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Ethylene in Organic Synthesis. Repetitive Hydrovinylation of Alkenes for Highly Enantioselective Syntheses of Pseudopterins

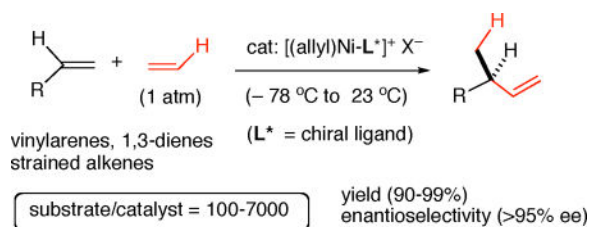
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Abstract

In this report we highlight the significant potential of ethylene as a reagent for the introduction of a vinyl group with excellent stereoselectivity at three different stages in the synthesis of a broad class of natural products, best exemplified by syntheses of pseudopterins. The late-stage applications of the asymmetric hydrovinylation reaction further illustrate the compatibility of the catalyst with complex functional groups. We also show that depending on the choice of the catalyst, it is possible to either enhance or even completely reverse the inherent diastereoselectivity in the reactions of advanced chiral intermediates. This should enable the synthesis of diastereomeric analogs of several classes of medicinally relevant compounds that are not readily accessible by the existing methods, which depend on ‘substrate-control’ for the installation of many of the chiral centers, especially in molecules of this class.

Ethylene is one of the most abundantly available feedstocks, providing up to 30% of all petroleum-based commodity chemicals, yet its applications in complex organic synthesis are just beginning to emerge.¹ Among the handful of catalyzed asymmetric C-C bond-forming reactions that use a feedstock carbon source, is the asymmetric hydrovinylation (HV), a reaction in which ethylene is added, as a vinyl group and a hydrogen, to common organic precursors such as an activated olefin, a 1,3-diene or a strained alkene, to produce an enantiomerically pure product (Eq 1).²



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Supporting Information Available: Full experimental details for the preparation of the intermediates and hydrovinylation reactions, spectroscopic and chromatographic data for characterization of all compounds, Crystallographic Information File for the ketone **16**. This material is available free of charge via the Internet at <http://pubs.acs.org>

While contemplating applications of this reaction in complex molecule synthesis, we envisioned that three of the four chiral centers (each marked with an asterisk in **1**, Figure 1) of pseudopterosin aglycones could be installed *independently* by *repeated* use of the asymmetric hydrovinylation reaction. Any synthesis of the core skeleton might also provide facile entry into other more complex molecules shown in Figure 1. Late-stage applications of the asymmetric hydrovinylation in such complex settings would rigorously test the limits of this reaction in two important ways: will the Ni(II)-catalyst system be compatible with substrate with several Lewis-basic centers? Perhaps more importantly, is it possible to enhance or even override, by ligand tuning, any inherent diastereoselectivity dictated by the resident chirality already present in an advanced intermediate? It can be convincingly argued that even in the most developed catalyzed reactions, absolute control of diastereoselectivity in reactions of chiral substrates can be a more formidable challenge than achieving useful levels of asymmetric induction in a prochiral substrate. In the event, we have completed a highly stereoselective total synthesis of the aglycone of pseudopterosins G-J. Since an advanced enantiopure intermediate synthesized during this study has already been converted into pseudopterosins A-F aglycone³ this report also represents a formal stereoselective synthesis of this molecule and its enantiomer, pseudopterosins K-L aglycone. Among the sequence of reactions employed, the asymmetric hydrovinylation was used three times with excellent yield and stereoselectivity (yields/selectivity as expressed in enantiomeric or diastereomeric ratio: 99%/er = 96:4; 92%/dr = 92:8 and 99%/dr >99:1). We also show that the configuration of the *asymmetric centers* can be *independently controlled by the judicious choice of catalysts and/or reaction conditions*. This report discloses the details of this study.

