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Broadly Applicable Stereoselective Syntheses of Serrulatane, Amphilectane Diterpenes and Their Diastereoisomeric Congeners using Asymmetric Hydrovinylation for Absolute Stereochemical Control

Srinivasarao Tenneti,‡ Souvagya Biswas,‡,† Glen Adam Cox, ‡,† Daniel J. Mans, ‡,† Hwan Jung Lim,† T. V. RajanBabu*

Department of Chemistry and Biochemistry, 100 West 18th Avenue, The Ohio State University, Columbus, Ohio 43210 United States

Supporting Information

ABSTRACT: A stereogenic center, placed at an exocyclic location next to a chiral carbon in a ring to which it is attached, is a ubiquitous structural motif seen in many bioactive natural products including di- and tri-terpenes and steroids. Installation of these centers has been a long-standing problem in organic chemistry. Few classes of compounds illustrate this problem better than serrulatanes and amphilectanes, which carry multiple methyl-bearing exocyclic chiral centers. Nickel-catalyzed asymmetric hydrovinylation (HV) of vinylarenes and 1,3-dienes such as 1-vinylcycloalkenes provide an exceptionally facile way of introducing these chiral centers. This manuscript documents our efforts to demonstrate the generality of the asymmetric HV to access not only the natural products, but also their various diastereoisomeric derivatives. Key to success here is the availability of highly tunable phosphoramidite Ni(II)-complexes useful for overcoming the inherent selectivity of the chiral intermediates. The yields for HV reactions are excellent, and selectivities are in the range of 92-99% for the desired isomers. Discovery of novel, configurationally fluxional, yet sterically less demanding, 2,2'-biphenol-derived phosphoramidite Ni-complexes (fully characterized by X-ray) turned out to be critical for success in several HV reactions. We also report, a less spectacular, yet equally important role of solvents in a metal-ammonia reduction for the installation of a key benzylic chiral center. Starting with simple oxygenated styrene derivatives we iteratively install the various exocyclic chiral centers present in typical serrulatane [e.g., a (+)-*p*-benzoquinone natural product, elisabethadione, *nor*-elisabethadione, helioporin D, a known advanced intermediate for the synthesis of colombiasin and elisapterosin] and amphilectane [e.g., A-F, G-J and K,L- pseudopterosins] derivatives. Our attempts to synthesize a hither-to elusive target, elisabethin A, led to a stereoselective, biomimetic route to pseudopterosin A-F aglycone.

INTRODUCTION

Serrulatanes and their annulated congeners amphilectanes (Figure 1) are important classes of natural products exhibiting diverse biological activities including anti-inflammatory, analgesic, anti-tuberculosis and anti-malarial properties.[1] These compounds are derived from both plant[2] and marine[1j,3] sources and differ considerably in the configuration of the stereogenic centers and the oxygenation pattern around the carbon frame (**1**, **2**), which is essentially conserved through a family of compounds. Prototypical examples include helioporins (e.g., **3**),[1k,4] *seco*-pseudopterosin A (**4**),[5] leubethanol (**5**),[6] elisabethadione (**6a**),[7] a (+)-*p*-benzoquinone containing serrulatane (**7**),[8] pseudopterosins (**8**, **9**),[1f,1j,9] pseudopteroxazole (**10**),[1b,1i,10] and antimalarial amphilectane isonitrile **11**.[1e,11] One of the most prolific sources of these compounds, West Indian and Caribbean sea whip *Pseudopterogorgia elisabethae* is also the source of more complex metabolites such as colombiasin A (**12**),[12] elisapterosin B (**13**)[13] and a key biogenic precursor, elisabethin A.[14]

The relatively simple structures of many of these compounds belie the synthetic challenges presented by the variations in the configurations of the stereogenic centers in these molecules. These carbons are often placed at exocyclic locations next to a chiral carbon on a ring (highlighted in Figure 1), with no obvious functional groups nearby capable of directing the installation of these centers. As exemplified by the serrulatanes, *seco*-pseudopterosin A (**4**) and leubethanol (**5**), there are variations in the configurations at the key centers C_1, C_4 and C_{11} (serrulatane numbering). Leubethanol (**5**) has the same configuration of a C_{11}-*epi* diastereomer of enantiomeric *seco*-pseudopterosin aglycone. Among pseudopteropsins, aglycone of the A-F series (**8a**) bears an enantiomeric relation with the aglycone

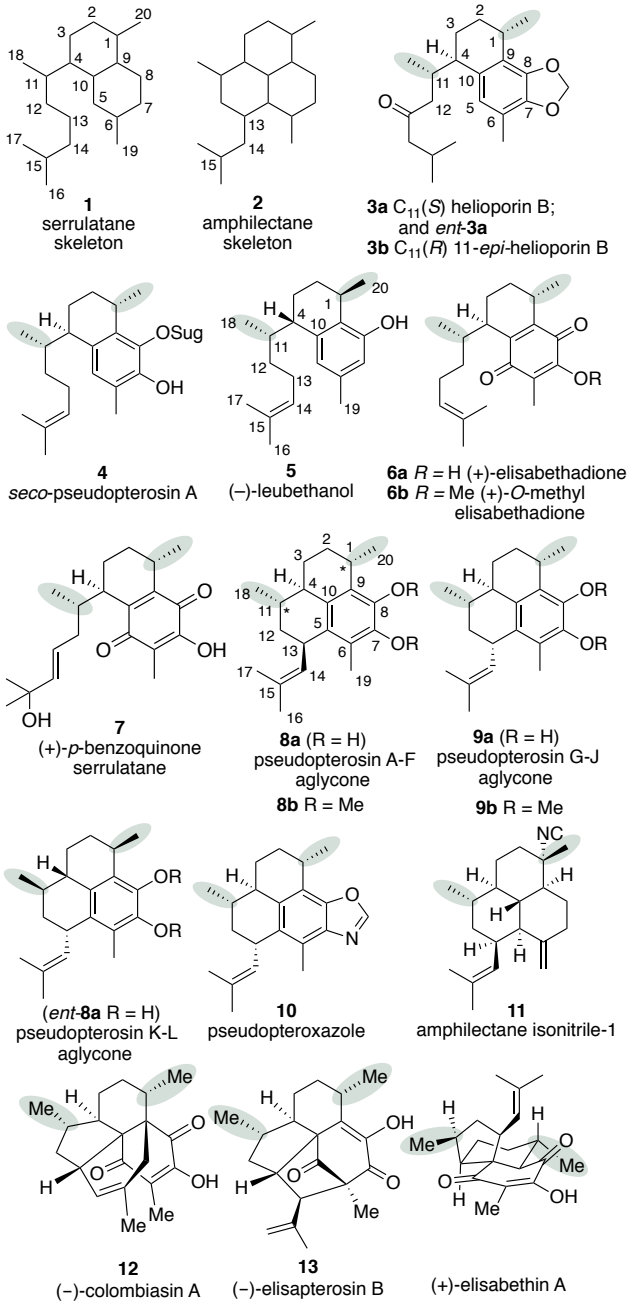
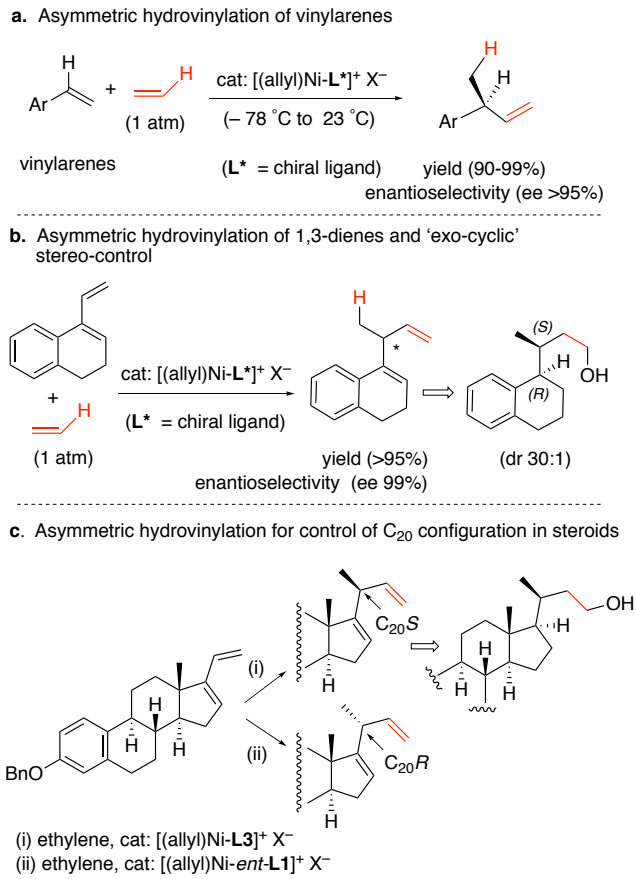


Figure 1. Serrulatanes and Amphilectanes. For the sake of uniformity in this manuscript serrulatane numbering is followed.

of the K-L series. In pseudopterosins G-J (**9**) and, the potent anti-tuberculotic pseudopteroxazole (**10**), the carbons bearing the 1-(2-methylpropenyl) groups (C_{13}) have configurations opposite to that of pseudopterosins A-F.

