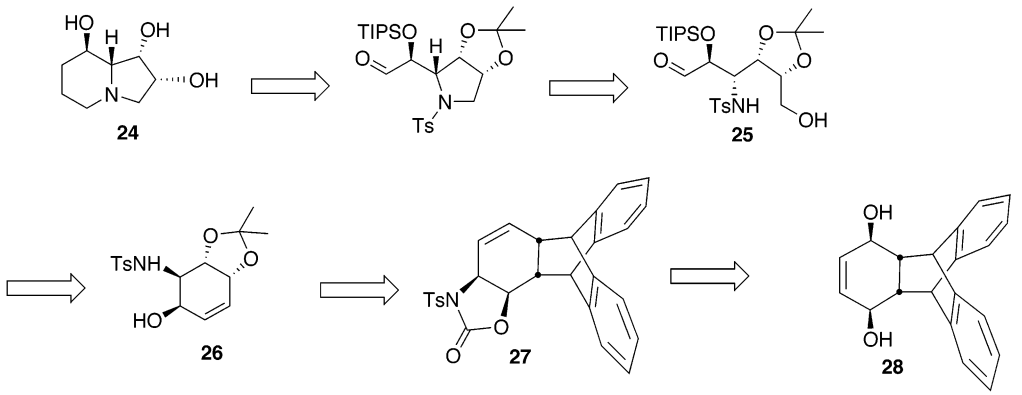
FIGURE 1. Four diastereomeric possibilities for (+)-broussonetine G.

four diastereomeric possibilities become easily accessible. While the side chain, in principle, could have two diastereomeric possibilities (four total isomers), presumably the spiroketal center is determined by the stereochemistry of the secondary alcohol of triol **7**. A Noyori-type enantioselective reduction of the alkynone **8** would provide either enantiomer of triol **7**, which in turn would provide both enantiomers of the side chain **6**.

The cyclic core becomes pivotal, not only for the synthesis of the broussonetines but also many other pyrrolidine-based glycosidase inhibitors. A *trans*-dihydroxylation of the alkene **9** should provide this pivotal intermediate. The accessibility of the latter by an olefin metathesis of diene **10** reveals a double asymmetric allylic alkylation involving deracemization of butadiene monoepoxide as an excellent source.

Benzylamine as nucleophile underwent the initial alkylation with reasonable selectivity but gave an unacceptable mixture of 1,2- and 1,4-regioisomers in the second alkylation, in which the latter predominated.

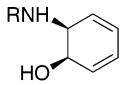
SCHEME 5. Retrosynthetic Analysis of Swainsonine



Resolution of the regioselectivity problems of the second alkylation involved performing the two alkylations with butadiene monoepoxide in two separate events outlined in Scheme 4. Indeed, phthalimide provides excellent regio- and enantioselectivity in the initial alkylation and the resulting adduct can be readily transformed into the oxazolidin-2-one **12** in two steps from **11.** The oxazolidinone **12** also reacts with excellent regioselectivity. The reaction is a catalyst-controlled event since the *R*,*R* ligand **13** provides the anti-adduct **15**, whereas the *S*,*S* ligand **14** gives the diastereomeric **16**. Metathesis using the 2nd generation Grubb's catalyst **17**[12] completes the synthesis of **9**. The strain of the bicyclo [3.3.0] system imparted stability problems in subsequent transformations. As a result, a monocyclic system **18** was prepared in two steps in quantitative yield.

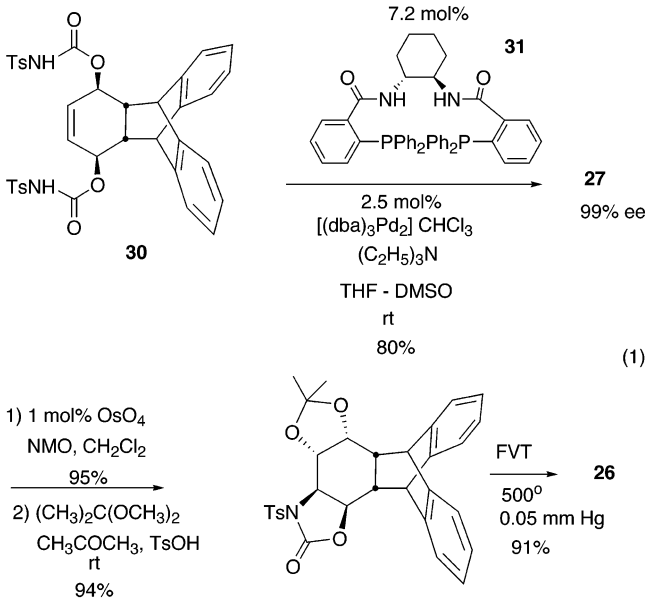
Both enantiomers of the spiroketal **6a** are equally available as outlined retrosynthetically in Scheme 3 wherein the chirality is established by a Noyori-type asymmetric hydrogenation[13] of an alkynone. The Weinreb amide **19**, derived from alcohol **18** in just two steps, was converted in five steps using the two enantiomeric Grignard reagents derived from iodide **6a** followed by diastereoselective reduction of the resulting ketone and *trans*-dihydroxylation to provide diastereomers **20**−**23**. Spectroscopic properties indicated the correct structure was either diastereomer **22** or **23**. The optical rotation, however, clearly indicated that **23** was ultimately correct. This dihydropyrrole serves as a useful intermediate that can access many pyrrolidine, pyrrolizidine, and indolizidine alkaloids (Figure 1).

While swainsonine **24**[14] may also derive via a similar strategy wherein the allylation of oxazolidine **12** would be performed with allyl acetate, it also may derive from an acyclic building block **25** as outlined in Scheme 5.[15] The key initial disconnect involves formation of the two heterocyclic rings by intramolecular alkylations ultimately from the aminohexitol **25**, which lacks only two carbons that can be introduced by straightforward chain extension. This six-carbon fragment bearing hydroxyl groups at the two termini in turn can be formed by oxidative cleavage of an olefin followed by reduction. The recognition of the olefin **26** as a suitable intermediate suggested that an enantiomerically pure cyclohexadiene such as **29**, which would allow easy chemodifferentiation of the two double bonds, would be an excellent building block, potentially not only for swainsonine but also more broadly. The simplest way to differentiate the two double bonds involves "protecting" one as a Diels−Alder adduct as in **27**, which simultaneously offers an easy solution for its asymmetric synthesis using desymmetrization of a *meso*-diol **28** via the Pd-AAA.



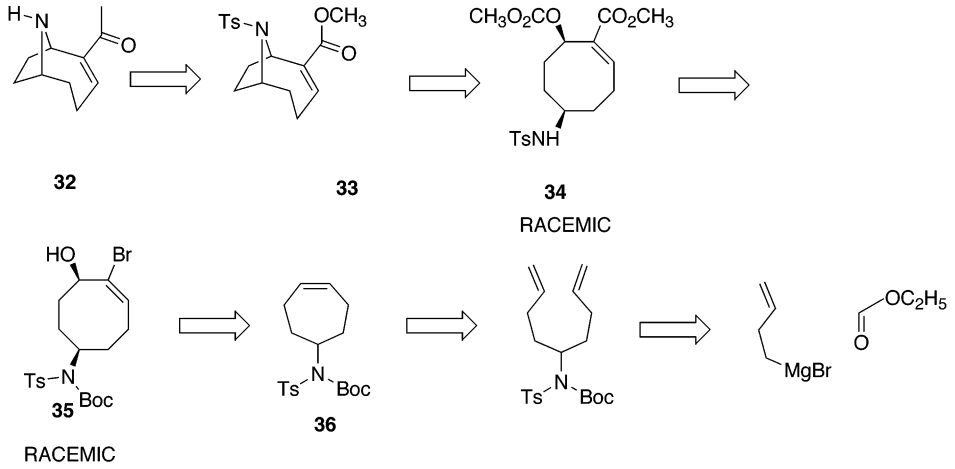
29

The diol **28** derives from the metal hydride reduction of the Diels−Alder adduct of benzoquinone and anthracene. Simple mixing with 2 equiv of *p*-toluenesulfonylisocyanate generates the biscarbamate **30** in 90% yield (eq 1). Without any purification, the latter was directly

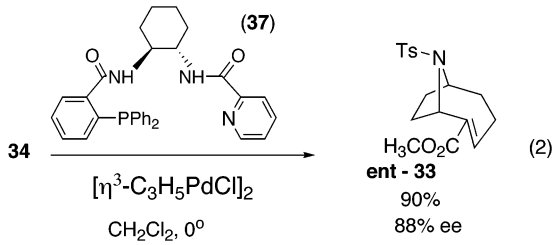


subjected to a Pd(O) complex in the presence of ligand **31** to give virtually enantiomerically pure oxazolidin-2-one **27** in 80% isolated yield. This product is a surrogate for a chemodifferentiated diene amino alcohol **29**. After diastereoselective dihydroxylation and protection of the diol as the acetonide, passing the resulting tetrasubstituted product through a hot tube in vacuo (a technique referred to as flash vacuum thermolysis or FVT) effects a smooth retro-Diels−Alder reaction to liberate the cyclohexene **26**, which was carried on to complete the synthesis of swainsonine as sketched in Scheme 5.

SCHEME 6. Retrosynthesis of Anatoxin-a



Anatoxin-a (**32**), also known as "very fast death factor" as a result of its potency to induce respiratory paralysis, possesses a pyrrolidine embedded in a bicyclo [4.2.1] nonane system.[16] Examination of the structure reveals that deracemization of a racemic allyl ester **34** using an internal nitrogen nucleophile can induce the proper chirality.[17] This recognition allows the racemic vinyl bromide **35** to serve as a precursor via carbonylation. The juxtaposition of functionality present in **35** logically derives via a well-developed ring expansion involving intermediacy of a dibromocyclopropane derived from cycloheptene **36**. Using ring-closing metathesis, the starting materials become the Grignard reagent made from 4-bromo-1-butene and ethyl formate (Scheme 6).

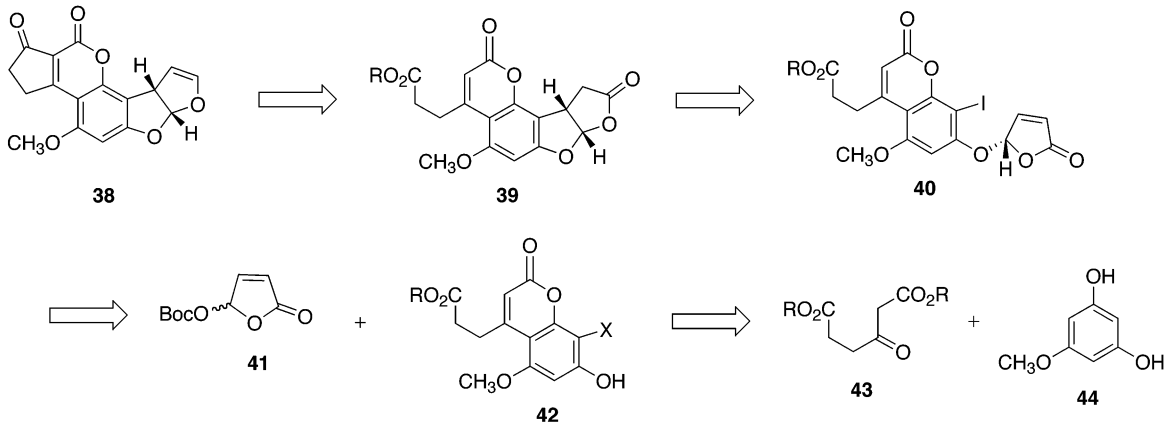


Racemic allyl carbonate **34** did not react well with a catalyst involving the typical bidentate phosphine ligands, presumably because of steric restrictions of the chiral space. A modified ligand **37** removing some of the steric barriers was designed. As a result, instead of requiring a reaction temperature of 100° with the bisphosphine-type ligands such as **31**, reaction with complexes bearing ligand **37** proceeded even at 0° within 14 h to give full conversion and formation of the enantiomeric series with excellent ee (eq 2). Conversion of ent-**33** to (−)-anatoxin-a followed straightforward methodology. The natural (+)-enantiomer would be equally accessible simply by switching the chirality of the ligand.

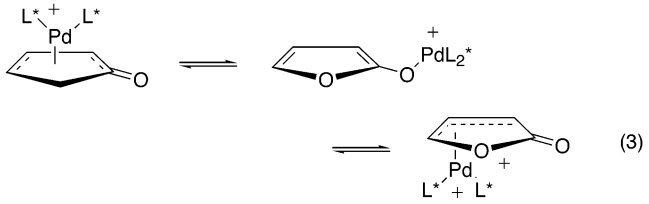
Polyhydrofurans. The aflatoxins, mycotoxins that infect a variety of agricultural products such as peanuts, rice, wheat, and soybeans as well as edible animal products such as meat, cheese, and butter,[18] possess a polyhydrofuran substructure wherein lies the stereogenic centers. Using aflatoxin B (**38**) to illustrate (Scheme 7), the chirality of the target may stem from the single stereogenic center of butenolide **40**, which immediately reveals a simple convergent approach from racemic 4-acyloxybutenolide **41** and phenol **42** involving a metal-catalyzed allylic alkylation.[19] The latter becomes available via a classical Pechmann condensation of ketoester **43** and phloroglucinol monomethyl ether **44**. The former arises by the singlet oxygen degradation of furfural.

The key question is how racemic **41** might serve as an enantiomeric building block. The most obvious is a kinetic resolution using the Pd-AAA. However, the limit of the yield to 50% makes such an approach less desirable. The prospect of a dynamic kinetic asymmetric transformation

SCHEME 7. Retrosynthesis of Aflatoxin B_1

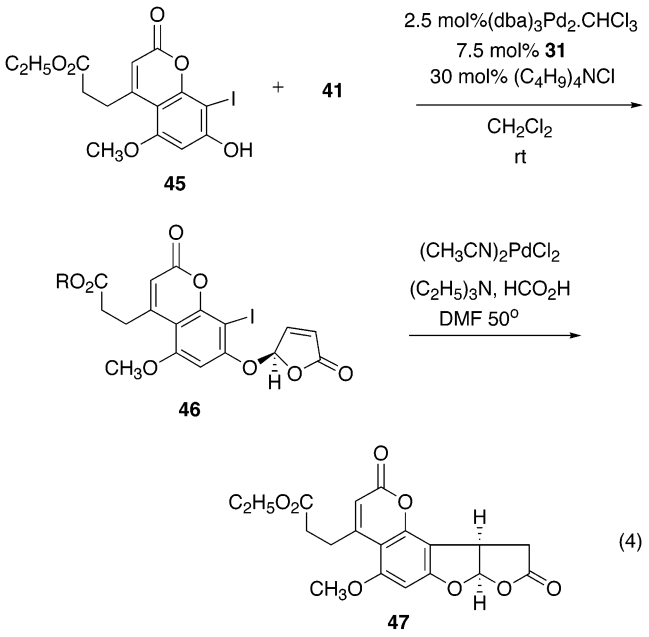


because the π-allylpalladium intermediate may undergo facial equilibration (eq 3) constitutes a much more



(3)

efficient approach. Indeed, reaction of coumarin **45** with butenolide **41** using the "standard" *R*,*R* ligand **31** gave the deracemized alkylation product **46** of >95% ee in 89% yield (eq 4). Reductive Heck cyclization to furanofuranone

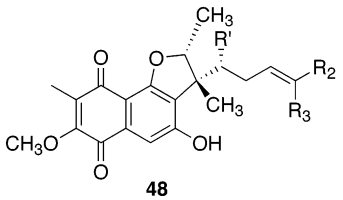


(4)

47 introduces the second stereocenter and sets the stage for completion of the synthesis by standard procedures.