West Indian and Caribbean sea whip *Pseudoptergorgia elisabethae* has been a rich source of biologically active compounds of varying structural complexity.⁴ These include (Figure 1) anti-inflammatory pseudopterosins,^{5a} and compounds with significant anti-mycobacterial properties such as pseudopteroxazole,^{5b} colombiasin A,^{5c} elisapterosin B^{5d} and a key biogenic precursor, elisabethin A.^{5e} Even in cases where the structures are not very complex, the major challenge associated with the synthesis of these compounds has been the control of the stereocenters at locations with no neighboring controlling functionalities. An exocyclic methyl-bearing carbon such as C₃ or C₇ in pseudopterosins is a very common structural motif in many of these structures, and a chain carrying this carbon is often attached at a stereogenic center in a ring. Even though several creative solutions to tackle this so-called 'exocyclic stereochemistry' problem have been advanced, no broadly applicable method that uses an easily accessible precursor has emerged.^{6a,b} In pseudopterosins there is the additional challenge of stereoselectively introducing the 2-methylpropenyl group at the C₁ carbon. An examination of the various published procedures^{3,7-10} for the syntheses of pseudopterosins exposes the limitations of the current methodology to address the synthetic problems associated with the installation of these chiral centers. The best stereoselective syntheses solve these problems by starting with naturally occurring monoterpenes which already possess one or two of the chiral centers of the final products, and installing the others via diastereoselective transformations, with varying degrees of success. Such approaches always depend on the availability of both enantiomers of the starting materials and, often, involve difficult skeletal modifications to reach the eventual target. For example, in earlier work (-)-limonene^{7,8} and (+)-menthol,⁹

served as the starting materials for the syntheses of the aglycone of pseudopterosins A-F (**1**). Kocienski later reported^{10a} the use of (–)-citronellal and (–)-isopulegol for the syntheses of both pseudopterosin A-F, and the enantiomeric pseudopterosin K-L (**3**) aglycones. While the Kocienski approach is better in overall stereoselectivity, his scheme, like the previous syntheses, also relies on a cumbersome aromatic annulation, which consumes several avoidable steps if one were to start with a more logical aromatic precursor. Because of the ‘substrate-control’ nature of the key reactions by which the chiral centers are introduced, *all these syntheses* have serious limitations if stereoisomeric congeners of these compounds are needed. Asymmetric hydrovinylation allows a high degree of reagent control in the installation of three of the four chiral centers of the pseudopterosin core. Since both enantiomers of the ligands are readily available, either enantiomer of the natural product maybe synthesized from the same prochiral precursor.

Enantioselective Synthesis of Pseudopterosin Core

In our synthesis we targeted the tricyclic ketone **16** as a common key intermediate from which the aglycones of *all* pseudopterosins can be synthesized. The synthesis (Scheme 1)¹¹ started with an exceptionally efficient Ni-catalyzed asymmetric hydrovinylation of 2,3-dimethoxy-4-methylstyrene (**6**) using the ligand **L1**, which was chosen from a collection of ligands we prepared for optimization of the hydrovinylation reaction.¹² This reaction gives a quantitative yield of **7**, which incorporates the correct configuration (*S*) at the C₇ center for the pseudopterosin A-J series. This compound was converted into the ketone **10** in a series of simple steps, starting with the hydroboration/oxidation of **7**,¹³ iodide formation and displacement with CN[–] resulting in the chain-extended product **9**. The cyanide **9** was hydrolyzed to an acid and subsequently converted into an acid chloride, which was cyclized under Friedel-Crafts conditions to form **10**. The diene **11** was synthesized in 86% yield from **10** via a Stille reaction¹⁴ of a vinyltriflate generated in situ from the ketone. The compound **11** is set up for the installation of the chiral center at C₃ via a *second hydrovinylation*, this time that of a 1,3-diene. Even though the starting material is a nearly enantiopure diene, the resident chirality (at the benzylic position, C₇) in the molecule has little influence on the stereoselectivity of the second hydrovinylation. Indeed, the reaction using an achiral ligand **L3** shows only a slight preference [C₃(*S*):C₃(*R*) = 59:41] for the desired compound **12a**. However, this preference for **12a** can be reinforced and a dr of 92:8 (**12a**:**12b**) can be obtained with the use of the phosphoramidite **L2** in the Ni-catalyzed asymmetric hydrovinylation reaction. In a powerful demonstration of the versatility of asymmetric catalysis, it can be shown that an enantiomeric catalyst generated from the ligand *ent*-**L2** overcame the inherent preference for the C₃(*S*) isomer and gave a ratio of 3:97 for **12a**:**12b**, with C₃(*R*) predominating. Thus, the configuration of the C₃ and C₇ centers can be controlled *independently*, an option not available in any of the previous syntheses of these molecules or its congeners. The ensuing installation of the correct configuration at C₄ turned out to be a challenge. After much experimentation, the correct C₄(*R*)-center (dr: >20:1) was established by a lithium/NH₃ reduction¹⁵ of a primary alcohol that was prepared from the alkene **12a** by hydroboration/oxidation procedure. Various directed hydrogenations of **12a** or **13** using either Rh(I) or Ir(I), including Crabtree¹⁶ or Pfaltz¹⁷ hydrogenation catalysts were either sluggish or led to mixtures of products. Incidentally, catalytic hydrogenation