The exocyclic methyl-bearing carbon such as C_1 or C_{11} (**1** in Figure 1) is a very common structural motif in many of these structures, and a chain carrying this carbon is often attached to a stereogenic center in a ring and installation of such centers has been a long-standing problem in organic synthesis.[15] There are ample examples in the literature to suggest that the biological activity of compounds with such a motifs depends on the configuration of this exocyclic

Scheme 1. Nickel-Catalyzed Asymmetric Hydrovinylation[a]



[a] See Figure 2 for structures of ligands

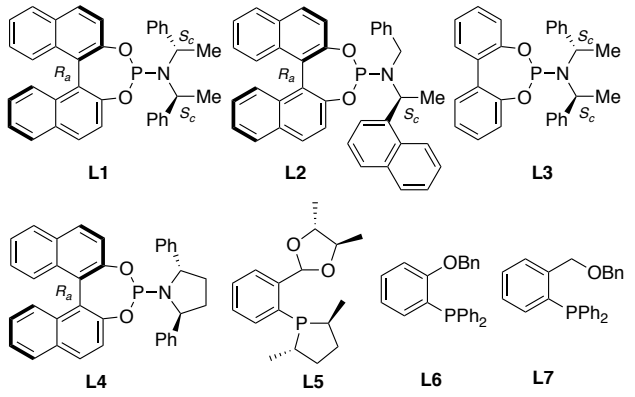


Figure 2. Ligands for asymmetric hydrovinylation

methyl-bearing carbon, such as seen in C_{20}(S) vs. C_{20}(R)-vitamin-D analogs. While such effects have been extensively investigated in the steroid series with the C_{20}-epimeric analogs[16] and the anti-tumor glycosides such as OSW-1,[17] only limited studies have been undertaken in serrulatanes or amphilectanes.[1d,1g,6a,9c,18] Almost invariably biological

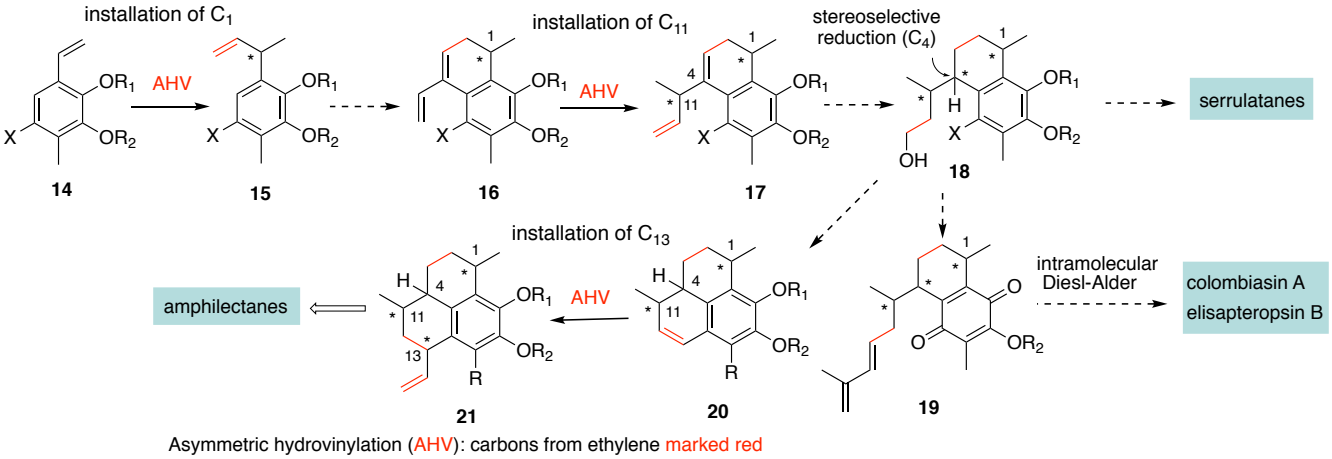


Figure 3. A general approach to serrulatanes and amphilectanes

studies in these molecules have concentrated on the peripheral appendages and seldom involved configurational changes in the carbon frame.[1c] This might be due to a dearth of facile methods for the preparation of the requisite diastereoisomeric congeners.[19] In a notable example, Aggarwal et al have reported the syntheses of all diastereomers of a serrulatane, erogorgiaene, using stoichiometric chiral born reagents to introduce the chiral appendage.[19b] Any general synthetic approach to these molecules should address the installation of these centers *independent* of one another if a broadly applicable strategy for syntheses of diastereomers of these natural products is the goal. It can be reasonably argued that the absolute control of diastereoselectivity in catalytic reactions of *chiral* substrates can be a more formidable problem than achieving useful levels of asymmetric induction with a *prochiral* substrate. For this to be successful, the catalyst design must be sufficiently flexible to overcome the inherent diastereoselectivity dictated by the resident chirality of the substrate. Even though several creative solutions to tackle this so-called 'exocyclic stereochemistry' problem have been advanced, broadly applicable methods that use easily accessible precursors are still needed.[15] We believe that the asymmetric hydrovinylation of vinylarenes (Scheme 1, **a**)[20] and of 1,3-dienes (Scheme 1, **b**, **c**)[21] provide an especially attractive opportunity to fill this gap in the synthesis of serrulatanes and amphilectanes and here we document the full details of our work in the area. In addition to the enantioselective total or formal syntheses of several natural products, we describe how reagent control maybe exercised for the preparation of selected congeners with high diastereoselectivity.[19b]

RESULTS AND DISCUSSION

A General Strategy for the Synthesis of Serrulatanes and Amphilectanes.

In order to maximize the flexibility in the synthesis we plan to start with a prochiral starting material, a vinylarene (e.g., **14** in Figure 3), and install the *stereogenic centers one at a time* in a catalytic asymmetric hydrovinylation reaction (e.g., **14** –> **15; 16** –> **17; 20** –>**21**), fully recognizing that such an approach is likely to be longer in terms of step count,[22] but will offer unprecedented opportunities in reagent-controlled installation of these centers. Such a strategy would also have advantages over diastereoselective synthesis starting from chiral pool precursors, which possess one or two of the chiral centers in the target.[9d] As examples of the early such syntheses of pseudopterosins[23] and other related compounds[10,24] amply illustrate, the stereochemical challenges are addressed to varying degree of success via diastereoselective transformations. This approach always depends on the availability of both enantiomers of the starting material, and, may involve difficult and sometimes circuitous skeletal transformations to reach the final target. In addition, substrate control for the syntheses of different diastereomers of a final product comes with its own challenges as alluded to earlier. We hoped that the outstanding flexibility in the design of ligands for nickel in the asymmetric hydrovinylation reaction would allow installation of the C_1 and C_{11} centers of serrulatanes, and, also the additional chiral center C_{13} (serrulatane numbering, see Figure 1) present in some of the amphilectanes.

In order to provide a proper perspective of our synthetic efforts, which put this work in the context of complete stereocontrol, we have added an extensive Table in the Supporting Information (Table S1, pp. S39-S50), which compares various approaches to key compounds among these classes of compounds. This table provides the step count, overall yield, how the stereochemical issues were addressed, and limitations and advantages of various approaches.

Our synthesis will start from the vinylarene **14**, which upon Ni-catalyzed asymmetric hydrovinylation would give **15**, from which a second hydrovinylation substrate **16** will be synthesized in preparation for the installation of the chiral center at C_{11}. The power of the asymmetric hydrovinylation to overcome the inherent stereochemical preference

of a substrate will be tested in this reaction. We hoped that the highly tunable phosphoramidite and other ligands (Figure 2) we developed[20b,25] would help address this issue. Moving forward, there was some uncertainty about how we might install the C_4 configuration, even though earlier we had shown in model systems (Scheme 1, **b** and **c**) hydroboration followed by catalytic heterogeneous (Pd/C) or homogeneous Ir-catalyzed directed hydrogenation using Crabtree's catalyst[26] would result in high diastereoselectivity at the ring carbon in some model systems.[21a,27] Single electron-transfer reductions have also been shown to have modest control in the installation of benzylic configuration in related systems.[28] The generic structure represented by the alcohol **18** is a key compound in our plans since it sets the stage for further elaboration into serrulatanes and amphilectanes including several more complex members of the family. An appropriately functionalized serrulatane 1,4-quinone-diene such as **19** has been converted into colombiasin A (**12**) and elisapterosin B (**13**) in one or two steps. Thus the preparation of this compound (**19**) or one of its precursors would represent formal stereoselective total syntheses of these compounds, *but with unprecedented control over selectivity in the installation of the various chiral centers.*

Synthesis and Asymmetric Hydrovinylation of Alkoxystyrene Precursors

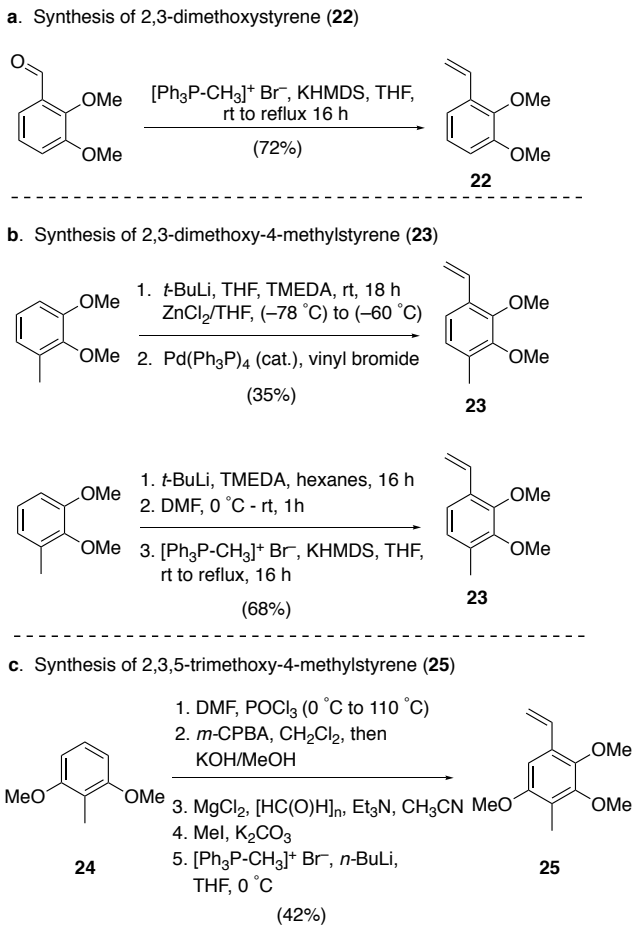
Most of the serrulatane and amphilectane diterpenes are characterized by varying levels of oxidation, and dense functionality around the aromatic ring. We chose two of the most oxygenated vinylarene precursors (**23** and **25**) in addition to 4-methoxystyrene and 2,3-dimethoxystyrene (**22**) as prototypes to initiate hydrovinylation studies. Since the corresponding aromatic units are present in several of these diterpenes, we expect a synthetic sequence that works in these systems should be broadly applicable. These electron-rich aromatic rings can also be used to prepare more oxidized compounds such as the 1,4- or 1,2-quinones.

We examined a number of options for the syntheses of the styrenes and the most scalable routes are shown in Scheme 2. All these compounds are commercially available, yet somewhat expensive (especially **23** and **25**). We chose to prepare them. While the synthesis of **22** is quite straightforward, starting from 2,3-dimethoxybenzaldehyde, the other two are more involved.