The cytotoxic furaquinocins **48** consist of a benzodihydrofuran core that differs in the side chain (Chart 1).[20] In preparing analogues, variation of the quinone moiety would also be desirable. A modular strategy based upon the synthesis of a chiral core **48**, to which a side chain and a quinone ring can be attached wherein the Pd-AAA reaction provides the core enantioselectively, emerges

CHART 1



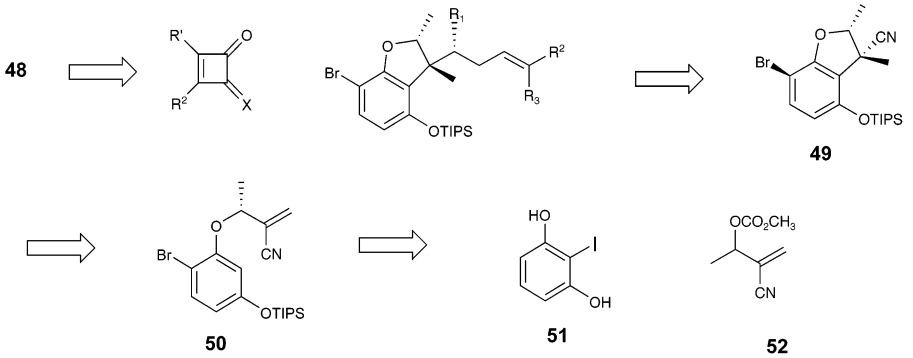
48

A	R_1 = OH	R_2 = CH_3	R^3 = CH_2OH
B	OH	CH_2OH	CH_3
C	H	CH_3	CH_3
D	OH	CH_3	CH_3
F	H	CH_2OH	CH_3
H	OH	CH_2OH	CH_2OH

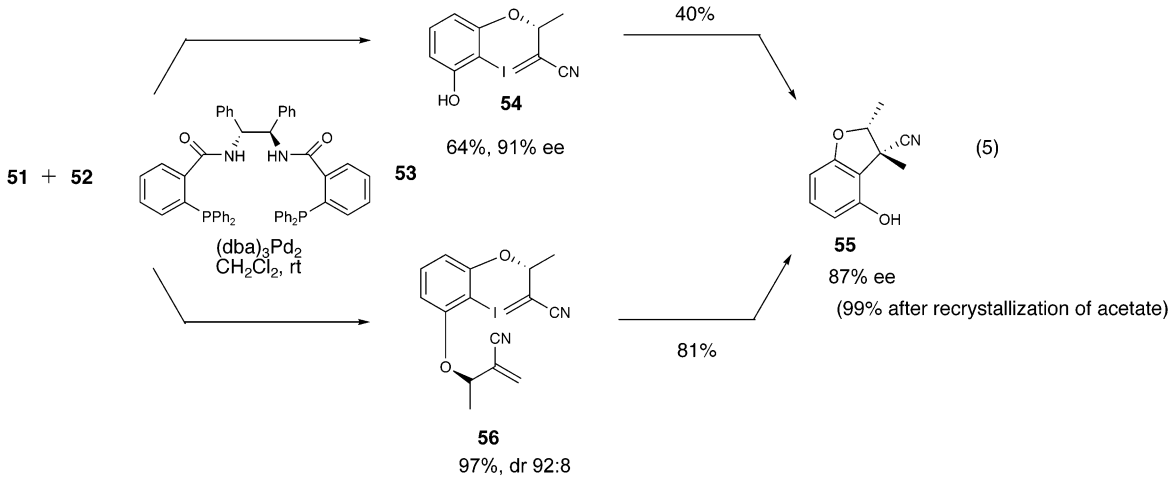
(see Scheme 8).[21] As in the aflatoxin synthesis, the chiral dihydrofuran ring involves initial establishment of the chirality by a Pd-AAA reaction using 2-iodoresorcinol (**51**) and a Baylis−Hillman adduct **52**,[22] followed by a diastereoselective reductive Heck cyclization. Thus, a deracemization of such adducts with regioselective allylation at the more substituted allyl terminus is required.[23] The ease of availability of Baylis−Hillman adducts by direct addition of acrylate derivatives to aldehydes makes such a strategy very attractive.

Initial results proved quite promising. The monoalkylation to alkylated product **54** proceeded in a reasonable yield with excellent ee (eq 5, Scheme 9) using the stilbene diamine ligand **53**. The reductive Heck reaction to dihydrofuran **55** proceeded with excellent diastereoselectivity but in only 40% yield. Sensing the presence of the free phenol might be an issue in the cyclization, a simple solution that also significantly improves the Pd-AAA step emerged. Using 2 equiv of the Baylis−Hillman substrate **52** provided the dialkylation product **56** in near quantitative yield. The reductive Heck reaction now also proceeded in excellent yield and ee, the latter being raised to enantiomeric purity by recrystallization of the corresponding acetate. Bromination of the TIPS ether installs the bromide with complete para selectivity. Reduction of

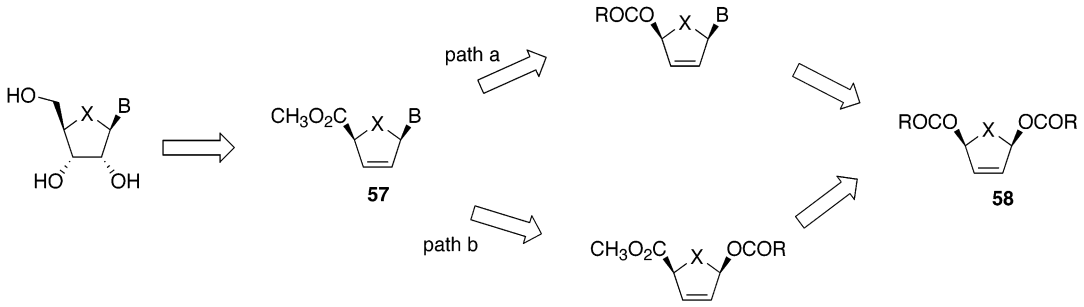
SCHEME 8. Retrosynthetic Analysis of Furaquinocins



SCHEME 9. Equation 5.



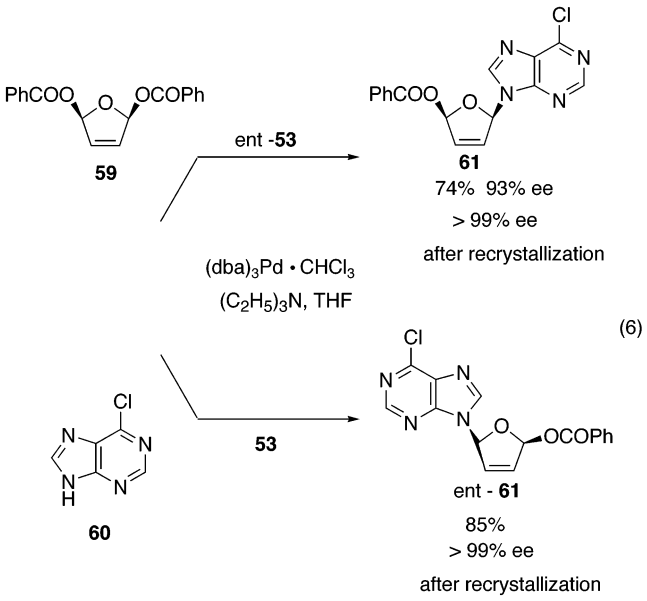
SCHEME 10. Retrosynthesis of Nucleosides/Carbanucleosides



the nitrile to the aldehyde then sets the stage for diastereoselective attachment of the side chain and completion of the synthesis[24] as outlined in Scheme 8. The flexibility offered by this strategy led to the synthesis of furaquinocins A, B, and E and several analogues involving the quinone moiety.

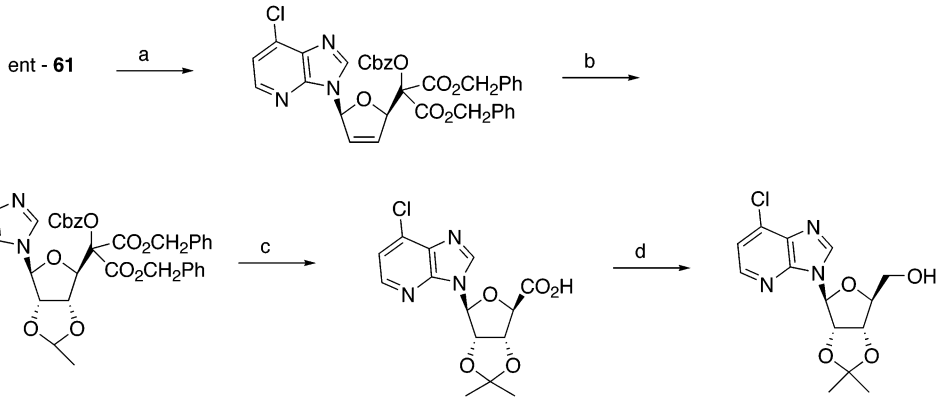
Nucleosides and Carbanucleosides. Whereas the syntheses of the 2,3-dihydrofurans involve mechanisms requiring dynamic kinetic asymmetric transformations to install chirality, the tetrahydrofurans of nucleosides invoke a different mechanism, the desymmetrization of *meso*-substrates. The advantage of a de novo asymmetric synthesis stems from the flexibility it offers both with respect to generating any enantio- or diastereomer as well as ease of controlling the nature of the substituents on the furan ring. Scheme 10 outlines the generalized strategy.[25] The olefin **57** is pivotal because it not only provides the standard building blocks of DNA and RNA but also provides access to analogues with varying substituents at the 3,4-positions, a type of substitution that has proven clinical relevance.[26] Installation of the double bond immediately reveals the prospect to install the 2- and 5-substituents by allylic alkylation, the initial one being the enantioselective process in desymmetrizing *meso*-diester **58** and the second being a Pd-catalyzed regio- and diastereoselective process. As indicated by paths a and b, either the base or the C-1 fragment can be introduced in either step. Because X can be elements other than oxygen, notably carbon, this strategy becomes independent of the nature of the ring. Indeed, all of these permutations have been realized.

Thus, the dibenzoate **59** and 6-chloropurine **60** form the monoalkylation product **61** with the ligand ent-**53** and the mirror image product ent-**61** with ligand **53** (eq 6).[25]



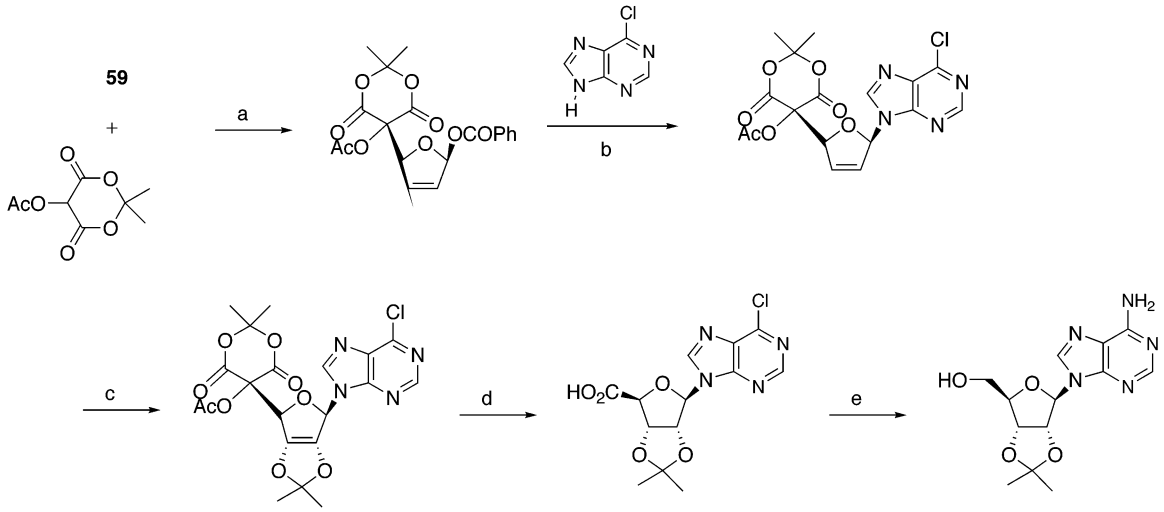
An alkoxymalonate was used as an alkoxycarbonyl anion equivalent to introduce the C-1 fragment as demonstrated in a synthesis of ent-adenosine summarized in Scheme 11. To provide greater efficiency in varying the "base", the reverse sequence wherein the alkoxycarbonyl

SCHEME 11. Synthesis of ent-Adenosine Acetonide[a]



[a] (a) 12 mol % Ph_3P, 1.7 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, $CbzOCH(CO_2CH_2Ph)_2$, Cs_2CO_3, 1:1 THF/CH_3CN, rt, 97%. (b) 4 mol % OsO_4, NMO, CH_2Cl_2, H_2O, rt then $(CH_3)_2C(OCH_3)_2$, CH_3COCH_3, PPTS, CH_2Cl_2, 35 °C, 90%. (c) H_2 (1 atm), 5% $Pd/BaSO_4$, 1:1 C_2H_5OAc/CH_3OH, rt, 59%. (d) HOBT, DCC, THF, rt then −10 °C $NaBH_4$, followed by NH_4OH, CH_3CN, H_2O, rt, 63%.

SCHEME 12. Synthesis of Adenosine by Reverse Order[a]

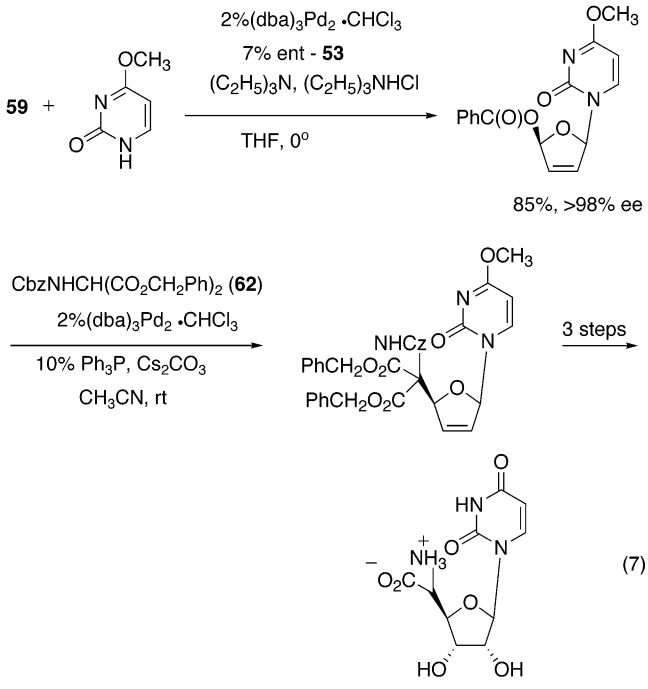


[a] (a) 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 7.5 mol %, **31**, DBU, THF, −40 °C, 82%, 91% ee. (b) 2.5 mol % $(dba)_3$ $Pd_2{\cdot}CHCl_3$, 7.5 mol % ent-**31**, $(C_4H_9)_3SnOAc$, THF, rt, 89%. (c) 5 mol % OsO_4, NMO, CH_2Cl_2, H_2, then $(CH_3)_2C(OCH_3)_2$, CH_3COCH_3, TsOH, rt, 83%. (d) CF_3CO_2H, neat then $Pb(Oac)_2$ CH_3COCH_3, 0 °C, 77%. (e) HOBT, DCC, then $NaBH_4$, followed by NH_4OH, CH_3CN, H_2O, rt, 62%.