using Pd/C/H₂ gave the C₄ epimeric compound **14b** as the major product (**14a:14b** =1:13), once again demonstrating the flexibility of a reagent-based strategy for the control of stereoselectivity. The alcohol **14a** was readily converted into the tricyclic ketone **16** in a series of high-yielding reactions (Swern oxidation to an aldehyde, **15**, Lindgen-Kraus-Pinnick oxidation to an acid, acid chloride formation with oxalyl chloride, and, finally intramolecular Friedel-Crafts cyclization). This sequence involved just one chromatography to purify the final product **16**. Recrystallization of the crude product gave an overall yield of 47% of a highly crystalline tricyclic ketone from the alcohol **14a** as a *single enantiomer*. The solid-state structure of this ketone as revealed by X-ray crystallographic analysis confirmed the correct configurations at the various chiral centers. As described below the intermediate **16** is useful for stereoselective syntheses of aglycones of pseudopterosin A-F and G-J.

Stereoselective Installation the C₁ Side-chain of Pseudopterosins G-J via Asymmetric Hydrovinylation

While the synthesis of pseudopterosin A-F aglycone with the C1- isobutenyl group in the more stable quasi-axial orientation is quite straight forward as previously reported^{3,9,18} (Scheme 2), approach to the C1-epimeric G-J aglycone is less apparent. Again we find that hydrovinylation provides a very attractive solution for the installation of the last of the stereogenic centers in pseudopterosins G-J. The requisite substrate for this process was readily synthesized from the ketone **16** as shown in Scheme 3. Sodium borohydride reduction of **16** gave a mixture of alcohols (1:1), which was quantitatively converted into the tetrahydrophenalene **17** upon treatment with camphor sulfonic acid in CH₂Cl₂. Hydrovinylation of **17** with Ni(allyl)(**L2**)/BARF gave **18** in nearly quantitative yield with complete stereoselectivity (dr >99.5:0.5). Conversion of the vinyl group into the aldehyde and a subsequent Wittig reaction proceeded without incident giving the pseudopterosin G-J aglycone dimethyl ether **2B**. Depending on the reaction conditions, varying amounts (up to 13%) of isomerization of the intermediate aldehyde was observed during the Wittig reaction, giving the aglycone of pseudopterosin A-F as a byproduct. Incidentally, a more direct route involving Ru-catalyzed cross-metathesis,¹⁹ in spite of considerable effort, only gave unacceptable (<10%) yields.