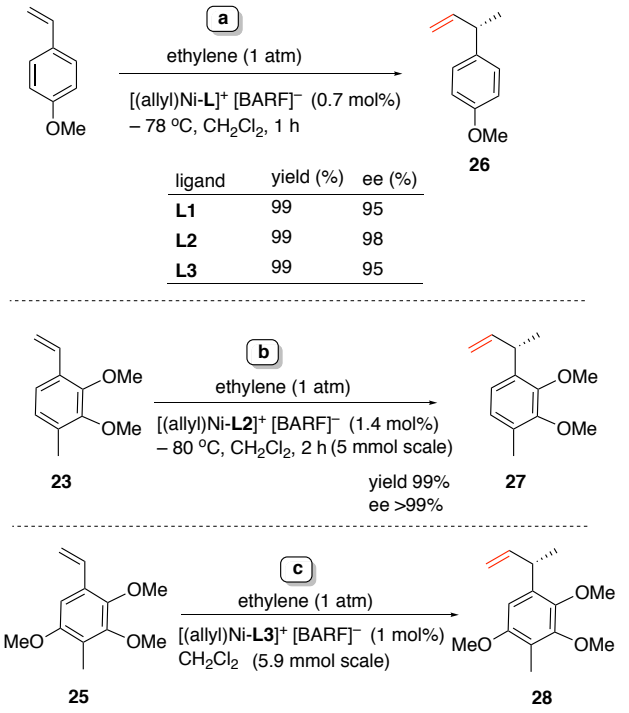
Several syntheses of 2,3-dimethoxy-4-methylstyrene (**23**) have been described in the literature,[29] but none convenient for large-scale preparation. We investigated two new routes (Scheme 2, **b**). The one-pot, 2-step process involves formation of the aryl zinc reagent followed by Negishi coupling which proceeds in a modest 35% yield. The other route proceeding through an intermediate aldehyde was reported to give poor yields for the Wittig reaction.[29] However, we find that using KHMDS as the base and conducting the reaction at slightly elevated temperatures acceptable yields (over all 68%) in two steps from 2,3-dimethoxytoluene can be achieved. We also investigated other routes[30] involving an aryl iodide[31] and a modified Stille coupling.[32] The aryl iodide is a versatile intermediate and could be used to prepare the styrene **23** via Cu-catalyzed cyanation, DIBAL reduction and Wittig reaction. Styrene **25** was prepared in an easily scalable 5 step-process from 2,6-dimethoxytoluene (Scheme 2, **c**), adapted and modified from recipes in the literature.[33]

Even though we have had extensive experience with asymmetric hydrovinylation reactions including that of 4-methoxystyrene[20b] it became apparent that further optimization of the ligand system would be needed as we looked at even more electron-rich styrenes. For example, we found that 2,3-dimethoxy-4-methylstyrene (**23**), a key precursor for several diterpenes targets, while giving excellent yields, gave enantioselectivity of only ~ 90% ee under the standard conditions using the original Feringa ligand, **L1**. However, nickel complex of a modified ligand **L2** gave a quantitative yield of the product (**27**) with exceptionally high enantioselectivity (>99% ee) in a highly reproducible reaction that could be performed on large scale (Scheme 3, **b**).[34]

Scheme 2. Synthesis of Vinylarenes



Scheme 3. Asymmetric Hydrovinylation of *mono-*, *di-*, and *tri*-Methoxystyrenes[a]



ligand	yield (%)	ee (%)
L1	99	95
L2	99	98
L3	99	95

cat	mol%	temp	time (h)	yield	%ee
L1	5	–50	5	100	87
L2	5	–50	18	70	74
L3	1	–60	20	99	96

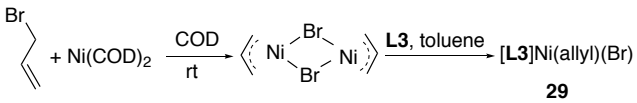
[a] See Figure 2 for the structures of ligands

A Diversion. A Fluxional Ligand and Induced Conformational Rigidity in the Catalyst

Further optimization was also needed for the styrene **25**, which reacted surprisingly slowly with catalysts bearing ligands **L1** and **L2** giving only modest selectivities (Scheme 3, **c**). However, a complex bearing a sterically less encumbered biphenyl backbone (**L3**) was found to give excellent yield and enantioselectivity (96% ee) for the asymmetric hydrovinylation reaction of this substrate (Scheme 3, **c**). Note that the reaction was carried out at a lower temperature (–60 °C) with no substantial loss of yield. The discovery of a simpler (and cheaper) ligand (**L3**) had further implications beyond the first hydrovinylation of a demanding vinylarene. For example, as documented later, the nickel complex derived from this ligand (**L3**) was even more critical in the subsequent hydrovinylation of the 1,3-diene (**33**) that was used to install the C_{11} stereocenters in serrulatane intermediates (Scheme 6).

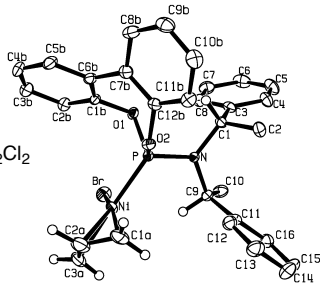
We were surprised by these results since it appears that the axially chiral (and more expensive) 1,1'-binaphthalene-2,2'-dioxy backbone (e.g., as in **L1** and **L2**) is not needed for the phosphoramidite ligands to give high asymmetric induction in the hydrovinylation reactions. From temperature dependent NMR studies, the ligand **L3** itself appeared fluxional, which suggested that upon complex formation with nickel, the pendant chiral α-methylbenzyl amine must impart conformational rigidity to the catalytically active complex. This has indeed been confirmed by obtaining a solid-state structure of the complex **L3**(allyl)Ni(Br) (**29**, Scheme 4). Further temperature-dependent NMR studies of the preformed complex (**29**) showed no fluxional behavior, thus suggesting that even in solution the active complex retains its axial chirality. Note that the axial configuration of the biphenyl moiety in this complex is the same as what was found in the (*R*)-2,2'-binaphthol-derived complexes used in Schemes 3 **a, b**, and **c**, all resulting in (*S*)-configuration of the product. Further support comes from the HV reaction with the enantiomeric catalyst, *ent*-**L3**(allyl)NiX, which, as expected, gives the opposite enantiomer of the product. This catalyst was also used to prepare 11-*epi*-**34** from diene **33** (Scheme 6).

Scheme 4. A Biphenol-Derived Catalyst for Asymmetric Hydrovinylation of Methoxystyrenes



[**L3**]Ni(allyl)(Br) (**29**)

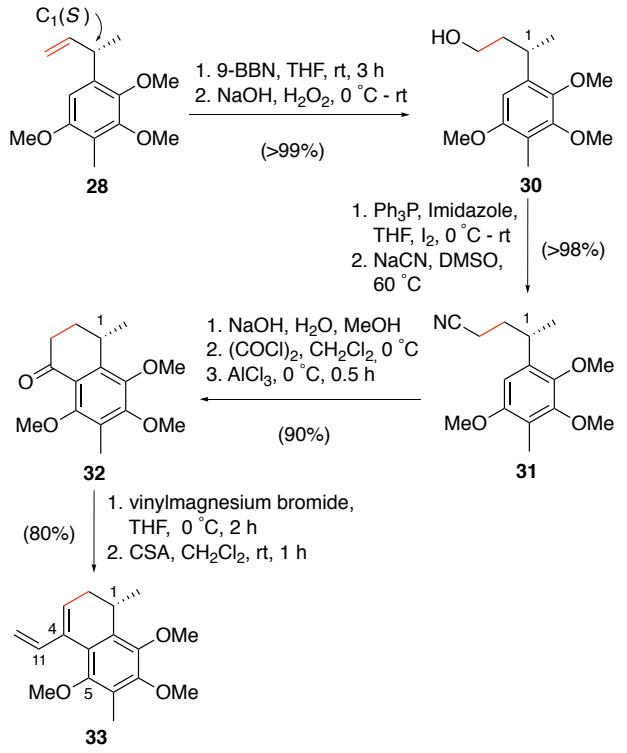
- Recrystallize from benzene/CH_2Cl_2 by slow diffusion of hexane



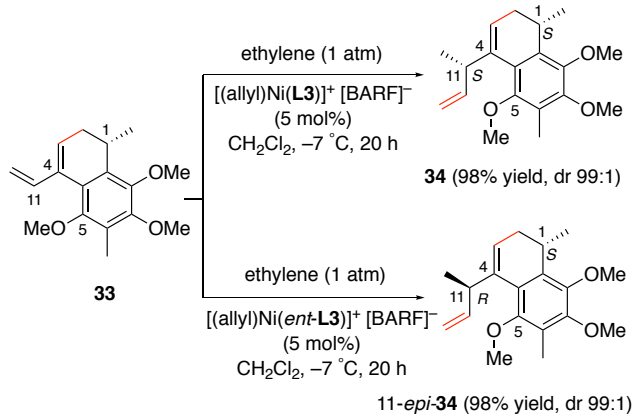
Diene Precursor (33) for Installation of the Stereocenter at C_{11}

We reasoned that a second hydrovinylation of an appropriately substituted diene would give unprecedented opportunities to control the configuration of C_{11}. A route to such a compound (**33**) from the hydrovinylation product **28** is shown in Scheme 5. The alkene **28** undergoes highly regioselective hydroboration with 9-BBN followed by oxidation of the resulting borane with H_2O_2 give **30** from which the nitrile **31** is readily prepared in nearly quantitative yield in two steps. Hydrolysis of this nitrile to the acid, the corresponding acid chloride (with oxalyl chloride), followed by intramolecular Friedel-Crafts reaction proceeds in excellent yield (90% in 3 steps) to give the ketone **32**. Addition of vinylmagnesium bromide followed by a surprisingly facile acid-catalyzed dehydration with anhydrous camphorsulfonic acid give an excellent yield of the key diene **33** (a substrate without the C_5-methoxy group gives very low yields of the diene, see later in Scheme 13).