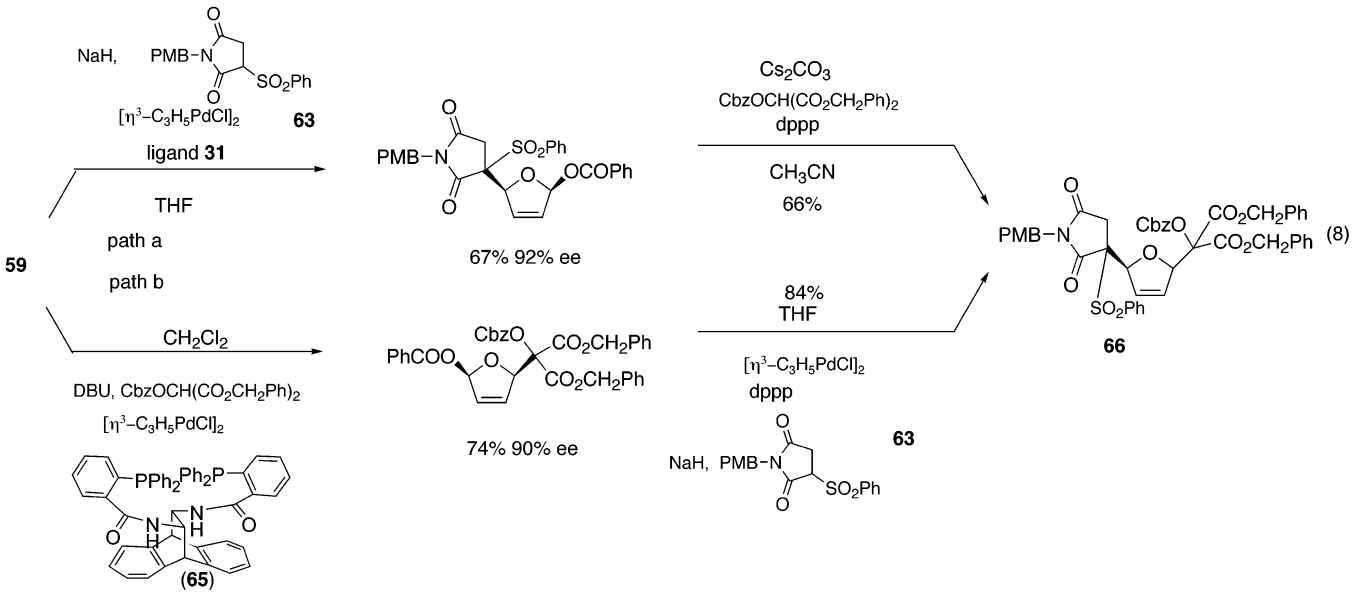
group was introduced in the initial enantiodiscriminating step was also performed. As summarized in Scheme 12, an acyloxy Meldrum's acid was employed as the alkoxycarbonyl anion.[27] Interestingly, the best yields in the second Pd-catalyzed step employed the chiral ligands, although they are not required for the regio- or diastereoselectivity.

Using path a, the polyoxin-nikkomycin nucleoside core was synthesized as shown in eq 7. Use of aminomalonate **62** allows access to the α-amino acid side chain directly. It should be noted that endemic to this strategy is facile access to 2,3-dideoxy and monodeoxy nucleoside analogues that have important clinical relevance, as well as uronic acids that possess the one-carbon substituent at the oxidation level of the carboxylic acid.

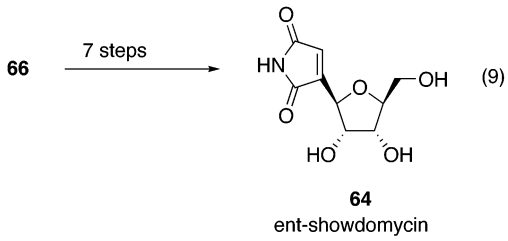
Replacing the typical nucleoside base with a 2-phenylsulfonylsuccinimide **63**, the antibiotic showdomycin (cf. **64**),[28] i.e., a C-nucleoside analogue, becomes available. Focusing on a synthesis of its mirror image, both paths a and b were examined as shown in eq 8 (Scheme 13).[29] Although the standard ligand **31** functioned well using the sulfone **63** as the nucleophile, the ee's dropped to 78% using the substituted malonate. Switching to the an-



SCHEME 13. Equation 8.

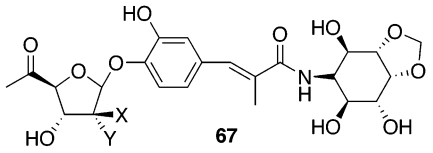


thracene-derived ligand **65** restored the ee to 90%. In both cases, regio- and diastereoselective installation of the second nucleophile proceeded well with the achiral dppp ligand. Dihydroxylation and fragmentation of the malonate to a simple carboxylate as described in Scheme 9 followed by straightforward transformations completes the synthesis of ent-showdomycin **64** (eq 9). Of course,



the natural enantiomeric series is equally accessible by simply switching the chirality of the catalysts.

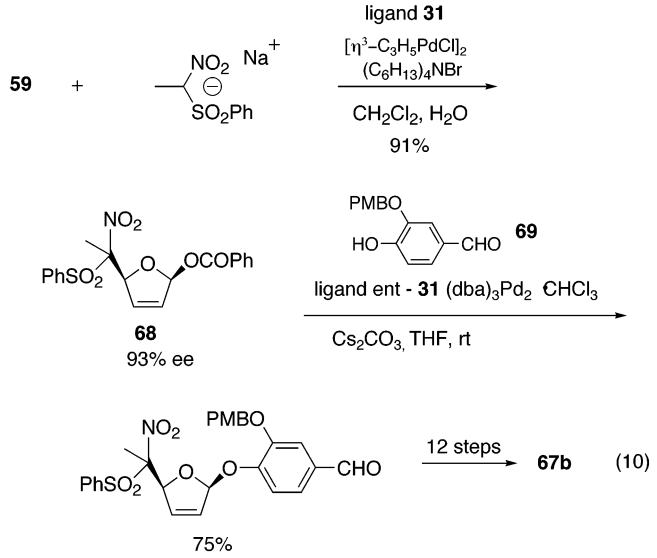
Hygromycin (**67a**), an agent used for the treatment of swine dysentery, contains yet a different set of 2,5-substituents, an acetyl and a phenol.[30] Phenylsufonyl-



a) X = OH, Y = H

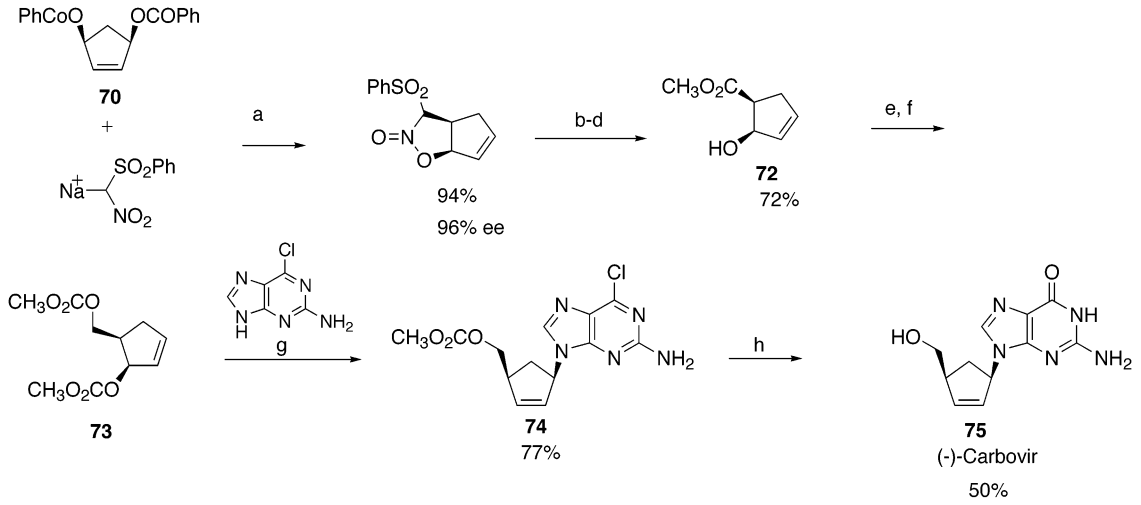
b) X = H, Y = OH

nitroethane serves as an acetyl anion synthon. Indeed, deracemization of *meso*-dibenzoate **59** with this nucleophile proceeds in excellent yield and ee to provide nitrosulfone **68** (eq 10).[31] Replacement of the remaining benzoate with retention of configuration using phenol nucleophiles can be performed with achiral Pd catalysts. However, in the case of the PMB ether **69**, the best yields were obtained by using chiral catalysts, of course the enantiomeric series from that used in the first alkylation. Conversion of the chiral core to the target involves straightforward transformations with one exception, transforming the nitrosulfonyl fragment to an acetyl group. This transformation proceeds readily under reductive conditions ($TiCl_3$, NH_4OAc, H_2O, THF, rt) in over 80% yield.



The beauty of this strategy is its equal applicability to the all-carbon system. The synthesis of the antiviral agent carbovir (**75**)[32] highlights the effectiveness of this type of strategy (Scheme 14).[33] Employing phenylsulfonylnitromethane as the nucleophile, a one-pot double alkylation occurs to provide the novel heterocycle **71** directly. The heterocyclic ring can be cleaved to a *cis*-hydroxy nitrile or ester (e.g., **72**). Simple conversion to the biscarbonate **73** sets the stage for the second Pd-catalyzed allylic substitution with a suitable base such as 2-amino-6-chloropurine, which occurs with equally impressive regio- and diastereoselectivity to form **74**. Aqueous base hydrolysis unmasks the target. Thus, the

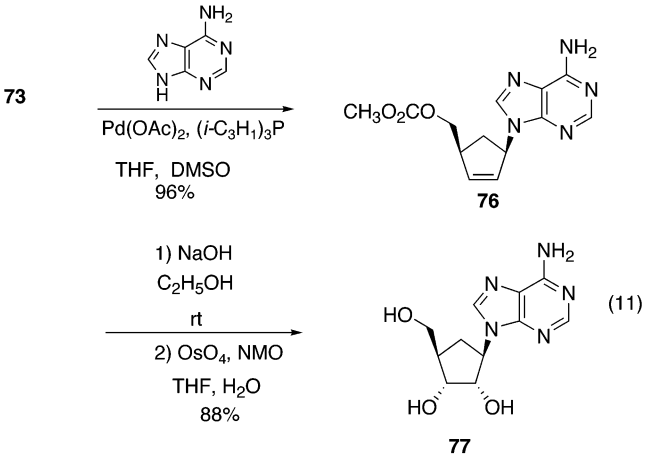
SCHEME 14. Synthesis of (−)-Carbovir[a]



[a] (a) Ligand **31**, $(dba)_3Pd_2{\cdot}CHCl_3$, THF, rt. (b) $SnCl_2{\cdot}2H_2O$, CH_3CN, rt. (c) K_2CO_3, CH_3OH, 50 °C. (d) $Mo(CO)_6$, CH_3CN, H_2O, H_3BO_3. (e) LAH, ether, rt. (f) nC_4H_9Li, THF, $ClCO_2CH_3$, −78 °C. (g) $[\eta^3C_3H_5PdCl]_2$, Ph_3P, THF, rt. (h) NaOH, H_2O, reflux.

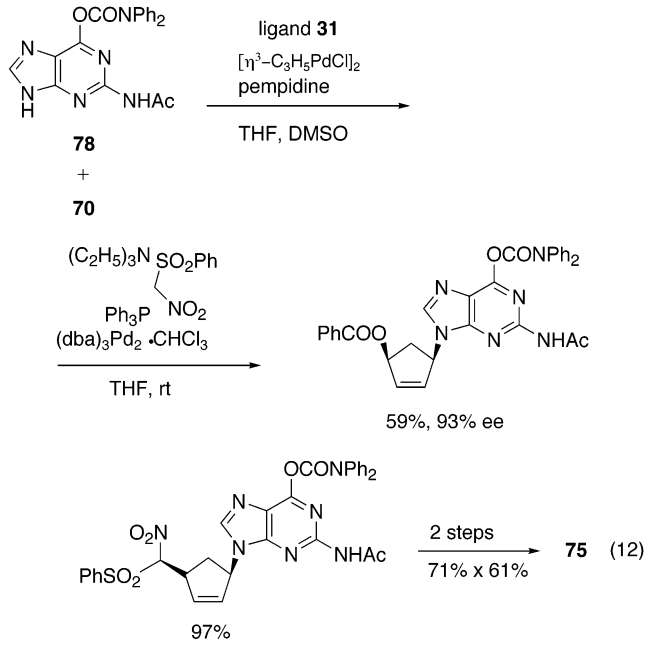
double bond in the final product derives intrinsically from this strategy. Further, simple reduction of the double bond provides the dideoxynucleoside analogues.

On the other hand, this same double bond also allows for further transformations, notably dihydroxylation. Thus, biscarbonate **73** equally well provides a direct carbocyclic analogue of a nucleoside illustrated by aristeromycin **77**[34] (eq 11) via the intermediacy of chiral cyclopentene **76**.



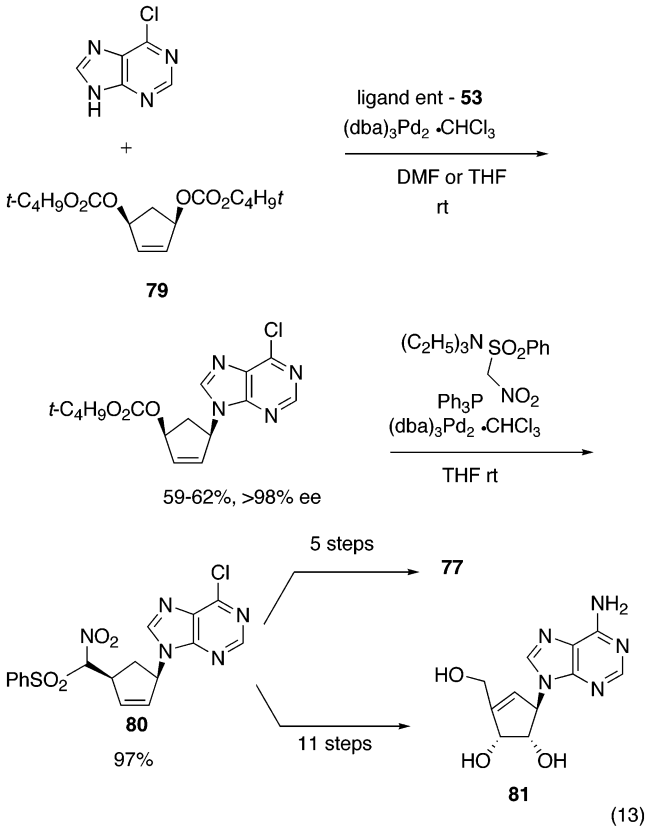
(11)

A second generation synthesis of (−)-carbovir inverts the two nucleophiles, i.e., the purine base is employed in the initial enantiodiscriminating allylic alkylation and the C_1 unit in the second one.[35] A modified guanine equivalent **78** was employed as shown in eq 12. The advantage of this route is its conciseness, requiring only four steps from dibenzoate **70**. The same strategy also led to a synthesis of the antiviral agent (−)-neplanocin (**81**), as well as a second generation synthesis of aristeromycin via a common intermediate **80**. For minimization of regioselectivity issues with respect to 6-chloropurine and polyalkylation, the bis-Boc **79** was employed as substrate in the enantiodiscriminating desymmetrization in the absence of any base. The resulting alkylated purine was obtained enantiopure. The regio- and diastereoselective second Pd-catalyzed allylic alkylation proceeded smoothly and nearly quantitatively to produce the pivotal intermediate **80** enantiopure.