In conclusion, we demonstrate the utility of ethylene for highly enantioselective syntheses of aglycones of *all* known pseudopterosins. This approach provides unprecedented flexibility with regard to the preparation of other diastereomeric analogs of these molecules. In addition, the stereochemical features associated with some of the advanced intermediates (e. g., alcohol **14a**) are common to a number of important diterpenes including pseudopteroxazole,^{5b,20} colombiasin A,^{5c,21} elisabethin A,^{5e,22a} elisapterosin B^{5d,22b} and helioporins.²³ With the stereochemical issues largely resolved, it should now be possible to design expeditious entry into these molecules and their congeners. Such studies are currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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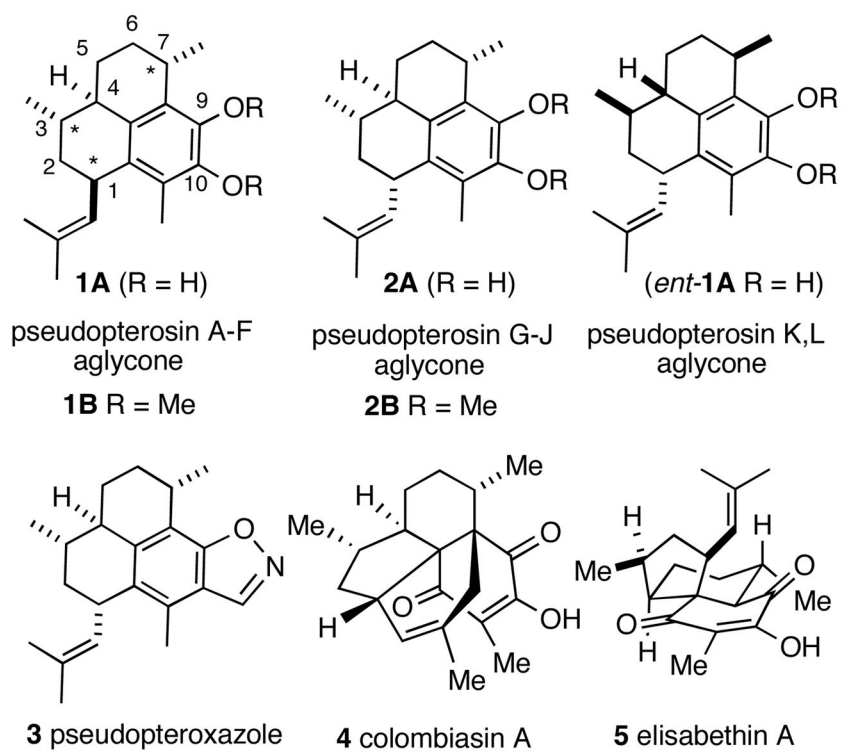
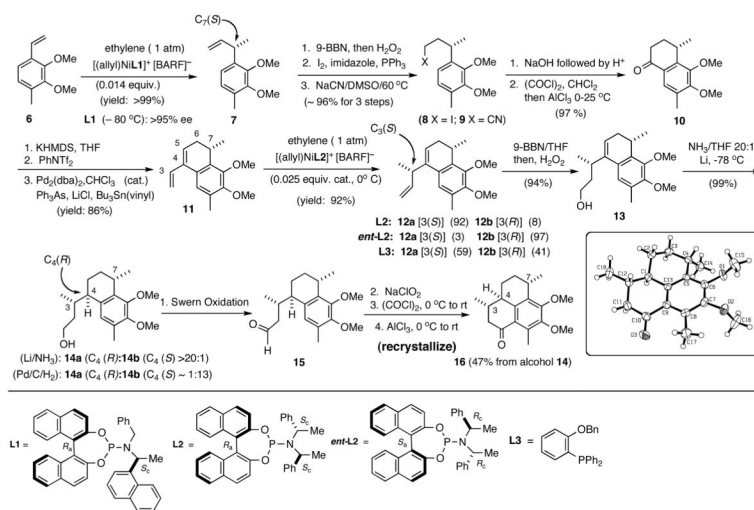
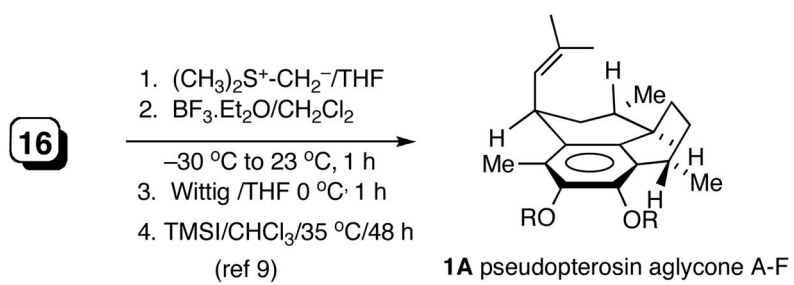


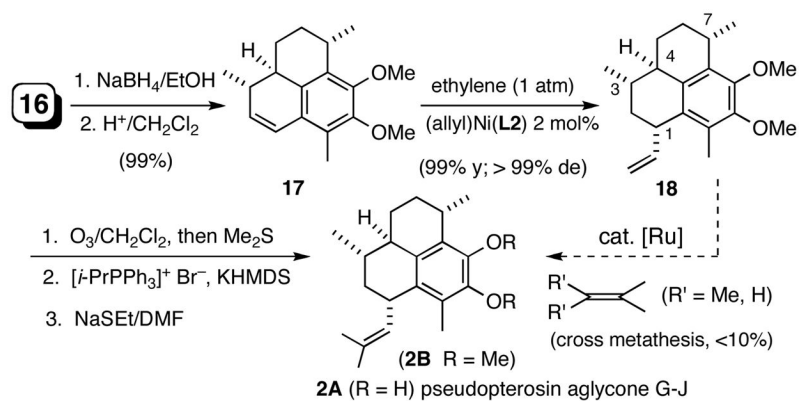
Figure 1.
Structures of Pseudopterosins and Related Compounds



Scheme 1.



Scheme 2.
Stereoselective Synthesis of Pseudopterosin A-F Aglycone



Scheme 3.
 Stereoselective Synthesis of Pseudopterisin G-J Aglycone via Installation of the C₁ Side-chain Using Asymmetric Hydrovinylation