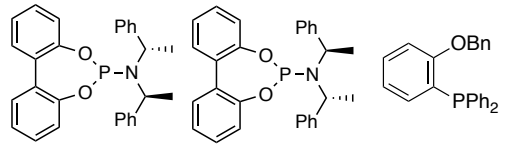
Scheme 5. A Diene Substrate for Installation of C_{11} Stereocenter



Scheme 6. Asymmetric Hydrovinylation of a 1,3-Diene



- Low temperature gave incomplete conversion
- Complexes of ligands **L1** and **L2** (Scheme 3) gave unacceptable yield/selectivity
- Authentic diasteromeric mixture (1*S*,11*S*)/(1*S*,11*R*) was prepared via complex of ligand **L6**



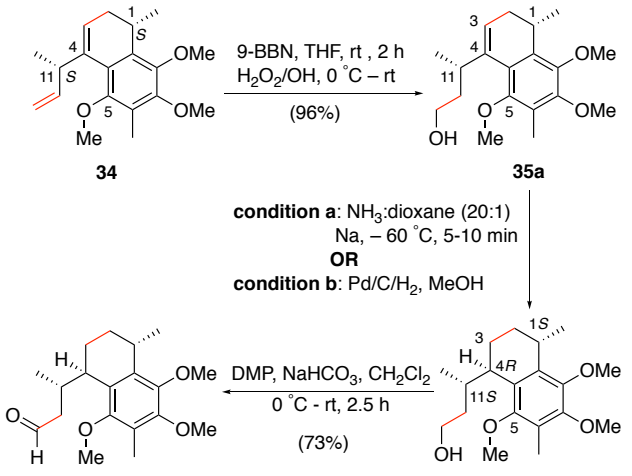
L3 *ent*-**L3** **L6**

Asymmetric Hydrovinylation of Diene 33 and Installation of Stereocenters C_4 and C_{11}. Making either the C_{11}(*S*)- or the C_{11} (*R*)-diastereomer

The asymmetric hydrovinylation of the 1,3-diene **33** posed considerable challenges since *none* of the most commonly used phosphoramidite ligands derived from binaphthols including the hugely successful ligands **L1** and **L2** (Scheme 3)[35] gave good yields at low temperatures. At elevated temperatures, not unexpectedly, low enantioselectivities were obtained. However, the ligand **L3** (Scheme 4) with the biphenyl backbone gave excellent yield (98%) and diastereoselectivity (99:1) in the formation of the 1,2-adduct (**34**, Scheme 6) with the indicated (*S*) configuration at C_{11}, commonly found in most serrulatanes and amphilectanes. The diastereoselectivity in the reaction was initially confirmed by the absence of signals corresponding to a diastereomer in the ^1H or ^{13}C spectra and subsequently by separation on a CSP GC column.[30] The configurations of the newly created stereocenter C_{11} (*S*) was initially assigned based on precedents, but later confirmed by comparison of full spectroscopic and chiroptical properties of advanced intermediates and natural products derived from **36a** with those of known compounds in the literature (vide infra).

We have since carried out this hydrovinylation using the enantiomeric ligand *ent*-**L3**, which most gratifyingly gave the expected product 11-*epi*-**34** in excellent yield (98%) and diastereoselectivity (>98:2).[30] This product has the C_1(*S*):C_{11}(*R*) configuration (11-*epi*-**34**, Scheme 6).

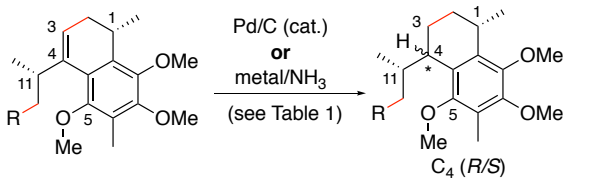
Scheme 7. Reduction of C_3-C_4 Double Bond and the Configuration of C_4



The hydrovinylation product **34** was subjected to hydroboration using 9-BBN followed by oxidation to get the primary alcohol **35a**, which serves as a suitable precursor for **36a** [C_4-(*R*)] and its diastereomer 4-*epi*-**36a** [i.e., C_4-(*S*)] (Scheme 7). While the former is important for majority of naturally occurring diterpenes of these classes, any broadly applicable methodology should be able to install the latter configuration as well, since biologically active serrulatanes with both C_4 configuration are known.[36] Table 1 summarizes results of various hydrogenation and metal-

ammonia reduction experiments directed towards this goal. In addition to the alcohol **35a**, corresponding TBDMS (**35b**) and TBDPS ethers (**35c**), the aldehyde **35d** and Wittig product of the aldehyde **35e** were included in these attempts to control the configuration of C_4 (Scheme 8).

Scheme 8. Reduction of C_3-C_4 Double Bond



35a R = CH_2OH
35b R = $CH_2OTBDMS$
35c R = $CH_2OTBDPS$
35d R = -C(=O)H
35e R = -C(H)=CH_2

36a R = CH_2OH
36b R = $CH_2OTBDMS$
36c R = $CH_2OTBDPS$
36d R = -C(=O)H
36e R = -C(H)=CH_2

Table 1. Reduction of C_3~C_4 Double Bond. Setting the Configuration of C_4

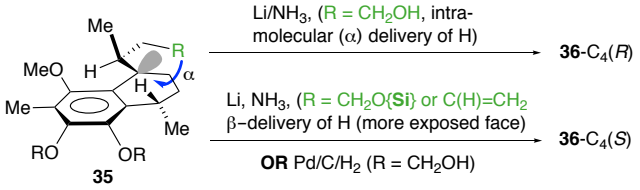
entry	substrate	conditions	product yield (%)	C_4 (*R*): C_4 (*S*)
1	**35a**	H_2, Pd/C, EtOH, rt	**36a**, >99	0:100
2	**35a**	Li, NH_3:THF (20:1), -78 °C, 5 min	**36a**, 78	63:37
3	**35a**	Li, NH_3:THF (20:1), -78 °C, EtOH or *i*-PrOH, 5 min	**36a**, 78	70:30
4	**35a**	Li, NH_3:Et_2O (20:1), -78 °C, EtOH or *i*-PrOH, 5 min	**36a**, 78	70:30
5	**35a**	Li, NH_3:1,4-dioxane (20:1), -78 °C, 5 min	**36a**, 80	70:30
6	**35a**	Na, NH_3:1,4-dioxane (20:1), -60 °C, <5 min	**36a**, 83	>85:15[a]
7	**35b**	Li, NH_3:THF (20:1), -78 °C, 5 min	**36b**, 61[b]	3:97
8	**35c**	Li, NH_3:THF (20:1), -78 °C, 5 min	**36c**, 66[b]	8:92
9	**35d**[c]	Li, NH_3:THF (20:1), -78 °C, 5 min	**36d,** 76	58:42
10	**35e**[d]	Li, NH_3:THF (20:1), -78 °C, 5 min	**36e**, 58[e]	0:100

[a] After purification by column chromatography >97:3. See Supporting Information for details. [b] In two steps from **35a**. [c] Substrate made by DMP-oxidation (81%) of **35a**. [d] Alkene **35e** made from **35a** by DMP oxidation followed by Wittig reaction with Ph_3P=CH_2. [e] Yield for 3 steps from **35a**.

Initial attempts to effect the diastereoselective conversion of **35a** to **36a** started with simple catalytic reduction of the double bond using 5% Pd/C and hydrogen in methanol. This reaction gave in quantitative yield of a single diastereomer which was subsequently identified (see later) as the C_4 (*S*)-derivative, 4-*epi*-**36a** [C_4(*S*)] (Table 1, entry 1).

For the preparation of the diastereomer with the C_4-(*R*) configuration, which turned out to be more challenging, we resorted to metal/liquid ammonia reduction of **35a** at low temperature. Even though we found this reaction to be capricious in the beginning, running the reaction at low temperature (-78 °C) and for brief periods (~5 min) using lithium in liquid ammonia in THF (v/v 20:1) gave acceptable yields of the product, but with only a modest diastereoselectivity of 63:37 in favor of the desired (*R*)-isomer (Table 1, entry 2). Adding varying amounts of external protic sources such as ethanol or *i*-propanol to the THF/ammonia solution, or, carrying out the reaction in diethyl ether or dioxane in place of THF as a solvent only marginally improved the selectivity (entries 3-5). Careful maintenance of the reaction in *anhydrous* ammonia:1,4-dioxane mixture (20:1) at -60 °C and use of sodium gave the best and reproducible results giving yields above 80% and diastereomeric ratios consistently above 85:15 in favor of the desired isomer (entry 6). However, the diastereomers were readily separable by chromatography and pure C_4(*R*)-can be isolated in high yield and diastereoselectivity, dr >97:3). The hydroxypropyl side-chain is important for the formation of the C_4(*R*)-diastereomer in the metal-ammonia reduction, as is clear from the similar reaction of the protected derivatives, the corresponding silyl ethers **35b** and **35c**. Both these compounds yielded the respective C_4(*S*)-diastereomer as the major product (entries 7 and 8). The aldehyde **35d** gave a *R*:*S* ratio of 58:42 and, the alkene **35e**, a ratio 0:100. Incidentally, all isomeric ratios were determined as the corresponding aldehydes (**36d**) since these show base-line separation on a chiral stationary phase GC column.[30] The ratios were further confirmed by ^{1}H NMR spectroscopy.

Scheme 9. Origin of Stereoselectivity in the Reduction of C_3-C_4 Double Bond



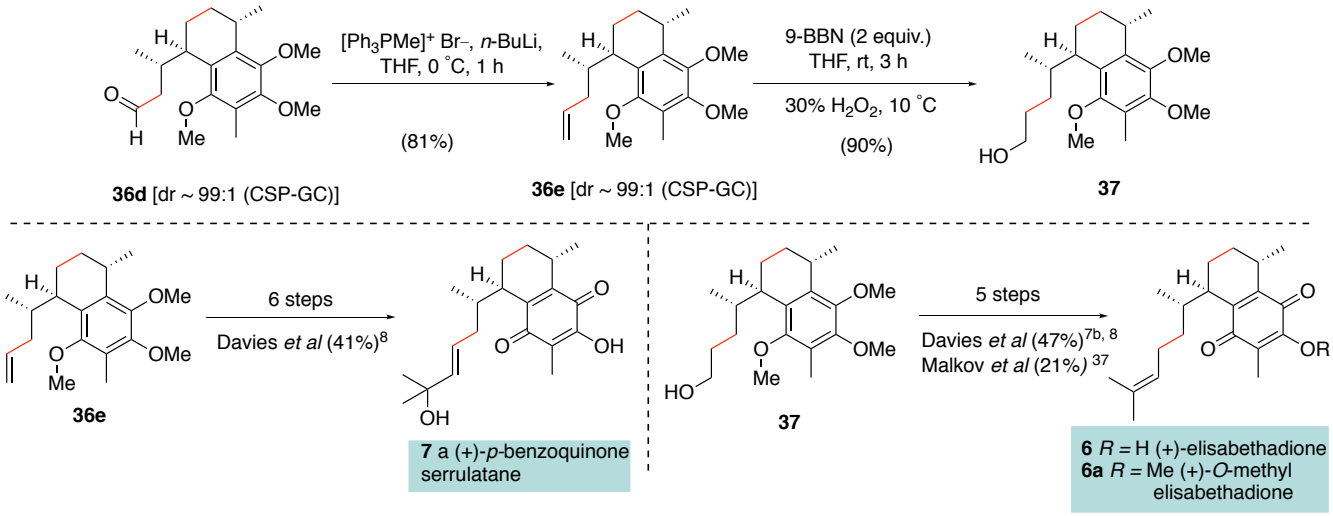
It is tempting to propose a model for these reduction reactions. If one assumes a favorable conformation for the side-chain in **35** based on 1,3-allylic strain (Scheme 9) the top and the bottom-face of the molecule are clearly differentiated with the bulky group blocking the approach from below, unless the proton delivery is of an intramolecular nature as in the Li/NH_3 reduction of the hydroxyethyl-bearing alcohol **35a**. This model correctly predicts the ob-

served configuration of the products in the catalytic and metal-liquid ammonia reductions.