(12)

The intrinsic presence of a double bond in the product of an allylic alkylation allows the combination of the Pd-AAA with ring-closing metathesis (RCM) to constitute an asymmetric synthesis of ring systems. The dihydrofuran ring system nicely illustrates the concept (eq 14, Scheme 15).[36] Using the naphthyl-derived ligand **14**, DYKATs of racemic vinyl epoxides **82a**−**c** provide the desired dienes **83** in high ee as single regioisomers. RCM using the first generation Grubb's catalyst provides the 2,5-dihydrofurans **84a**−**c** in excellent yield. In addition, Ru-catalyzed isomerization[37] creates an asymmetric synthesis of 2,3-dihydrofurans **85a**−**c** after silylation of the primary alcohol. Selenium-initiated addition followed directly by selenoxide elimination (eq 15)[38] then provides the dideoxydidehydro nucleosides in six steps form the vinyl epoxides. Although the sequence was illustrated in the



(13)

series enantiomeric to the natural nucleosides, it illustrates the virtues of this approach since both enantiomers are equally accessible by simple choice of chiral catalytst. Substituted analogues are also easily accessed, a feat not easily achievable via the classical carbohydrate-based methods. Because dideoxy analogues have great clinical interest, their direct synthesis via this strategy avoids the nontrivial deoxygenation of carbohydrates.

Polyhydroxycycloalkanes and Analogues. The inositol phosphates are important second messengers to mobilize intracellular calcium ions. 1,4,5-IP_3 (**86**),[39] one member of this family, illustrates the dual challenge of chemodifferentiation of the polyol concurrent with creation of chirality (Scheme 16).[40] Differentiation of the hydroxyl group of the cyclohexitol as in **87a** is known to permit chemoselective phophorylation of the remaining equatorial hydroxyl groups to provide access to the target **86**.[41] Replacing the *cis*-diol by a double bond as in **88** provides the link for creation of chirality by a Pd-AAA. In this case, the enantio- and chemodiscriminating event

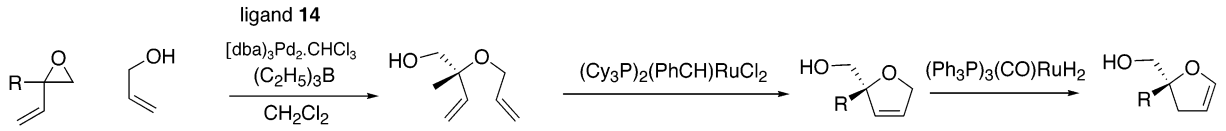
(15)

is the deracemization of the tetraester of racemic conduritol B **89** via a pseudo-*meso*-π-allylpalladium intermediate. Indeed, the DYKAT of racemic **89** using benzoic acid provides an 80% yield of enantiomerically pure differentiated tetraester **90** (eq 16). Base hydrolysis selectively cleaves the benzoates. On the other hand, Zn and acetic acid in THF selectively cleaves the carbonates to diol **91**. Thus, full differentiation of each pair of homotopic diols becomes available. Because of the symmetry of both **90** and **91**, dihydroxylation of either face provides the same cyclohexitol derivative such as **87b**, which in three steps completes a synthesis of 1,4,5-IP_3.

A glycosidase inhibitor, cyclophellitol (**92**), an inactivator of β-gluocosidase and an inhibitor of HIV,[42] also simplifies by involving an allylic alkylation strategy (Scheme 17).[43] Thus, the alkene **93** becomes a logical precursor to epoxide **92**. Since the primary alcohol of **93** should derive from chemoselective reduction of a carboxylic acid such as **94**, deracemization of the racemic conduritol tetraesters **89** with a hydroxycarbonyl anion equivalent would provide a simple route. From the work on the asymmetric syntheses of nucleosides, phenylsulfonylnitromethene becomes a logical choice. Indeed, as shown in eq 17, this DYKAT proceeds well to the monoalkylation product **95** and shows no indication of polyalkylation. Oxidation of the in situ generated nitronate anion with dimethyldioxirane provides the requisite acid **96**. Chemoselective reduction of the acid and epoxidation provides the target compound **92** after base hydrolysis.

The aminocyclohexitol moiety **97** of hygromycin (vide supra) also nicely derives from a similar strategy as illustrated in Scheme 18.[44] Recognizing that the differentiated oxazolidin-2-one **98** should arise by simple cyclization from a *trans*-vicinal diol and that the *cis*-methylenedioxy unit should derive from an alkene readily reduces the problem to a synthesis of cyclohexene **99**. The symmetry of the diol **91** allows sequential functionalization of the homotopic hydroxyl groups to set the stage for oxazolidin-2-one formation by intramolecular S_N2 displacement. As already indicated, differentiated tetraol **91** readily derives from racemic conduritol B as shown in eq 16. A 10-step synthesis with 23% overall yield of the aminocyclohexitol **97** from conduritol B results. Thus, both the furan core and the aminocyclohexitol portion of

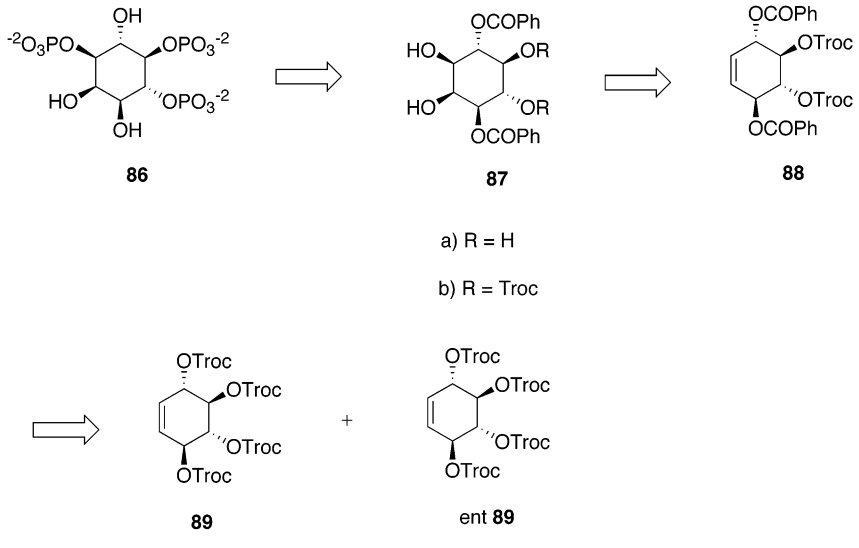
SCHEME 15. Equation 14.



(14)

	82	83		84	85
a) R = H	84%	90% ee		84%	83%
b) R = CH_3	86%	94% ee		85%	98%
c) R = Ph	45%	94% ee		86%	90%

SCHEME 16. Retrosynthetic Analysis of 1,4,5-IP$_3$



hygromycin benefits from strategies derived from the Pd-AAA, the former via a desymmetrization and the latter via a DYKAT.

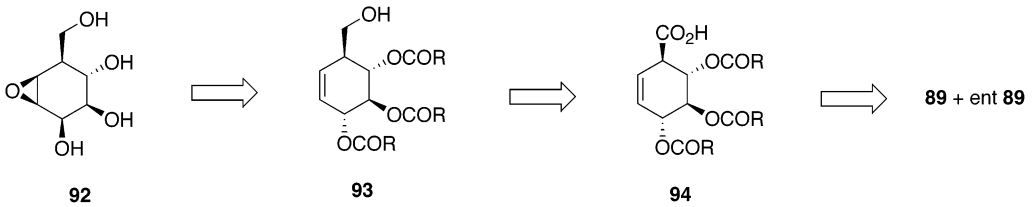
The aminocyclopentitol mannostatin **100**, a highly specific nontoxic nanomolar inhibitor of α-D-mannosidase,[45] represents another excellent target for a Pd-AAA strategy. As outlined in Scheme 19, a nine-step synthesis emerges in which desymmetrization of *meso*-diol **102** to the oxazolidin-2-one **101** constitutes the enantiodiscriminating event (eq 18).[46] In the initial work, the catalysts employing the diester ligand **104** gave a 65% ee in this desymmetrization. Subsequent work using what has become our standard ligand **31** increased that to 99% ee in the presence of triethylamine.[47]

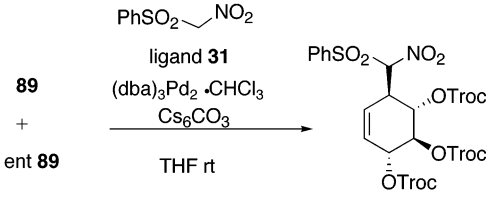
Allosamizoline (**105**), the aglycone of the potent chitinase inhibitor allosamidin,[48] readily factors to cyclopentene **106** (see Scheme 20).[46a,49] As just indicated, such oxazolidin-2-ones should readily derive from desymmetrization of *meso*-diols, the requisite one in this case, **107**, easily obtained in a single operation by alkylating cyclopentadienylthallium with benzyl chloromethyl ether followed directly by singlet oxygen addition and in situ reduction. At the time of the initial synthetic work, the desymmetrization of **107** to give oxazolidin-2-one **106** (R = Ts) was performed with BINAPO **108** as ligand[50] wherein an ee of 65% was obtained. Using stilbene diamine ligand **53** gave a small boost to 70% ee. Subsequent work[47] suggests that addition of triethylamine should further enhance the ee to >90%. It should be noted that this important aminocyclopentitol requires only six steps from cyclopentadiene using a Pd-AAA-based strategy.

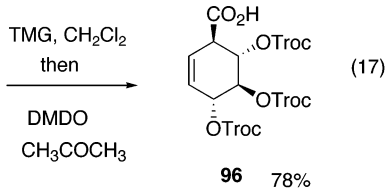
Chromanes. The chromanes constitute a broad class of natural products of diverse biological function and are illustrated in Figure 2. Many of the targets (i.e., **109**−**112**) involve creating a tetrasubstituted stereogenic center, a particularly challenging task. Scheme **18** outlines two strategies for their asymmetric synthesis. In the intramolecular strategy, tethering of the phenol to the allyl unit ensures the regioselectivity of the nucleophilic attack at the more hindered allyl terminus, a typically disfavored regioselectivity.[51] On the other hand, it is possible to envision that, in a catalyst-controlled reaction wherein chiral ligands induce asymmetry by control of regioselectivity of nucleophilic attack in pseudo-*meso*-π-allylpalladium intermediates, the chiral catalyst might direct the nucleophile to the more substituted allyl terminus even in a intermolecular process.[52]

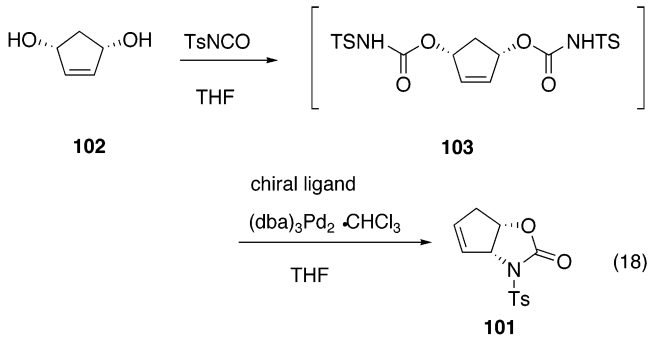
The chromane cores of targets **110**−**112** all share a common substitution pattern suggesting that chromane **116** would be a common intermediate since DDQ oxida-

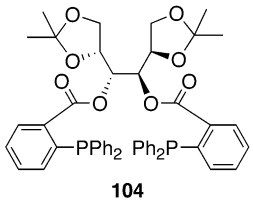
SCHEME 17. Retrosynthesis of Cyclophellitol









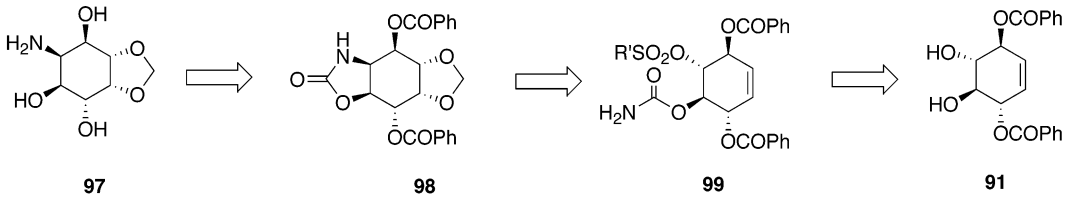


tion of chromanes provides access to chromenes (required for siccanin and siccanochromene B). Exposing phenol **114** to the chiral catalyst bearing the standard *R,R* ligand **31** in the presence of acid (not base!) provides the requisite chromane **116** with 84% ee (eq 19).[51] Envisioning the Z alkene **115** fits within the chiral space of the catalyst better, it was anticipated that a significant enhancement of the ee would occur, an anticipation that was observed, the ee rising to 97%. With chromane **116** in hand, attachment of the two prenyl subunits to the related aldehyde **117** provided the antitumor agent clusifoliol (**110**) and established its absolute configuration (eq 20).

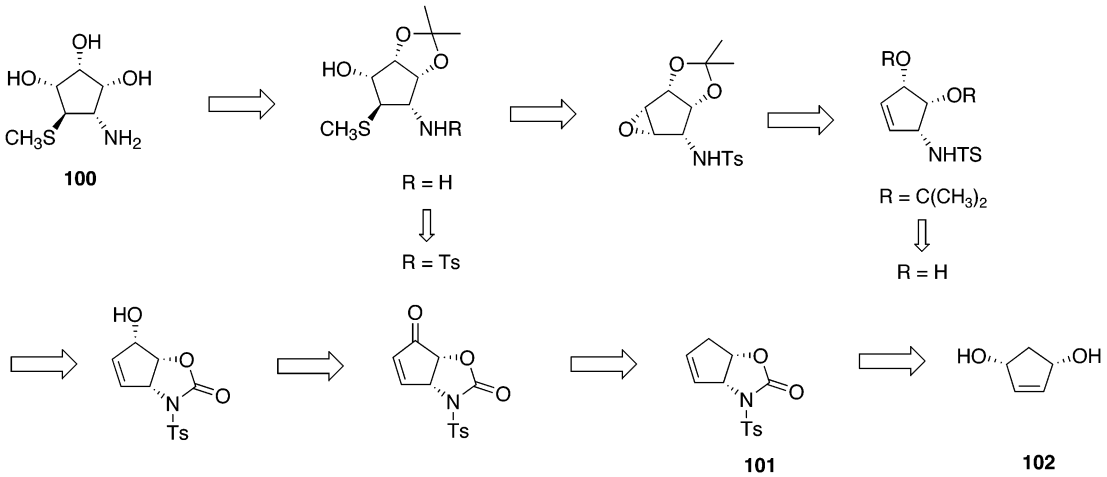
Envisioning a biomimetic approach to the antifungal agent siccanin (**111**) required access to siccanochoromane B **112**, whose cyclization is anticipated to constitute the key step of biosynthesis.[53,54] The latter should be available as outlined in eq 21 wherein the two subunits are joined by a Julia olefination[55] followed by subsequent hydrogenation. The sulfone **118** arises by sulfinate displacement on the corresponding known chiral alcohol.[56] Indeed, this sequence not only provided a facile route to siccanin and numerous siccanochromenes but also provided insight into the biocyclization of epoxide **112**.

The chromane core of vitamin E also arises from the cyclization of the properly substituted phenol as shown in eq 22.[51a] Alternatively, the intermolecular strategy offers the prospect of an even more concise synthesis. Thus, Scheme 22 details the route.[52] The Pd-AAA proceeded well both in terms of regio- and enantioselectivity.

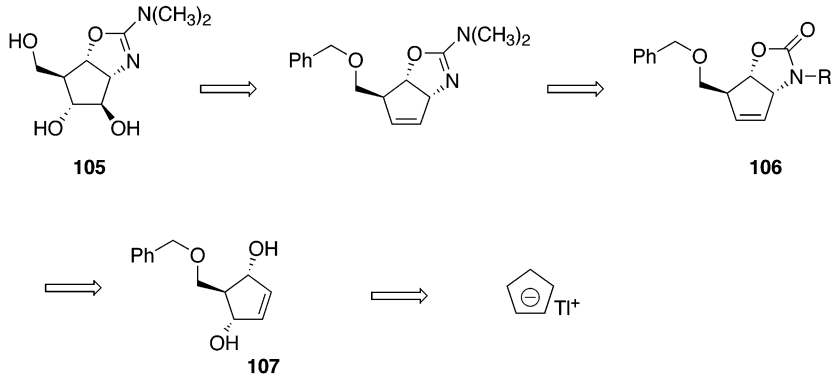
SCHEME 18. Retrosynthesis of Aminocyclohexitol of Hygromycin

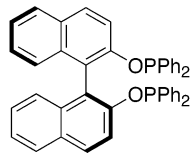


SCHEME 19. Retrosynthesis of Mamostatin A



SCHEME 20. Retrosynthesis of Allosamizoline





The vinyl unit in this strategy becomes the ring carbons of the chromane by an intramolecular Friedel–Crafts alkylation.

This intermolecular strategy for asymmetric construction is particularly applicable to targets in which the chromane core has additional substituents as in the case of antivirals calanolide A and B.[57] Scheme 23 details the retrosynthetic analysis.[52] The concept embraces introduction of the initial stereogenic center in the Pd-AAA of phenol **121** and tiglyl methyl carbonate and the remaining two centers controlled by subsequent diasteroselective reactions dictated by the initial stereogenic center. Annulation of the oxygen heterocycles of the coumarin and chromane rings onto a phloroglucinol core provides rapid simplification of the target to simple starting materials.

Three steps converted phloroglucinol and 3-methyl-2-butenoic acid to the requisite phenol **121** setting the stage for the critical Pd-AAA (eq 23). Using the standard *R*,*R* ligand **31** gave a nearly 1:1 regioisomeric mixture of the desired **120** vs attack at the primary carbon. Neverthe-

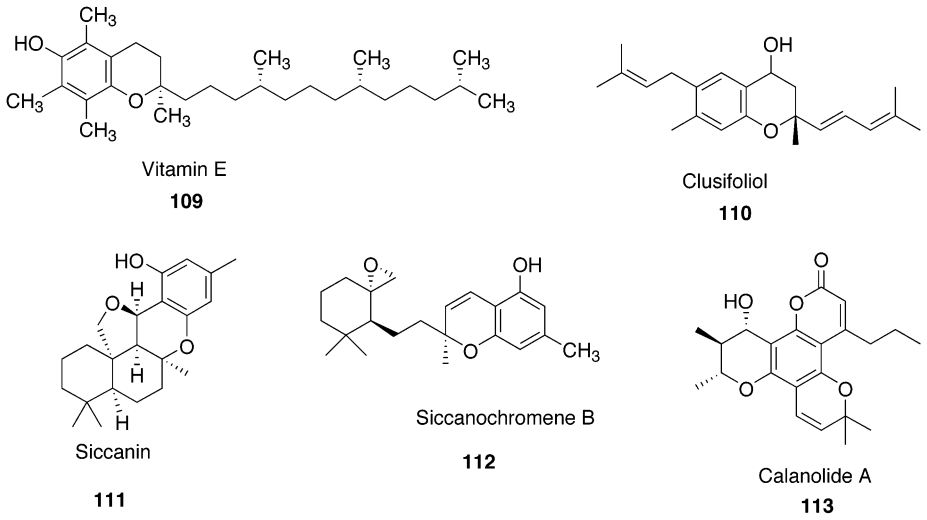
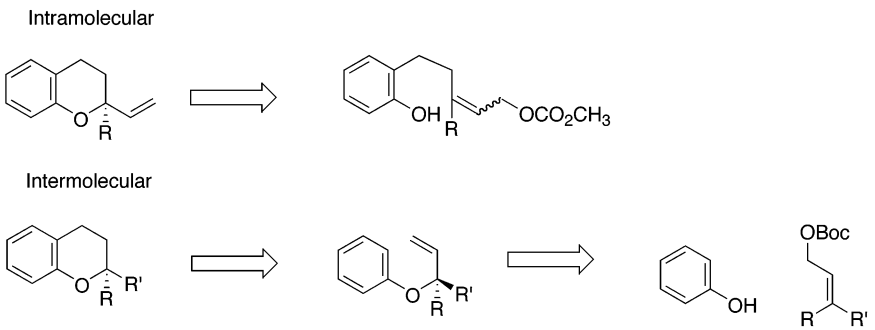
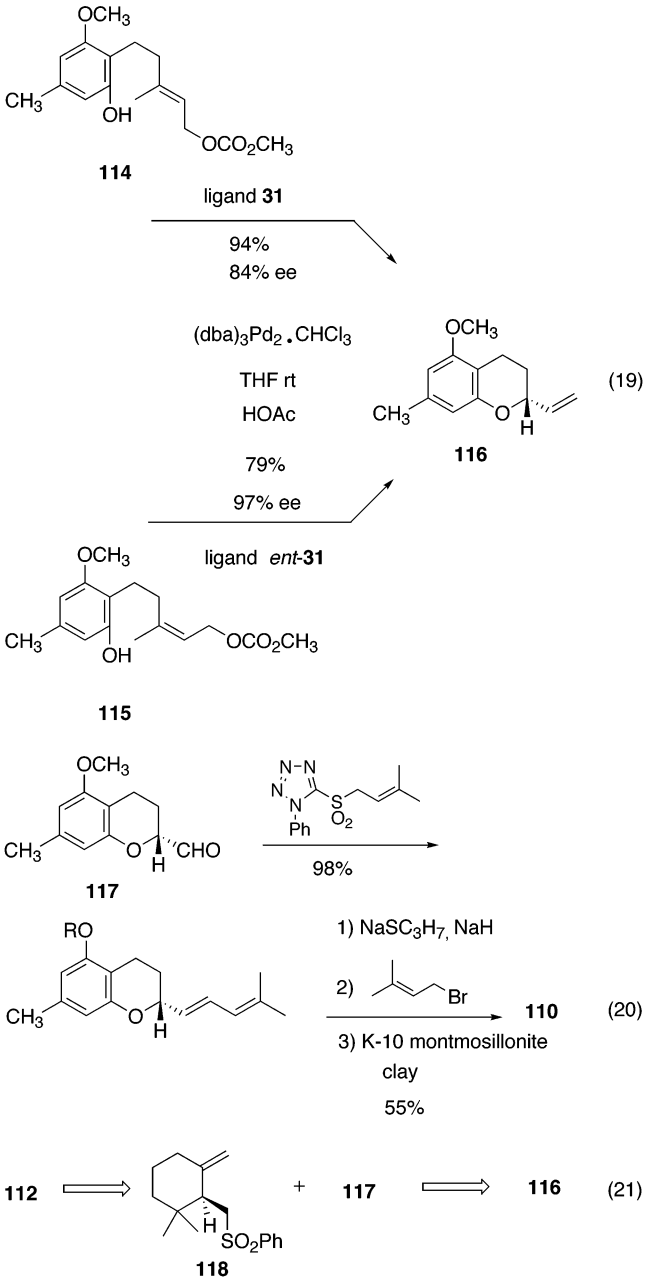
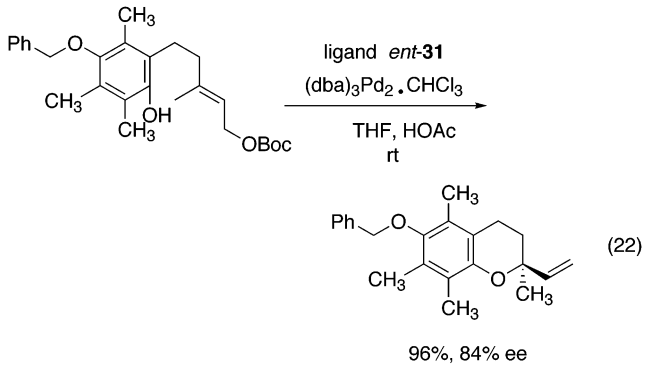


FIGURE 2. Chromane targets.

SCHEME 21. Strategic Designs to 2,2-Disubstituted Chromanes







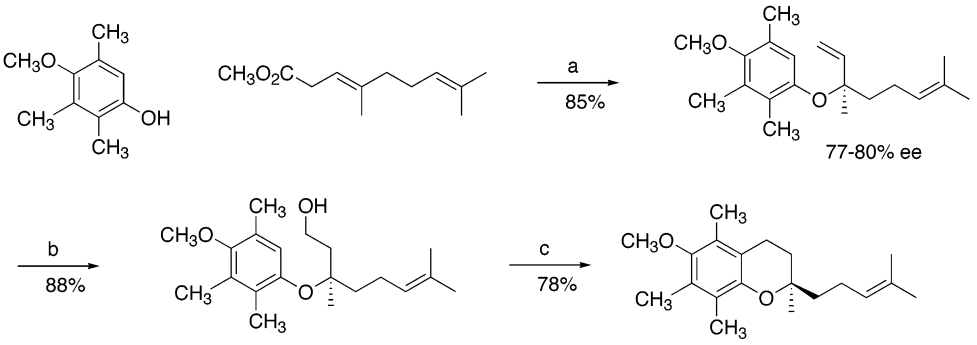
less, the ee in methylene chloride was quite good at 90%. Switching to the tighter naphtho linker *S,S* ligand **14** slightly improved the regioselectivity in formation of the enantiomeric **122** to 69:31 but saw a significant drop in ee to 56%. Increasing the bite angle by increasing the ligand dihedral angle as in *S,S* **65** increased both the regioselectivity to 80:20 and ee to 96%. Switching from methylene chloride to THF gave the best result, an 85% yield of a 92:8 regioisomeric ratio in which the ee of the major regioisomer was 98%. Introduction of the double bond with DDQ gave the coumarin **123**. Alternatively, the chromene analogue of **121** (i.e., wherein the double bond is already present) gave **123** directly with comparable results.[58] Diastereoselective hydroboration with 9-BBN-H set the second stereocenter in forming alcohol **124** (eq 24, dr 93:7). Oxidation and Lewis acid cyclization provided ent-calanolide B **125a** and, by inversion, ent-calanolide A **125b**. Whereas using the *S,S* ligand provided the enantiomer of the natural product, simply switching to the *R,R* ligand will give the natural enantiomer.

Amaryllidaceae and Opium Alkaloids. The opium alkaloids have become virtually synonymous with their most famous members, codeine **126** and morphine **126a**.[59] The Pd-AAA reaction combined with the very rarely used hydroamination[60] led to a particularly facile approach as shown in Scheme 24.[61] Envisioning an allylic oxidation to install the hydroxyl group, conceiving formation of the final piperidine ring by an intramolecular hydroamination reduces the problem to the tetracycle **127**. Two Heck reactions to form one carbocyclic and the dihydrofuran rings further simplifies the problem to O-allylated phenol **129**, which in turn should derive from racemic allyl ester **131** and bromovanillin **130**, the former derivable in two steps from glutaraldehyde and the Horner−Emmons−Wadsworth reagent.[62]

As shown in eq 25, the requisite Pd-AAA reaction proceeds well with the stilbene-derived ligand ent-**53**.[63] Temporary protection of the aldehyde to permit one carbon chain extension of the ester provides a pivotal intermediate **132** whose enantiopurity is raised to nearly perfect upon recrystallization. The initial Heck reaction, apparently assisted by facile oxidative addition by the carboxaldehyde functional group, proceeded in high yield (eq 26). Six steps including the second Heck reaction, this time a vinylation, and a hydroamination complete the synthesis of codeine in 15.4% yield and, by demethylation, morphine.

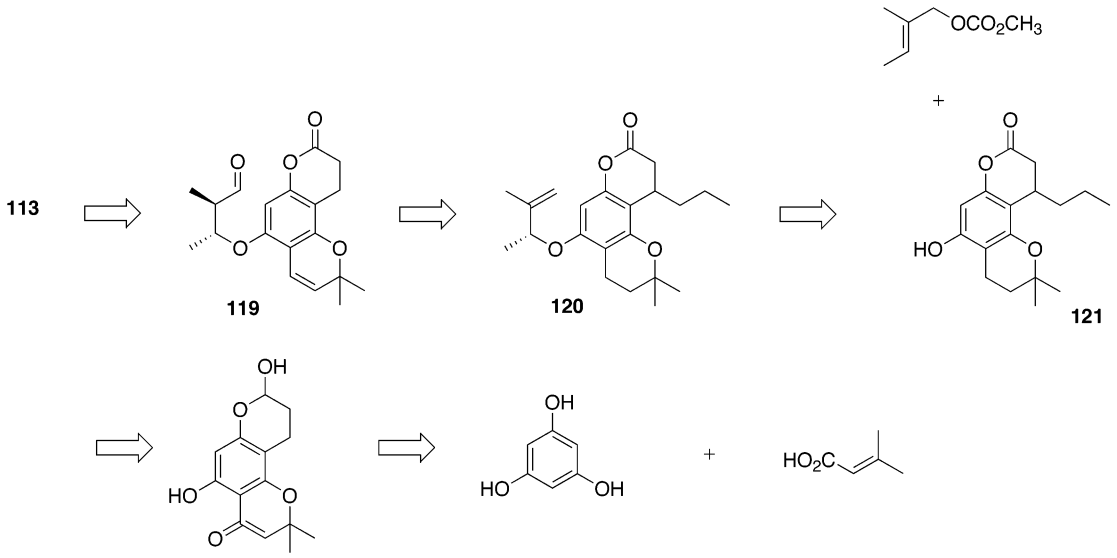
This type of strategy also created a simple asymmetric synthesis of synthetic analgesics, the benzomorphanes **133**[64] as outlined in Scheme 25.[65] Once again hydroamination of **134** completes the piperidine ring. Curiously, the conditions of hydroamination may also accomplish diastereoselective isomerization of **135** to the dihydronaphthalene **134**. Once again, this pathway becomes viable because amine **135** can be envisioned to derive by a Pd-AAA in which the enantiodiscrimination is at the nucleophile. Gratifyingly, this alkylation proceeds well using 0.5 mol % of the Pd(0) source and 1.1 equiv of allyl acetate, giving the product **137** possessing 91% ee (eq 27). Olefination, chemoselective oxidative cleavage of the monosubstituted alkene followed by reductive amination provides the penultimate intermediate **135** wherein the N-substituent can be varied at will. Indeed, simple base treatment of **135** cycloisomerizes the latter to give the benzomorphans quantitatively with excellent diastereo- and enantioselectivity.