Key Intermediate Alcohol 36a and the Synthesis of (+)-Elisabethadione (6a), (+)-*O*-Methyl Elisabethadione (6b) and a (+)-*p*-Benzoquinone Serrulatane (7)

The enantiomerically pure alcohol **36a** (>98% ee) has the correct configuration at C_1, C_4 and C_{11} and has the required latent functionality to prepare many of the naturally occurring serrulatanes, amphilectanes, helioporins and related diterpenes. Two examples are shown in Scheme 10. Thus DMP-oxidation of **36a** furnishes an aldehyde **36d**, which is readily converted into the alkene **36e** and subsequently to a primary alcohol **37**.

Scheme 10. Formal Syntheses of (+)-Elisabethadione (6) and (+)-*p*-Benzoquinone Serrulatane (7)

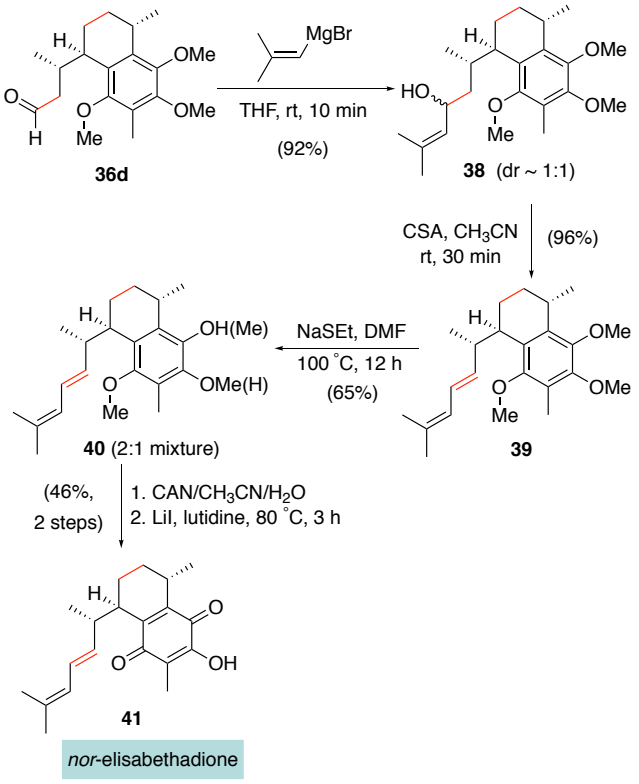


The alkene **36e** has been converted into a -*p*-benzoquinone natural product (+)-**7** by Davies.[8] Likewise the alcohol **37** is a key intermediate for the synthesis of (+)-elisabethadione. Davies synthesis of **37** in 10 steps (~ 26% yield) starting from 2,6-dimethoxytoluene relies on a combined C-H activation/Cope rearrangement in a key selectivity-determining step that gives 42% absolute yield of the desired precursor in 92% ee. Because of the high stereospecificity associated with the individual steps in the simultaneous generation of the 3 chiral enters, there are necessarily some limitations in this otherwise astonishingly efficient route for the synthesis of *other diastereomers* of this natural product.

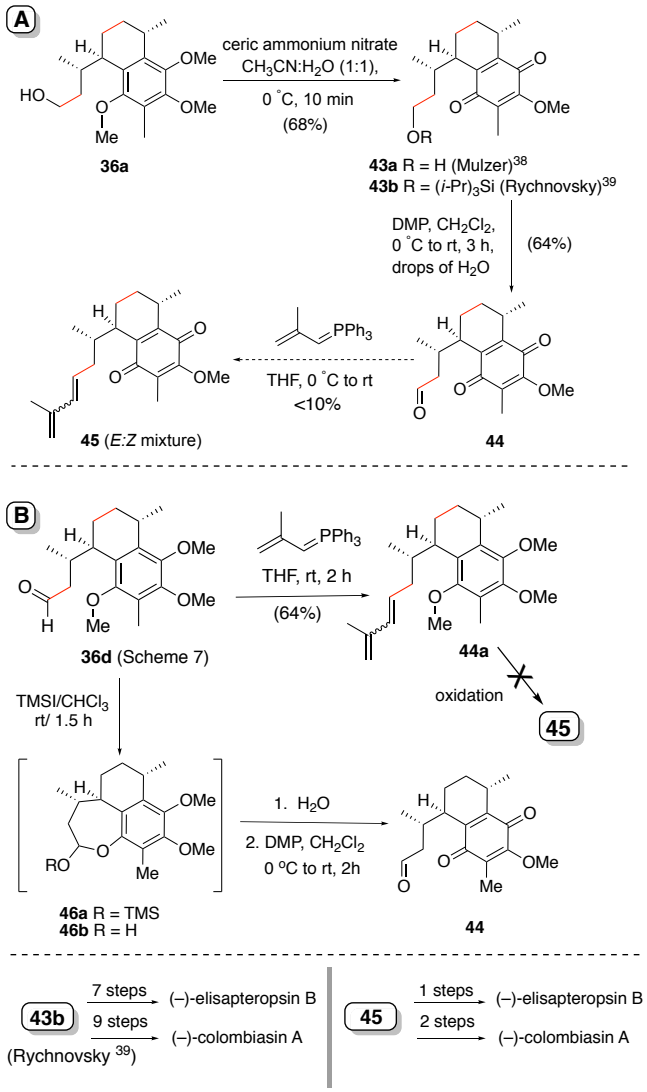
Yet another recent synthesis of **37** (in over all yield of ~ 9% from 1,3,4-trimethoxybenzene)[37,19b] involves a catalytic asymmetric crotylation of a suitable aldehyde (97% ee) to install the first asymmetric center followed by anionic oxy-Cope rearrangement to install the other two centers. The limitation of this method is the modest diastereoselectivity of the oxy-Cope reaction (3:1) which necessitates a chiral stationary phase LC separation of the diastereomers. Other methods that rely on [3,3]-sigmatropic rearrangements also have similar limitations when it comes to the synthesis of specific diastereomers of the natural products.[19] By contrast the hydrovinylation approach (~ 15 steps from the starting vinylarene, ~ 28% yield, >98% ee), though longer, provides excellent stereocontrol at every stereogenic center.

One further application of the aldehyde **36d** is for the synthesis of *nor*-elisabethadione (Scheme 11), whose methyl ether is a minor natural product isolated from *Pseudopterogorgia elisabethae*.[7b]

Scheme 11. Synthesis of *nor*-Elisabethadione



Scheme 12. Formal Total Syntheses of (-)-Colombiasin A and (-)-Elisapteropsin B



Intermediates for the Syntheses of (–)-Colombiasin A and (–)-Elisapterosin B

Alcohol **36a**, available in enantiomerically pure form via the asymmetric hydrovinylation route from 2,3,5-trimethoxy-4-methylstyrene in 12 steps (45-52%) is a valuable precursor for the synthesis of (-)-elisapterosin and (-)-colombiasin. For example, we find that **36a** is readily oxidized to a quinone-alcohol **43a** in modest yield (68%) upon brief exposure to ceric ammonium nitrate in aqueous acetonitrile. The structure of **43a** was confirmed by comparison of ^{1}H and ^{13}C NMR spectrum with a *racemic* variant of this compound that has been prepared by Mulzer[38] in 10 steps from 2,5-dihydroxy-4-methoxy-3-methylbenzaldehyde in ~22% yield. The corresponding tri-*i*-propylsilylether **43b** has been converted into colombiasin (**12**) and elisapterosin (**13**) by Rychnovsky[39], thus establishing formal syntheses of these two natural products. As alluded to earlier, our route has sufficient flexibility to make *any* of the 8 diastereomers of the precursor alcohol **43a**, and thus it should be possible to prepare the corresponding to colombiasin and elisapterosin diastereomers.

Incidentally, we found that the alcohol **43a** could be readily oxidized in a respectable 64% yield to an aldehyde **44**, which we were able to transform directly into **45**, a key diene in only low (<10%) yield in spite of considerable effort (Scheme 12). The diene **45** is only one step from (–)-elisapterosin (41%) and 2 steps from (–)-colombiasin (61%) by previously established routes.[39] The alcohol **36a** could also be oxidized by DMP to the aldehyde **36d** (Scheme 7), and subsequently transformed into **46,** by treatment with TMSI in $CHCl_3$. Oxidation of **46** with DMP also gave the quinone aldehyde **44**. Even though **36d** undergoes a facile Wittig reaction to give **44a**, this compound could not be transformed into the key quinone-diene **45**.