SCHEME 22. Asymmetric Synthesis of Vitamin E Core[a]

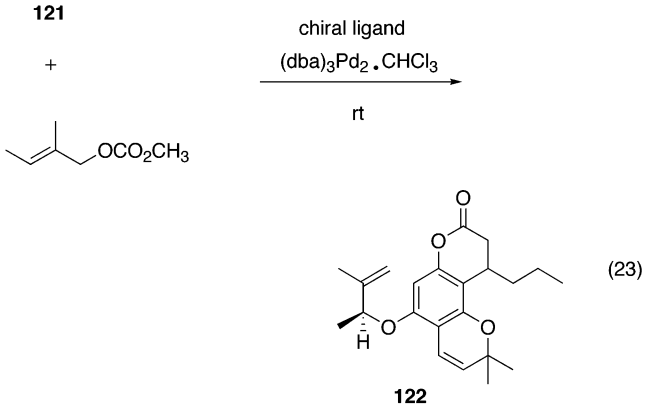


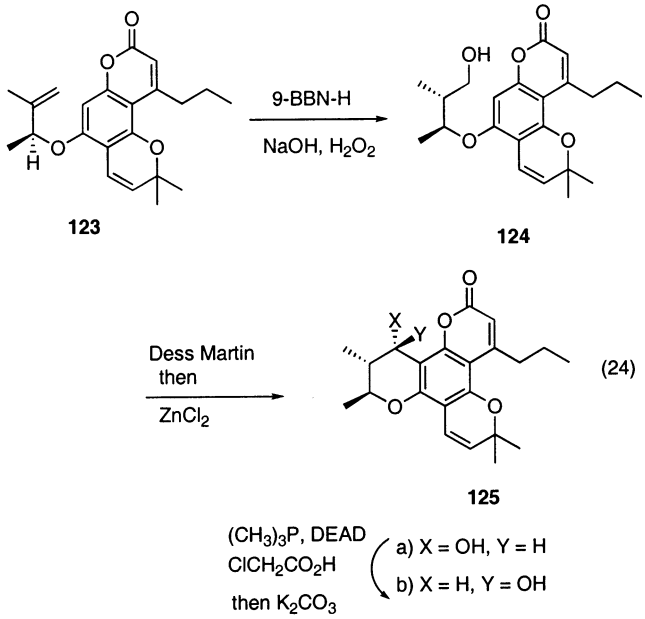
[a] (a) **31**, $(dba)_3Pd_2{\cdot}CHCl_3$, $(C_4H_9)_4NCl$, CH_2Cl_2, rt. (b) catechol borane, $(Ph_3P)_3RhCl$, THF, rt then NaOH, H_2O_2. (c) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C.

SCHEME 23. Retrosynthetic Analysis of Calanolide A

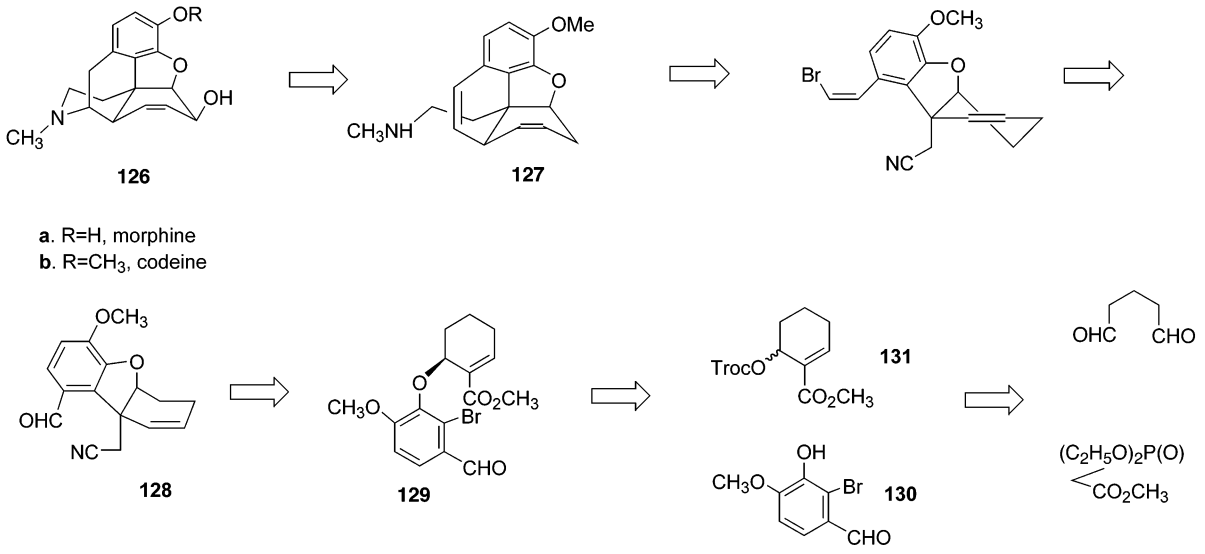


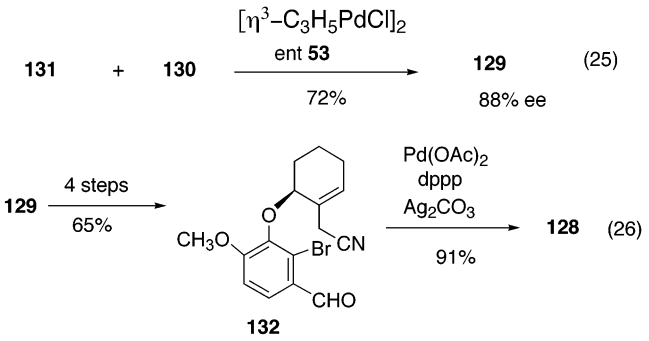
Galanthamine (**138**), an amaryllidaceae alkaloid that is useful for the treatment of Alzheimer's patients,[66] also derives from cyanoaldehyde **128** in just two steps, allylic oxidation and reductive amination (eq 28).[67] Oxidation of the allylic alcohol of galanthamine provides narwedine, whereas reduction of the double bond produces lycoramine.[68] Pancratistatin (**139**), a potentially significant antitumor agent of low natural abundance, constitutes a quite different type of amaryllidaceae alkaloid that is more akin to the cyclohexitols.[69] Recognition that the arylcyclohexene **141** requires just a net *trans* hydroxylation and carbonylation or carboxylation presumably via the *cis*-diol **140** involving a simple inversion rapidly simplifies the problem to a regio- and diastereoselective arylation with an arylcuprate of monoester **142** that





SCHEME 24. Retrosynthetic Analysis of Codeine and Morphine





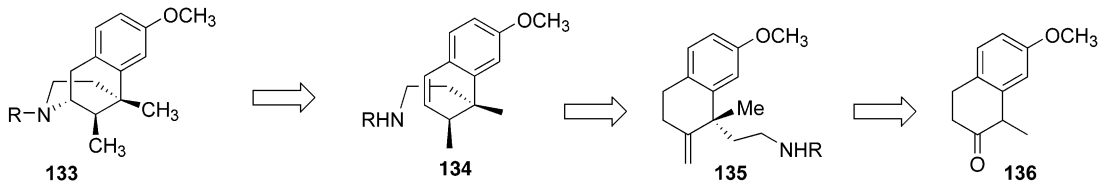
should be derived via a desymmetrization of diester **143** by a Pd-AAA.[70] Using our standard *R,R* ligand **31**, trimethylsilyl azide reacted with dicarbonate **143** (R = OCH_3) to give monoazide **142** (R = OCH_3) of >95% ee in 82% yield. The synthesis as sketched in Scheme 26 was completed in 14 steps from *meso*-diester **143**.

The allylic azide **142** also undergoes a [3.3] sigmatropic rearrangement to **144a** at around 60 °C to provide the regioisomeric azide **144** (eq 29).[71] If performed with the methylenedioxy derivative, the corresponding allylic azide **144** provides an altenative route to the amincyclohexitol **97**.[44]

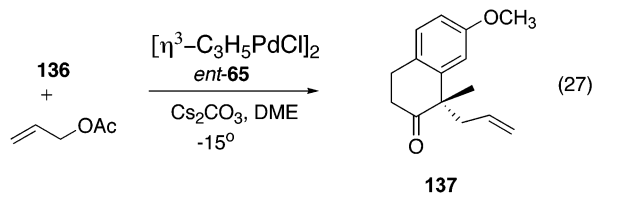
Cyclopentanoids. Brefeldin A, a natural product having a number of intriguing biological properties, provides a number of structural challenges including the issue of stereochemistry of the core ring as well as the distant stereogenic center.[72] The Pd-AAA provides useful insight for both. Scheme 27 outlines the strategy whereby the target is assembled from three units, ethyl propiolate, the chemodifferentiated cyclopentyl core **146** and the lower side chain in the form of sulfone **147** prepped for its joining to the core via a Julia-type olefination.[73] Realizing the ease of epimerization α to a carboxaldehyde, the *cis*-fused bicyclo [3.3.0] system **148**, which contains a masked aldehyde, becomes very attractive since diastereoselective cycloadditions to butenolide **149** proceed with good selectivity. As already demonstrated, the chiral butenolide should be accessible by deracemization of the racemic butenolide **41** analogous to the key asymmetric inducing reaction in the synthesis of aflatoxins (eq 4).[19] Indeed, the reaction of racemic butenolide **41** with *β*-naphthol as shown in eq 30 proceeds in excellent yield and ee.[74] Cycloaddition proceeds with complete diastereoselectivity to give the cyclopentyl core. Ultimately all the stereochemistry around this core derived from the Pd-AAA reaction. The last stereocenter also derives from a Pd-AAA reaction. Envisioning a chain extension from a chiral α-methylallyl alcohol derivative **150** to form sulfone **147**, the regio- and enantioselective alkylation of *E*-crotyl carbonate with a phenol provides this stereocenter.[75] Equation 31 indicates this requisite reaction occurs with excellent results.

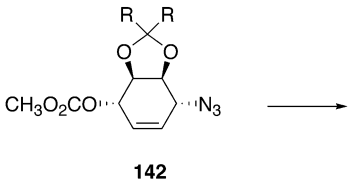
The antitumor antibiotic viridenomycin **151** resembles brefeldin A in that it consists of a cyclopentanoid ring annulated onto a macrocycle. Targeting the highly functionalized cyclopentene **152**, combining the double bond intrinsic to allylic alkylation with a suitably placed second double bond to perform a ring-closing metathesis,

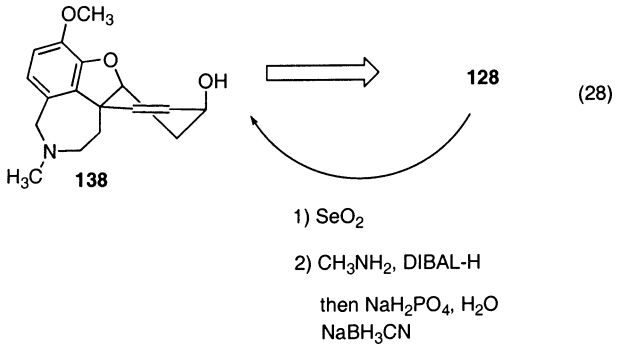
SCHEME 25. Retrosynthesis of the Benzomorphanes

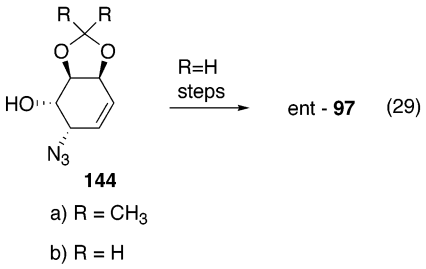


a) R = CH_3 metazocine
b) R = (CH_3), C = $CHCl_2$ pentazocine









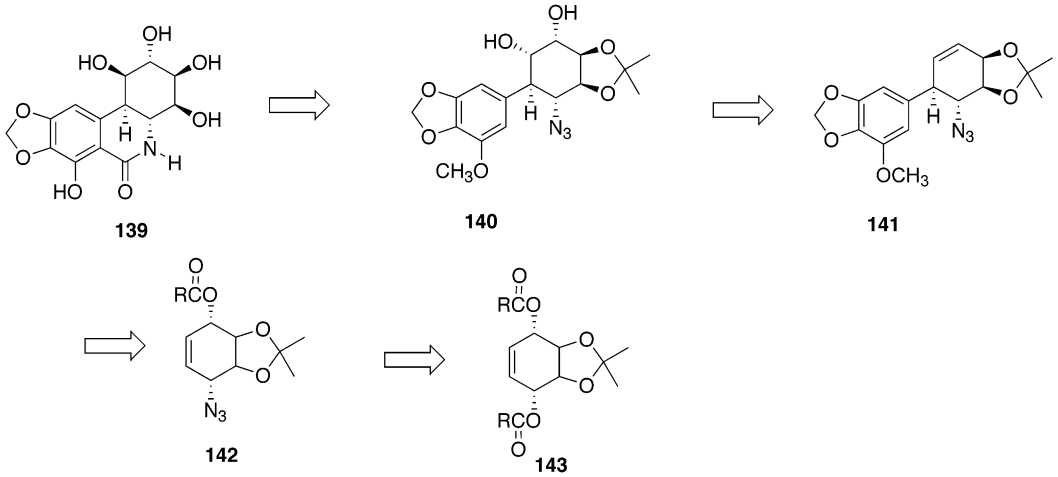
a synthetic strategy as summarized in Scheme 28 emerges.[76] The key enantiodiscriminating event is the Pd deracemization of isoprene monoepoxide with a carbon nucleophile wherein all remaining stereocenters will be created relative to that initial one.[77] Although the Nazarov reagent itself proved unsatisfactory in the Pd-AAA, a protected form **153**[78] performed with excellent regio- and enantioselectivity (eq 32) to hemiketal **154**. Silylation followed by elimination provided the diene **155**, which cyclized satisfactorily to the key cyclopentene **156** albeit sluggishly. A further six steps then completed the core, requiring overall only a total of 11 steps.

In contrast to the above, hamigeran B (**157**), a potent antiviral agent consisting of a polycondensed ring system,[79] lends itself to take advantage of the aromatic ring. Thus, the target nicely dissects into two "halves": a simple aromatic, dimethylorcinol, and a cyclopentanone **158** (Scheme 29). Conjugate addition−elimination allows construction of an isopropyl group from an alkoxymethylidene function, thereby setting the absolute configuration of all stereogenic centers from a Pd-AAA of a prochiral nucleophile, the enolate of cyclopentanone **159**.[80]

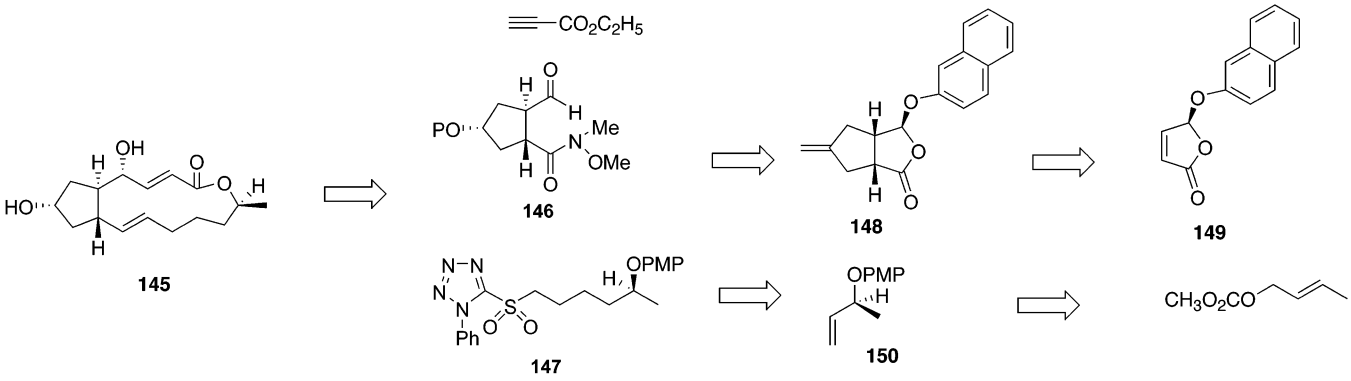
This task proved challenging since initial asymmetric allylations as in eq 33 were highly promising but proved irreproducible. The lack of reproducibility was ultimately correlated with the presence of alkoxides in the butyllithium, which proved crucial for high ee. Thus, deliberate addition of *tert*-butyl alcohol gave a very reliable protocol wherein the allylated ketone **160** was formed in 93−95% ee. Addition of 2 equiv of lithium dimethylcuprate and vinyl triflate formation completes the cyclopentyl "half" **161**. Oxidative cleavage of the terminal double bond followed by addition of lithiated dimethylorcinol joins the two halves and sets the stage for completion of the synthesis in 15 total steps from 2-methylcyclopentanone, the precursor of **159**.