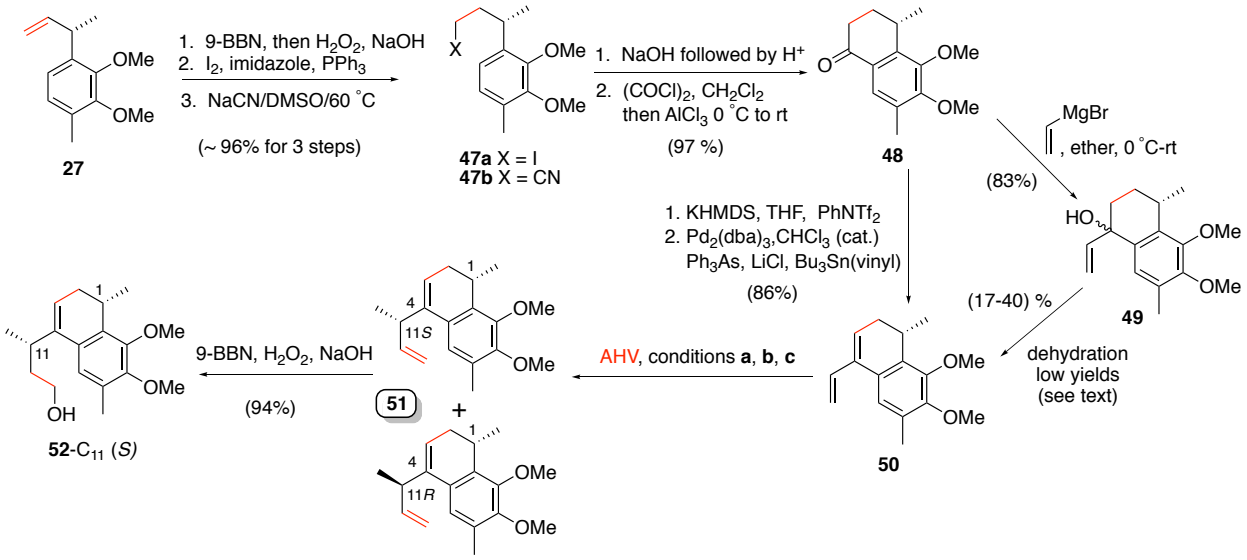
Total Syntheses of Aglycones of Pseudopterosins A-F, Pseudopterosins G-J and Pseudopterosins K-L

We have previously communicated our preliminary results on enantioselective syntheses of the aglycone of pseudopterosins G-J (Figure 1) using the asymmetric hydrovinylation at 3 different stages, to control the configurations of the carbons C_1, C_{11} and C_{13} (to be consistent across this article, we use the serrulatane skeletal numbering also for the pseudopterosins, which traditionally follows a different convention). Highlights of this synthesis and further details of key steps are included here for the sake of completion and to document the additional experiments that enabled the control diastereoselectivity at C_1, C_4, C_{11} and C_{13}. We also disclose a new biomimetic synthesis of pseudopterosins A-F aglycone (Scheme 19).

The synthesis (Scheme 13) starts with the hydrovinylation product **27**, which can be prepared on multi-gram scale using the ligand **L2** (Scheme 3, **b**). This product was converted into the ketone **48**, a potential precursor for a diene substrate **50** for a second hydrovinylation via a series of high-yielding reactions (Scheme 13). While the conversion of the HV product **27** to the ketone **48** proceeds without event, all direct routes to convert the ketone to the diene **50** gave only modest yields (Scheme 13). For example, addition of vinyl magnesium bromide followed by acid-catalyzed dehydration under a variety of conditions (0.2 equiv. CSA, $CHCl_3$, rt, 3 h; 3 equiv. CSA, THF, 40 h; $POCl_3$, pyridine, rt; 5 equiv. Burgess reagent, CH_2Cl_2, 40 °C, methyl xanthate pyrolysis) gave either mixtures of products or unacceptable yields. Acceptable yield of the diene **50** was obtained by Stille reaction of the vinyltriflate prepared from the ketone **48** using Commin's reagent.[40] From a practical perspective we realized that these reactions can be carried out in a single pot from **48** giving 86% yield of the diene **50.**

Hydrovinylation of the diene **50** was initially attempted using achiral hemilabile phosphine ligands **L6** and **L7** (see Figure 2 for structures of the ligands) to probe the preferred diastereoselectivity of the chiral precursor in the hydrovinylation reaction (Scheme 14, Table 2). Several key features of this reaction became immediately apparent in these early studies. The diene substrate was significantly less reactive vis-à-vis the vinylarenes, requiring temperatures > – 10 °C as compared to – 70 °C for the vinylarenes. Ligand **L7**, which we found[41] to be an exceptional ligand for the nickel-catalyzed hydrovinylation of vinylarenes, was ineffective for the hydrovinylation of the 1,3-diene. In sharp contrast, nickel complex of ligand **L6** gave quantitative yield of the product **50** in a diastereomeric ratio of 59:41 [$C_{11}(S)$:$C_{11}(R)$]. Unlike in the hydrovinylation of a vinylarene with this ligand,[41] no isomerization of the primary product was observed even at higher temperatures. Among chiral ligands, **L1** gave the best selectivity (Scheme 13, Table 2, entries 1 and 2).

Scheme 13. Intermediates for Psuedopterosin Aglycones. Stereocontrol at C_1 and C_{11}



Scheme 14. Diastereoselective Asymmetric Hydrovinylation of Diene 50. Ligand Effects (Table 2)

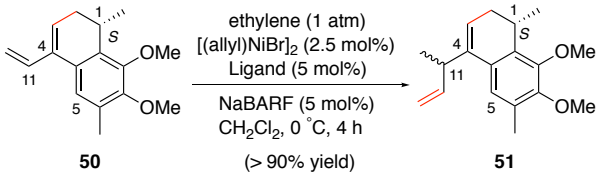


Table 2. Hydrovinylation of Diene 50. Ligand Effects[a]

entry	ligand[b]	conv.[c]	**51**-C_{11}(*S*):**51**-C_{11}(*R*)[c]
1	**L1**	>99	92:8
2	*ent*-**L1**	>99[d]	3:97
3	**L2**	62	82:12
4	**L4**	46	60:40
5	**L6**	>95	59:41
6	**L7**	0	-

[a] See Supporting Information for details including CSP GC traces showing diastereomeric ratios (dr). [b] See Figure 2 for structures of ligands. [c] Determined by CSP GC. [d] ~ 2% isomerization of 1-alkene.

Having established the C_1 and C_{11} configuration, we turned our attention to the C_4 center. Based on our previous experience,[25a] we had hoped to employ hydroxyl-directed Rh- or Ir-catalyzed hydrogenation to effect this stereoselective transformation. Accordingly, the alcohol **52**-C_{11}(*S*) was prepared from **51**-C_{11}(*S*) via hydroboration and oxidation (94% yield, Scheme 13). The alcohol was subjected to hydrogenation and other reduction conditions (Scheme 15) listed in Table 3. Crabtree's catalyst[26] gave an exceptionally clean product in modest yield under conditions shown (entry 1). The product **53** is formed in a diastereomeric ratio (*R*:*S*) of 17:83 at C_4. A cationic Rh complex (entry 2) known to effect such directed hydrogen-conditions[42] was unreactive under a variety of reaction. Reduction under heterogeneous conditions using Pd/C in ethanol gave a quantitative yield of **53**-C_4(*S*) product in excellent diastereoselectivity (entry 3, dr = 93:7).

Scheme 15. Intermediates for Pseudopterosins and Helioporins. Stereocontrol at C_4 (Table 3)

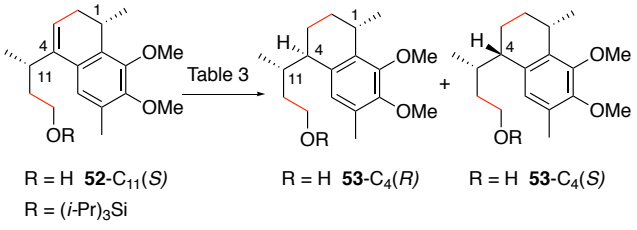


Table 3. Reduction of Alcohol 52-C_{11}(*S*) for Installation of C_4 Configuration[a]

entry	conditions	selectivity[b] **53**-C_4(*R*): **53**-C_4(*S*)
1	Ir^+(COD)(PCy_3)(py) PF_6^- (5 mol%), THF, H_2 (50 psi), 21 h	17:83[c]
2	Rh^+(dppe)(COD) SbF_6^- (5 mol%, H_2 (19 psi), THF, rt, 20 h	no reaction
3	H_2, Pd/C, EtOH, rt, 15 h	7:93
4	SmI_2 (2,5 equiv.), MeOH (50 equiv.), THF, -78 °C, 15 min.	no reaction
5	SmI_2 (2 equiv.), MeOH (4 equiv.), THF, rt, 20 h	no reaction
6	Li (10 equiv.), NH_3:THF (3:5), -78 °C, 15 min, MeOH or NH_4Cl	67:33
7	Li (10 equiv.), NH_3:THF (5:1), -78 °C, 15 min, MeOH or NH_4Cl	80:20
8	Li (15 equiv.), dry NH_3:THF (20:1), -78 °C, 15 min., then MeOH	97:3
9[d]	Li (10 equiv.), NH_3:THF (5:1), -78 °C, 15 min, MeOH or NH_4Cl	20:80[d]

[a] See Supporting Information for details. [b]Determined by NMR and GC. [c] Conversion 68%. [d] Tri-isopropylsilyl ether of **52**-C_{11}(*S*) was used as starting material.

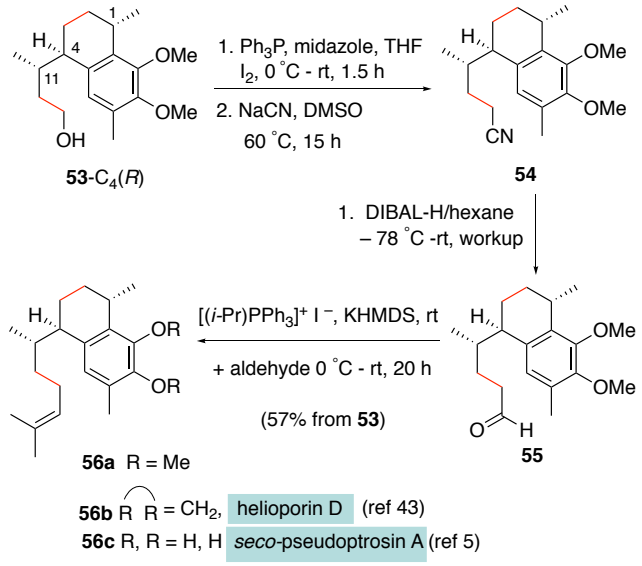
Electron-transfer reductions showed more promise for the formation of the desired C_4-(*R*)-isomer. Especially useful are the reductions using lithium and liquid ammonia, which gave the C_4-(*R*) as the major product. Optimization of the reaction indicate that brief reaction times and a large THF:NH_3 ratios help improve the selectivity (entries 6-8). Thus using 20:1 ratio of THF and NH_3 up to 97% of the C_4-(*R*)- product can be realized. The importance of the free –OH group in the Li/liquid-ammonia reactions is again revealed by the reaction of the tri-isopropylsilyl ether of **52**, which gave mostly the (*S*)-isomer. Incidentally, SmI_2 known to effect such reductions of styryl alkenes,[28a] failed to react with this substrate (entries 4 and 5).

Key Intermediates for Synthesis of Helioporins, *seco*-Pseudopterosins and Aglycones of Pseudopterosins. Confirmation of Configurations of C_1, C_4 and C_{11}.

Inspection of the structures of helioporins (Figure 1, **3**) and *seco*-pseudopterosins (**4**) reveal that alcohol **53**-C_4(*R*) and other intermediates in Scheme 16, could be converted into these molecules through very straight forward and reliable functional group transformations. An example of the use of **53**-C_4(*R*) for the synthesis of a known helioporin D precursor (**56**),[28a] is shown in Scheme 16. The ^1H and ^{13}C chemical shifts in this series of compounds are extremely sensitive to the configuration of the stereogenic centers [28a,43] and this conversion for the first time established absolute configuration of all such centers in the molecule. High-yield conversions of the dimethoxy-compounds to the naturally occurring methylenedioxy derivatives of heli-

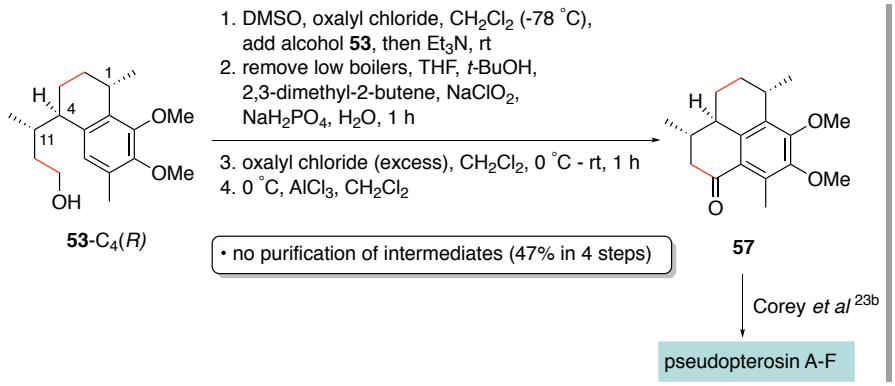
oporins and *seco*-pseudopterosins are well-documented in the literature. Applications of either of the nearly enantiopure **53**-$C_4(R)$ or the corresponding **53**-$C_4(S)$ derivatives for the synthesis of a myriad of diastereomeric congeners of these natural products are obvious upon reflection.

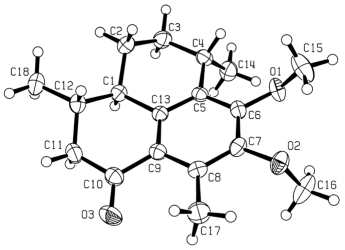
Scheme 16. Syntheses of Helioporin D and Confirmation of Configurations of C_1, C_4 and C_{11}



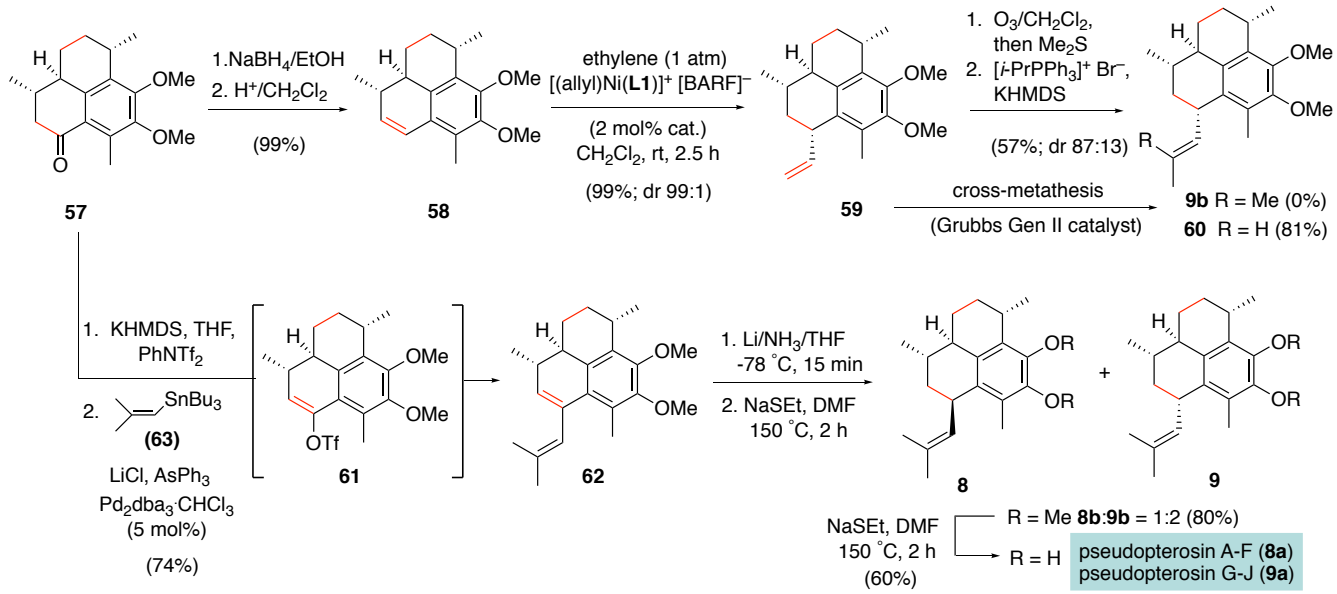
Synthesis of amphilectanes from the precursor alcohol **53** would involve further annulation of a third ring and stereoselective incorporation of the C_{13} side-chain. Details of these transformations[44] in the context of pseudopterosin G-J aglycone are shown in Scheme 17, along with the solid-state structure of an intermediate ketone **57**, which further confirms the configurations of all the newly created stereogenic centers.

Scheme 17. Synthesis of Ketone 57, a Precursor for Aglycones of Pseudopterosin A-F





Scheme 18. Installation of Stereocenter at C_{13}. Pseudopterosin Aglycones G-J



The ketone **57** is a key intermediate that has been transformed into pseudopterosins A-F aglycone.[23b] Since using the enantiomeric of ligands in the key steps in our synthesis *ent*-**57** can be prepared, this also is a formal synthesis of the corresponding enantiomeric compounds, aglycones of pseudopterosins K-L (*ent*-**8a**, Figure 1).

As compared to the pseudopterosins A-F, there has only been a limited effort towards enantioselective synthesis of the pseudopterosins G-J.[19,23d,45] A recent[45] highly innovative 11-step enantioselective synthesis (dr in a key step 5:1:1 in favor of the desired major isomer, overall yield ~ 1%) relies on two high pressure cycloadditions (19 kbar) of modest yields (~ 15% and 82%).[19b]

We wondered whether the vinylarene **58** (Scheme 18) derived from the key *enantiomerically pure* ketone intermediate **57**could serve as a precursor for pseudopterosin G-J aglycone. Using the asymmetric hydrovinylation of this alkene to install a vinyl group at the C_{13} position appeared especially attractive since there exists the possibility of reagent control to make both the C_{13}(*R*)- and C_{13}(*S*)-diastereomers. Accordingly, **58** was prepared by reduction of the ketone **57** with $NaBH_4$ in ethanol followed by acid-catalyzed dehydration (Scheme 18). The asymmetric hydrovinylations of this substrate under a variety of conditions were tried and the results are documented in Table 4.

The results suggest that the substrate **58** is much less reactive than simple vinylarenes (entries 1, 2 and 6) and the reaction requires higher temperatures (rt) and concentrations of the catalyst. Even the catalyst carrying the an achiral ligand **L6** (2-benzyloxyphenyl)diphenylphosphine) gave exceptionally high diastereoselectivity for the formation of the C_{13}(*S*)-isomer, thus displaying total substrate control in this reaction (entry 1). Complexes of ligand **L1** appears to be more active and the reaction can be performed at rt with near perfect selectivity for the major *S* isomer (entry 4). Disappointingly, the enantiomeric catalyst with *ent*-**L1**, failed to overcome the inherent preference of the substrate for the formation of the C_{13}(*S*)-isomer, and in a sluggish reaction yielded only this product (entry 5). During these

Table 4. Diastereoselective Hydrovinylation of 58. Installation of Stereocenter at C_{13}

entry	ligand[a]	conditions[b]	conv.	dr (C_{13}, *S*:*R*)[c]
1	**L6** (achiral)[d]	catalyst (0.05 equiv.), rt, 10 h	39	99:1
2	**L1** ($R_aS_cS_c$)	catalyst (0.2 equiv.), 0 °C, 15 min.	60	only *S*
3	**L1** ($R_aS_cS_c$)	catalyst (0.2 equiv.), rt, 2.5 h	100	only *S*
4	**L1** ($R_aS_cS_c$)	catalyst (0.02 equiv.), rt, 2.5 h	100	only *S*
5	*ent*-**L1** ($S_aR_cR_c$)	catalyst (0.05 equiv.), rt, 10 h	42	only *S*
6	**L3** (S_cS_c)	catalyst (0.2 equiv.), rt, 1 h	55	only *S*
7	**L4** (S_cS_c)	catalyst (0.2 equiv.), rt, 1 h	32	only *S*
8[e]	**L1** ($R_aS_cS_c$)	catalyst (0.2 equiv.), °C, 15 min.	65[e]	only *S*

[a] See Figure 3 for structures of ligands. [b] Conditions: ethylene (1 atm.), [(allyl)NiBr]$_2$ (0.x equiv.), **L** (2x equiv.), NaBARF (x equiv.), CH_2Cl_2. [c] Determined by CSP GC and NMR. [d] (2-Benzyloxyphenyl)diphenylphosphine. [e] A mixture of **58** and C_4-*epi*-**58** (65:35) was used. Only **58** was converted into the product.

investigations we also recognized that a diastereomeric mixture of alkenes **58** and *C_4-epi*-**58** (65:35) underwent highly selective hydrovinylation of the former, leaving behind the unreacted epimeric isomer (entry 8). Completion of the synthesis of pseudopterosin G-J aglycone involves the installation of the 2-methyl-1-propenyl side-chain. In principle, cross-metathesis to exchange the methylidene in **59** with isopropylidene (**59 –> 9b**) is an ideal way to complete the synthesis and we invested significant effort towards this goal.[30a] However, all attempts to effect this transformation failed, even though we found that using Grubbs 2nd generation catalyst[46] or Grubbs-Hoveyda 2nd generation catalyst[47] and 2-methyl-2-butene the corresponding ethylidene compound **60** could be prepared in 81% yield.