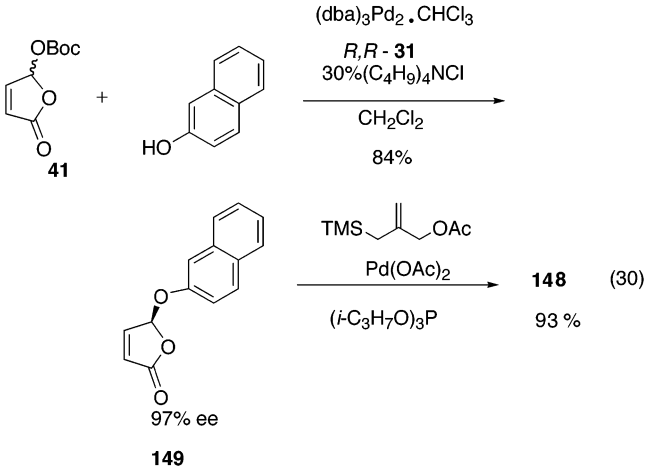
Amino Acids and Other Acyclic Structures. Although synthesis of normal amino acids via catalytic asymmetric hydrogenation is extremely powerful, there exists a number of unusual amino acids and close relatives that are not readily accessible by such methodology. Figure 3 illustrates some of these. The most complex of these are the sphingofungins **162**,[81] inhibitors of the biosynthesis of sphingolipids leading to apoptosis, and the closely related myriocin,[82] a remarkable immunosuppressive agent that is identical to sphingofungin E **162b** except that it lacks the allylic hydroxyl group. These compounds consist of a highly functionalized "warhead" **162** and a lipophilic tail **161**, which suggests a retrosynthetic analysis as shown in Scheme 30. The former envisions access to the vinyl iodide via a Takai iodoolefination, suggesting a diastereoselective hydroxylation

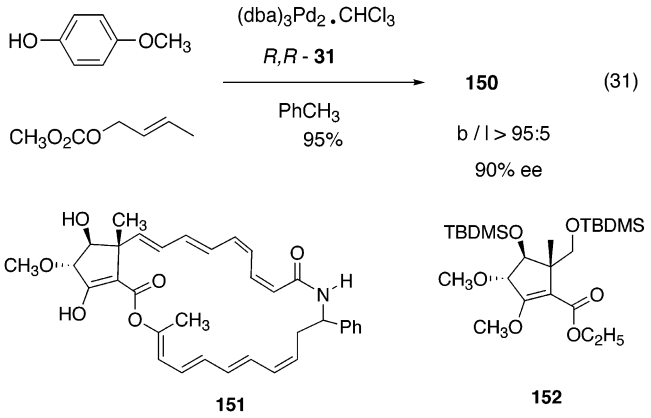
SCHEME 26. Retrosynthetic Analysis of Pancratistatin



SCHEME 27. Synthetic Strategy for Brefeldin A







of an[36] allylic alcohol **168**. Obtention of the correct stereochemistry of dihydroxylation requires the stereochemistry of the allylic alcohol to be inverted from the natural products. The most direct route to **168** questions the ability to induce stereochemistry at a nucleophile, in this case an azlactone **169**,[83] and to invoke an unusual desymmetrization of a *gem*-diacetate **170**.[84]

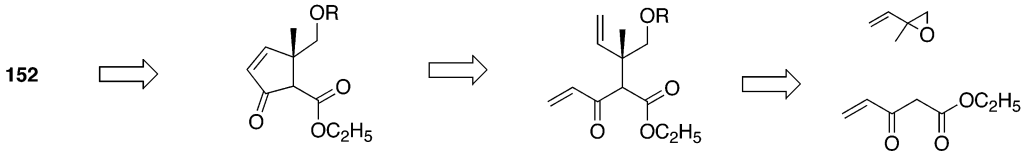
The synthesis of α-methylaspartic acid addresses the first of these issues, the difficult challenge of asymmetric induction at the nucleophile. Conceptualizing that a double bond is a synthon for a carboxylic acid by oxidative cleavage, this quaternary amino acid may be derived by a Pd-AAA of an azlactone. Thus, allylation of azlactone followed by ozonolysis and basic workup provides the target (eq 35).[83] The subtlety of the process is illustrated by the effect of the allylating agent on the facial selectivity using the identical catalysts. Thus, prenyl acetate (Scheme 31, eq 34, path a) provides (*S*)-α-methylaspartic acid, but cinnamyl acetate (eq 34, path b) provides the (*R*)-enantiomer.

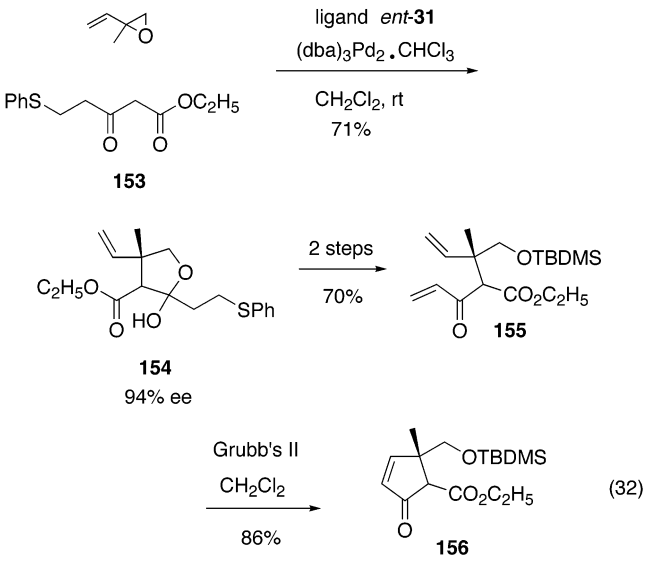
The synthesis of sphingofungin F requires the alkylation of **169** (X = H) with *gem*-diacetate **170**, which proceeds in 76% yield with excellent diastereoselectivity and 87−89% ee (eq 35).[85] Chemoselective opening of the azlactone **171** (X = H) with methanolic camphorsulfonic acid provided a quantatative yield of the amino ester **172** (X = H). Dihydroxylation with catalytic osmium tetroxide was accompanied with lactonization to form **173** as a single diastereomer (eq 36). Neighboring group participation inverted the center at C-3 to provide oxazoline **174**. Thus, all four stereocenters stem from the Pd-AAA. A final six-step sequence completed the synthesis of sphingofungin F (a total of 11 steps from azlactone **169** (X = H)).

For sphingofungin E, a hydroxyl group surrogate, a silyl group was chosen as X of azlactone **169** to avoid elimination issues. It participated well in the Pd-AAA (eq 35, 91% yield). Although the dr was modest, the ee was excellent. Following directly as before, dihydroxylation of alkene **172** (X = DMPS, Q) exclusively generated lactone **173** (X = DMPS). At the stage of this lactone, a Tamao−Fleming oxidation[86] converted the silyl group to the alcohol **173** (X = OH). The same three-step protocol then inverted the stereocenter at C-3 to establish all the stereochemistry shown in **174** (X = OPMB). A completely analogous six-step sequence completed the synthesis of sphingofungin E in a total of 12 steps from azlactone **169** (X = DMPS).

Vigabatrin (**164**)[87] for the treatment of epilepsy and drug dependence requires a different tactic. Thus, as

SCHEME 28. Retrosynthesis of Viridenomycin Core





summarized in eq 37 hydrolysis and decarboxylation of a malonate to access a carboxylic acid suggests the phthalimide **175** as a suitable precursor whereby simple alkylation chemistry of **176** should install the requisite malonate.[88] Deracemization of racemic vinyl epoxide with phthalimide then becomes the obvious starting materials. Although the standard ligand gave reasonable results in THF (87%, b/l 16:1, 77% ee), the optimum (99%, b/l 75:1, 99% ee) involved switching to the ligand bearing a naphtho linker, *R,R*-**13**. Thus, vigabatrin becomes available in four steps and 59% overall yield.

Intermediate **176** is a protected form of vinylglycinol that is now available in one step from two cheap starting materials, butadiene monoepoxide and phthalimide. Obviously, oxidative cleavage provides either enantiomer of serine. Alternatively, ethambutol, a treatment for tuberculosis,[89] is an obvious derivative of vinylglycinol. Straightforward derivatization leads to oxalamide **177** (eq 38), which upon reduction reveals ethambutol in a total of six steps from phthalimide and butadiene monoepoxide.[88]

The Lilly PKC antagonist LY 333531 (**178**), under clinical development for retinopathy associated with diabetic complications,[90] is assembled by an alkylation of an "aglycone" with a bis-alkylating agent **179** (eq 39).[91] The anti-Markovnikov hydration of a terminal alkene as in **180** then requires an asymmetric synthesis of a

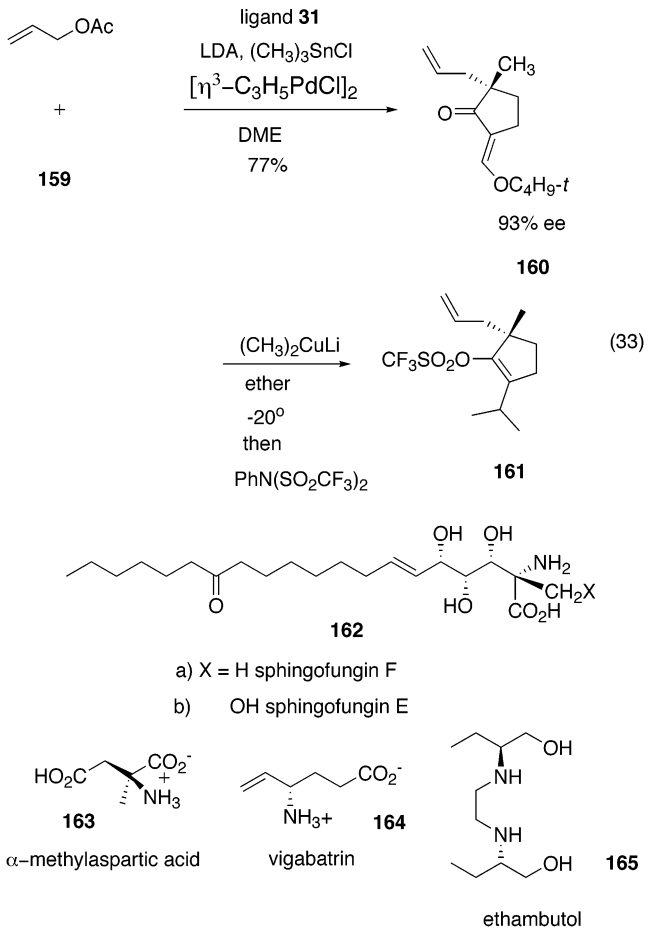
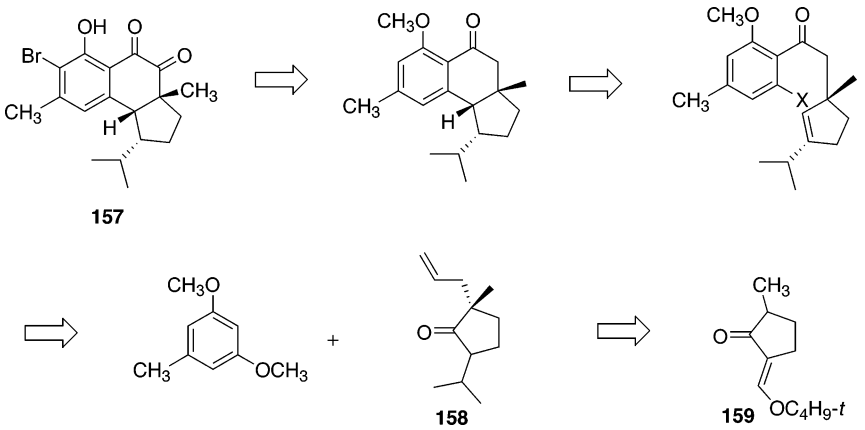


FIGURE 3. Unusual amino acids and related structures.

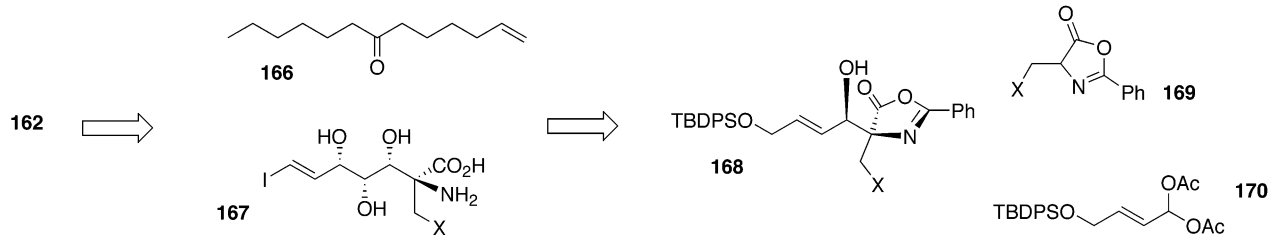
monoether of a vinylglycidol. In complete analogy to vinylglycinol, simple replacement of an amine with an alcohol should allow access to **180** via a deracemization of butadiene monoepoxide.[92]

Equation 40 demonstrates the efficiency of this strategy, made all the more remarkable considering 2-bromoethanol could undergo internal annihilation.[91] The vinylglycidol derivative **181**, obtained in 92% ee, was converted in three straightforward steps to the bis-alkylating agent **182**. The four-step sequence produced the enantiopure bis-alkylating agent in 46% overall yield from two cheap commercially available substances.