Finally, the synthesis of **9b** was accomplished in 2 steps by ozonolyis of the isolated double bond in **59** followed by Wittig reaction of the resulting aldehyde in a combined yield 57% (Scheme 18). Even though the aldehyde is formed with no erosion of stereoselectivity, the accompanying Wittig reaction causes some isomerization and the final product is contaminated with up to 13% of the C_{13}-epimer, which, corresponds to the pseudopterosin A-F series. The compounds in these two series are easily distinguished by the chemical shift of alkene H and the benzylic hydrogens.[30a]

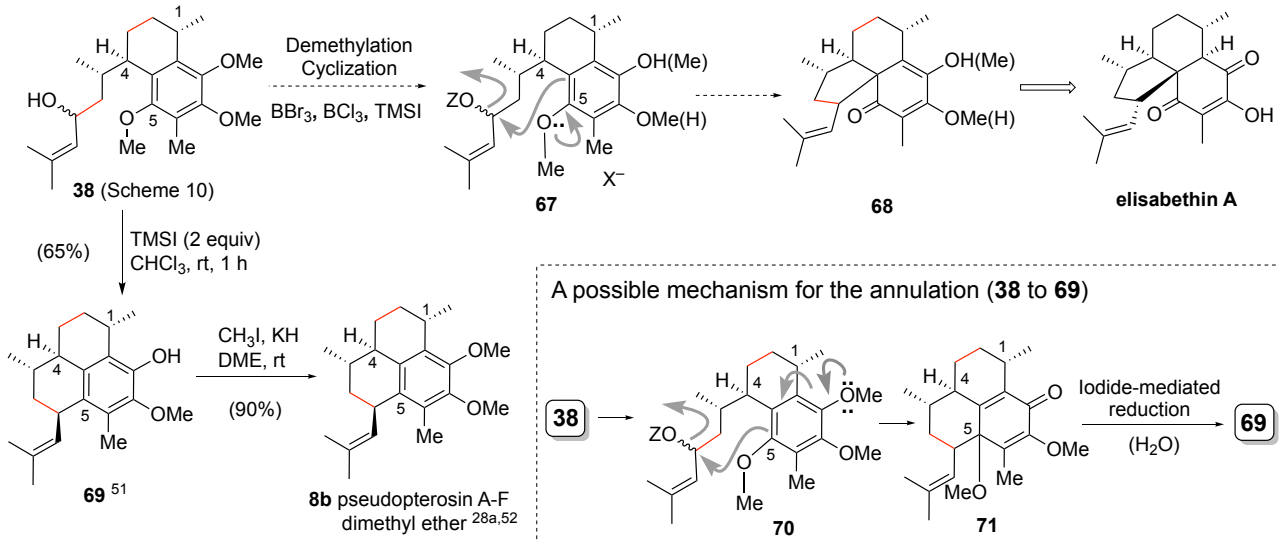
A less selective, yet operationally simpler route to the aglycones of both series of pseudopterosins (A-F and G-J) is also shown in Scheme 18. In this route, the ketone **57** is converted to a diene **62** via vinyl triflate (**61**) formation and a subsequent Stille coupling with 1-(tri-*n*-butylstannyl)-2-methylpropene (**63**). The conjugated alkene is reduced under Li/NH_3 conditions to give a mixture of **8b** and **9b** in a ratio of 1:2 in an overall yield of 80%. For identification purposes, the two dimethyl ether derivatives were converted into the aglycones of pseudopterosins A-F and G-J (60% combined yield) by treatment with NaSEt in DMF at 150 ^{o}C for 2 h.

An Unsuccessful Attempt to Synthesize Elisabethin A Skeleton and a Surprising Stereoselective, Biomimetic Route to Pseudopterosin A-F from the Allyl Alcohol 38

Elisabethin A (Figure 1), a possible biogentic precursor of colombiasin and elisapterosin,[14] remains an elusive molecule despite several efforts to synthesize this compound.[24a,38,48] The allyl alcohol **38** (Scheme 11), which was prepared as an intermediate for *nor*-elisabethadione, appeared to be an attractive precursor for this compound. We have explored the chemistry of this intermediate in an attempt to synthesize the core skeleton of elisabethin A via a spiroannulation shown in Scheme 19.[49] While these attempts have been unsuccessful for the preparation of the elisabethin skeleton, the new chemistry that emerged revealed a new route topseudopterosins.

In an attempt to effect abiomimetic spiroannulation as shown in Scheme 19 **(67 –> 68)** we treated **38** with boron trihalides and TMSI.[50] While no products resembling the elisabethane skeleton (**68**) were formed, we were pleasantly surprised to find, in the TMSI reaction, a 65% yield of a partially methylated aglycone of pseudopterosin A-F (**69**). This molecule has been described in the literature during the original isolation studies[51] and is a suitably protected derivative for the synthesis of pseudopterosin A-F by subsequent glycosylation.[23b] Further confirmation of the structure comes from the conversion of **69** to a dimethyl derivative **8b**, whose ^{1}H and ^{13}C spectra match with those of authentic compounds described in the literature.[28a,52] A possible mechanism for this transformation is also shown in Scheme 19, and, may resemble the biosynthesis of pseudopterosins. Indeed a C_5-oxygenated analog structurally related to **71** has been identified as a natural product and as a possible biogenetic precursor of pseudopterosins.[7a]

Scheme 19. An Approach to Elisabethin A Skeleton and an Unexpected Annulation for a New Stereoselective Synthesis of Pseudopterosin A-F Aglycones



CONCLUSIONS

Nickel-catalyzed asymmetric hydrovinylation (HV) of vinylarenes and 1,3-dienes is a powerful carbon-carbon bond-forming reaction, especially suited for the installation of methyl-bearing stereogenic centers attached to an aromatic or cycloalkene ring. In the latter class of compounds, the resident alkene provides further opportunities to control the configuration at the carbon to which is attached the methyl-bearing carbon. The resulting motif is ubiquitous among many natural products, none exemplifying this better than serrulatane and amphilectane diterpenes. In this paper, we present several examples of how the HV reaction can be used to synthesize different classes of serrulatanes and amphilectanes (Figure 3). Because of the availability of easily tunable ligands (Figure 2) that control these HV reactions, high yields and excellent diastereoselectivities can be achieved for disparate intermediates, which are otherwise difficult to prepare because of strong inherent stereochemical preferences of certain chiral precursors. This provides unprecedented opportunities for obtaining ligand-dependent selectivities for making diastereoisomeric congeners of biologically active compounds. Among the novel aspects which have not been disclosed before include the following: (i) stream-lined synthesis of highly oxygenated styrene derivatives (e.g. Scheme 2); (ii) biphenyl-based phosphoramidite-nickel complexes (Scheme 4) that are crucial for the HV reactions of sterically encumbered substrates (Scheme 6); (iii) optimization of metal-ammonia reduction procedures to control C_4-configuration (Tables 1 and 3); (iv) synthesis of enantiomerically pure intermediate **36a,** which has been converted into (+)-elisabethadione and a (+)- *p*-benzoquinone natural product **7,** and, **43a** which has been converted into (–)-colombiasin and (–)-elisapterosin; (v) cross-coupling (Stille reaction) route to pseudopterosins A-F and G-J (Scheme 18) and (vi) exploration (unsuccessful) of a spiroannulation strategy for the synthesis of elisabethin A that led to an unexpected discovery of a biomimetic route to pseudopterosin A-F (Scheme 19). In addition, several previously undisclosed details of the syntheses of pseudopterosin G-J are discussed.

Overall yields of several of the key products from commercially available starting materials are as follows:[19a] **36e** (14 steps, 30.7%; previous best: 10 steps, 17%), **37** (15 steps, 27.8%; previous best: 8 steps 22.8%), **43a** (13 steps 36%; previous best: 17 steps, 5%, racemic), helioporin D (17 steps, 29.3%; previous: 17 steps, 25.5%), pseudopterosin A-F aglycone (15 steps, 25.6%; previous: 20 steps, 13.5%), pseudopterosin G-J aglycone (20 steps, 13.6%; previous: 15 steps, 5.5%). Our yields are generally higher than those reported for these compounds, even with comparable or higher number of steps. However, yield in a chemical synthesis is only one of the several criteria for efficiency and practicality. Possibility of controlling the relative and absolute configurations of nearly all the stereogenic centers adds further value to this approach.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

Experimental procedures, syntheses and isolation of all intermediates. Spectroscopic and gas chromatographic data showing compositions of products under various reaction conditions. Crystallographic Information Files (.cif) for compound **29** whose structure was determined by X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author

* rajanbabu.1@osu.edu

ORCID

T. V. RajanBabu: 0000-0001-8515-3740

Notes

The authors declare no financial interest.

† **Present Addresses**

Souvagya Biswas, The Dow Chemical Company, Midland, MI

Glen Adam Cox, Lubrizol Corporation, Cleveland, OH

Daniel J. Mans, FDA, St. Louis, MO

Hwan Jung Lim, KRICT, Daejeon, Korea

Author Contributions

‡*These authors contributed equally.*

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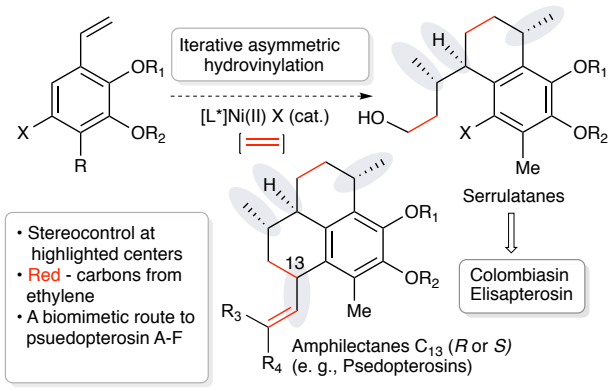
TOC GRAPHIC


Iterative asymmetric hydrovinylation
[L*]Ni(II) X (cat.)
OR1
OR2
X
R
HO
H
Me
Serrulatanes
Colombiasin
Elisapterosin
• Stereocontrol at highlighted centers
• Red - carbons from ethylene
• A biomimetic route to psuedopterosin A-F
13
R3
R4
Amphilectanes C13 (R or S)
(e. g., Psedopterosins)