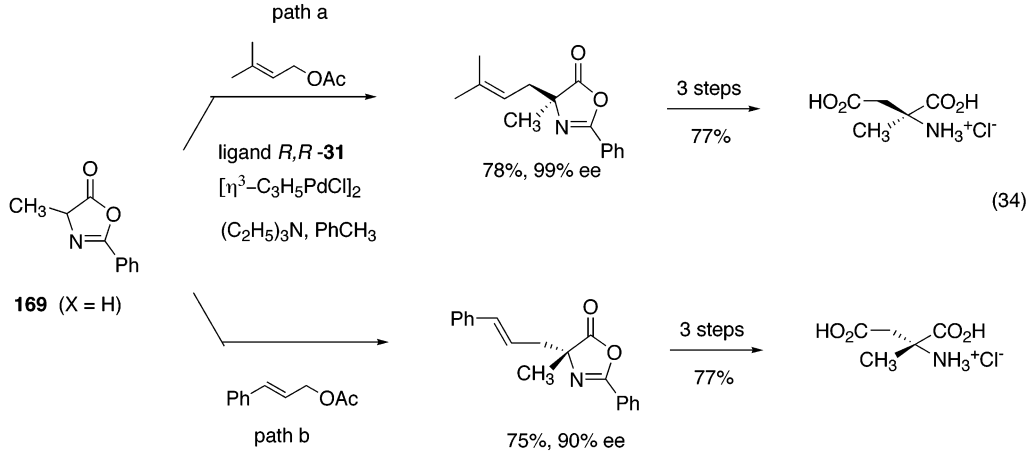
SCHEME 29. Retrosynthesis of Hamigeran B



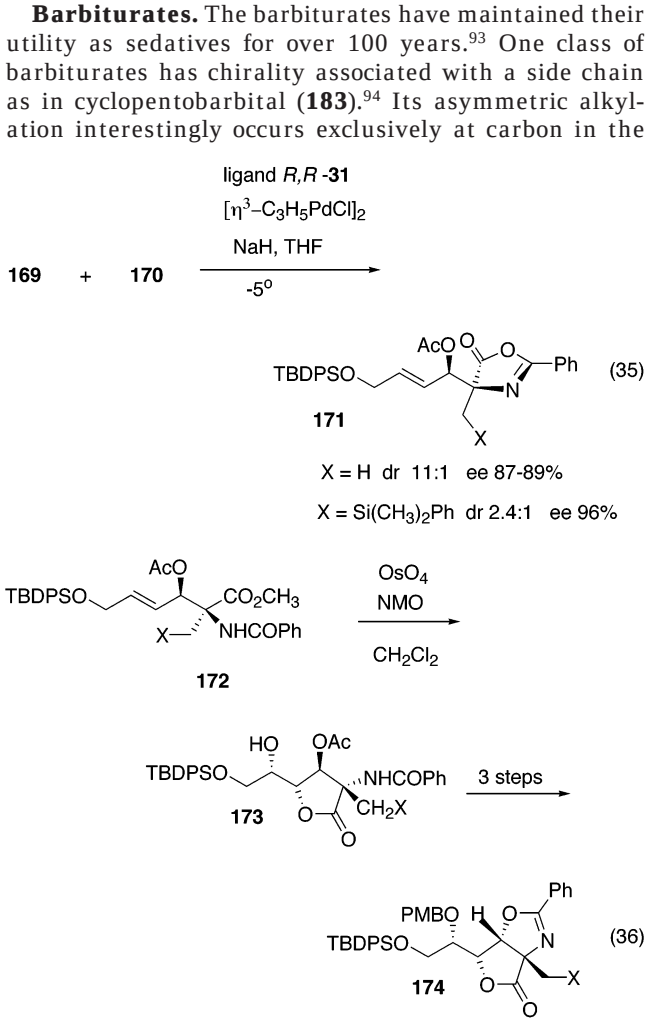
SCHEME 30. Retrosynthetic Analysis of Sphingofungins E and F

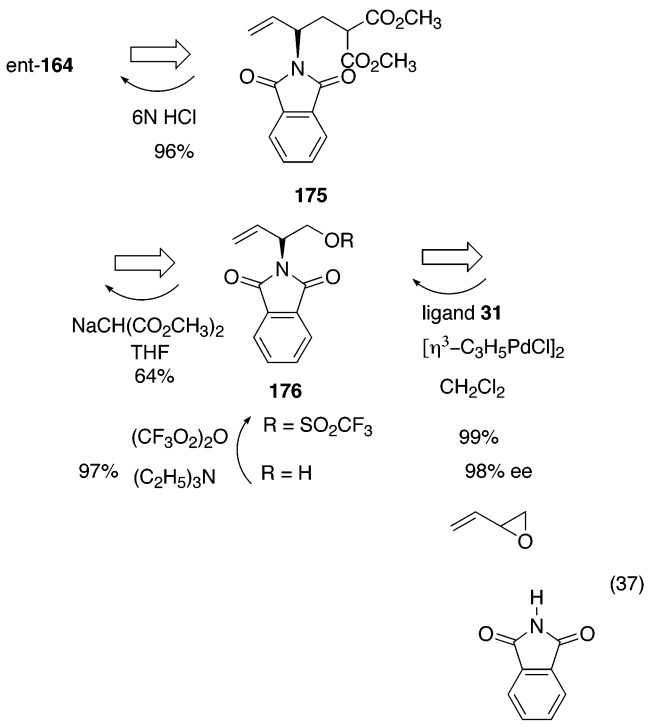


SCHEME 31. Equation 34.

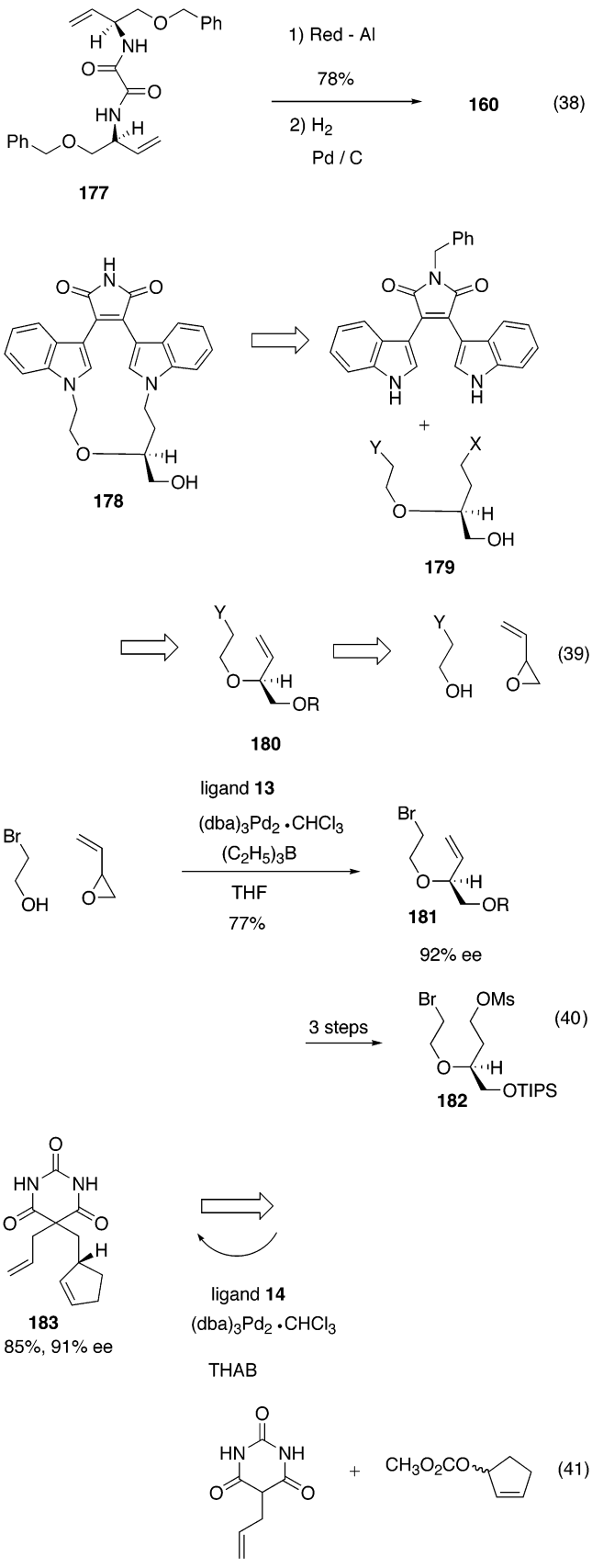


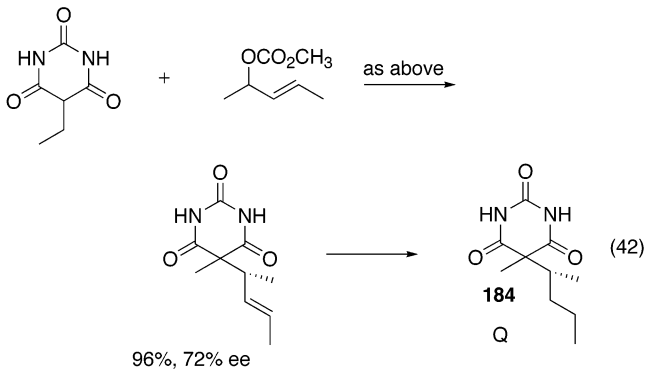
Barbiturates. The barbiturates have maintained their utility as sedatives for over 100 years.[93] One class of barbiturates has chirality associated with a side chain as in cyclopentobarbital (**183**).[94] Its asymmetric alkylation interestingly occurs exclusively at carbon in the presence of tetrahexylammonium bromide (THAB) in the presence of the catalyst employing naphtho linker ligand **14** (eq 41).[95] This is the first asymmetric synthesis of this compound. Pentobarbital (**184**) can derive by an equally direct approach as shown in eq 42. In this case, hydrogenation of the double bond completes the sequence.



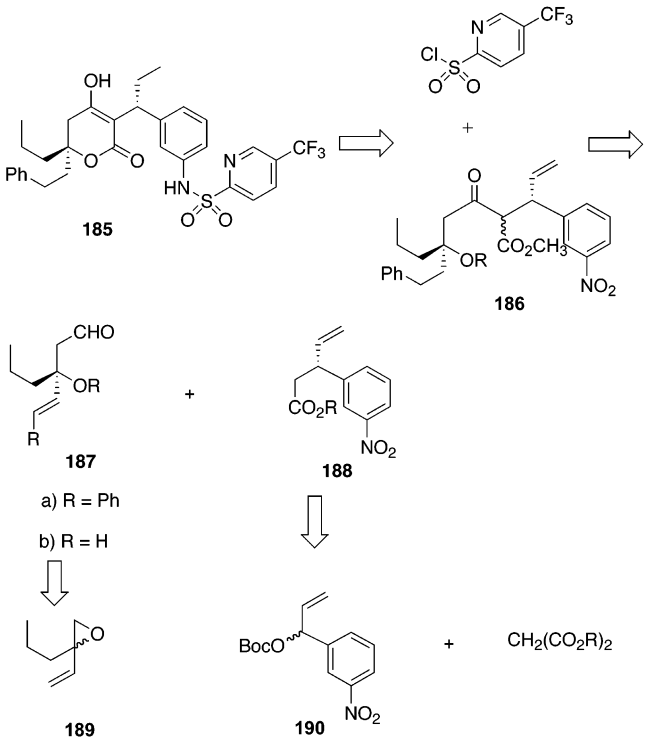


Tipranavir. Tipranavir, a non-nucleoside-based member of the class of HIV reverse transcriptase inhibitors,[96] poses the challenge that the two stereogenic centers are



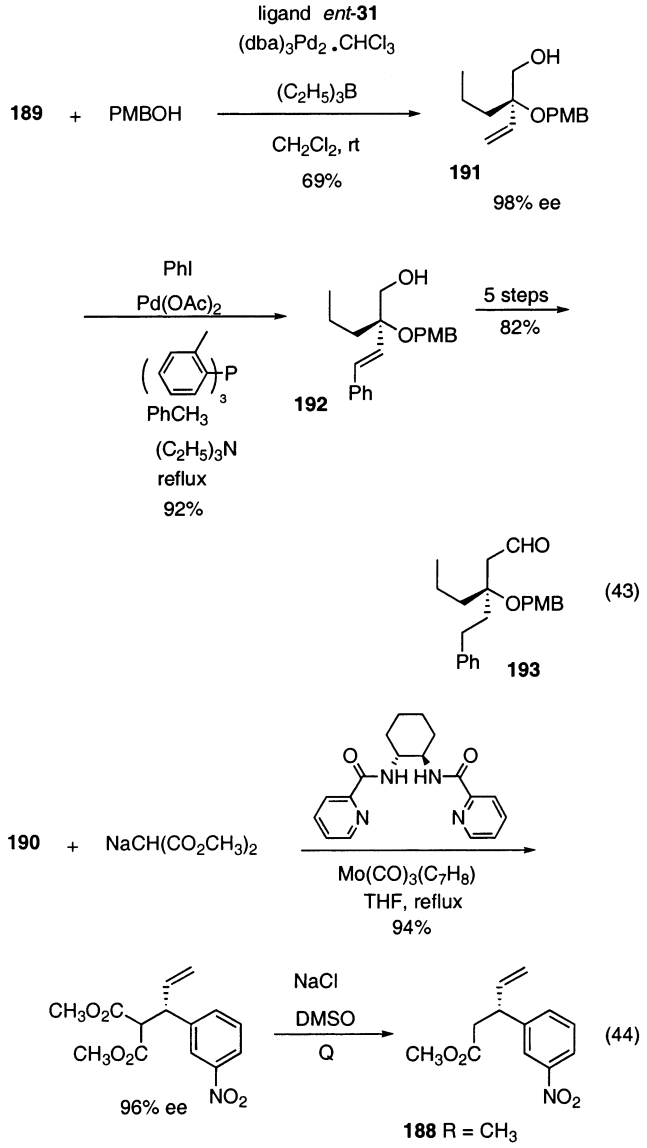


SCHEME 32. Retrosynthesis of Tipranavir



rather distant and one is tetrasubstituted. Scheme 32 outlines the retrosynthetic analysis. The main initial disconnect besides removing the pyridine subunit is opening the dihydropyrone and adding a double bond as in **186**. Since hydrogenation of the double bond can occur concommitment with that of the nitro group, its addition has no consequences to the total number of steps. Dissecting keto ester in about half leads to aldehyde **187** and ester **188**. In the former, addition of a double bond then recognizes that the stereochemistry of the tetrasubstituted center may be established by a deracemization of the vinyl epoxide **189**.[92] Furthermore, the ester **188** now obviously derives from a regio- and enantioselective alkylation of chiral racemic ester **190**, a type of selectivity available via asymmetric Mo-catalyzed allylations, not palladium.[6]

The vinyl epoxide **189**, derived from 1-chloro-2-pentanone, with PMB-OH gives the desired regioisomeric **191** exclusively and nearly enantiomerically pure (eq 43).[97] Heck reaction installs the phenyl ring (i.e., **192**). A straightforward sequence involving double bond reduction and one carbon homologation completes the asymmetric synthesis of one half, **193**, in eight steps and 48% overall yield from 1-chloro-2-pentanone. The other half, **188**, derives very directly by the asymmetric Mo-AAA as outlined in eq 44 with complete regioselectivity and near



perfect enantioselectivity. Decarbomethoxylation occurs quantitatively under Krapcho conditions. A six-step standard reaction sequence completes this convergent synthesis in a 25% overall yield from readily available starting materials.

Conclusions

The utility of a methodology lies in its ability to help simplify synthetic strategy to complex molecular targets. The metal-catalyzed allylic alkylation, by providing exceptional diversity in exercising control, represents a methodology of immense potential. This potential expands dramatically when it can be performed asymmetrically. There are five mechanisms for asymmetric induction, and all can be realized. Both partners, the electrophilic allylating agent and the prochiral nucleophile, are suitable for asymmetric induction. In addition to asymmetric C−H, C−O, and C−N bond formation, the same catalyst system extends to asymmetric C−C bond formation. As a result, virtually every type of natural product, including amino acids, carbohydrates, nucleosides, alkaloids, polyacetates, terpenes, and numerous types of non-natural biologically important molecules become suitable targets for simplification. Although the selected examples reported herein derive only from our laboratories, many other targets have benefited using the metal-catalyzed asymmetric allylic alkylation as a key step. This methodology empowers the synthetic chemist to design the optimum structure for function by simplifying routes to structural targets.

Acknowledgment. The work in my laboratories derived from an extensive group of co-workers who contributed so much in every respect, from conceptualization to realization. They are identified in the references. Among them, David Van Vranken stands out as the developer of the family of ligands that made an impossible dream possible. Financial support stemmed mostly from the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute.

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