Review

Synthetic Strategies Towards the Total Synthesis of Phyllanthocin and Breynolide. Application of Stereochemically Linear and Convergent Strategies.

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Phyllanthoside and breynin A are structurally related spiroketal glycoside natural products with potent, interesting and diverse biological activities. Due to their therapeutic potential and novel architecture, the respective aglycones, phyllanthocin and breynolide have attracted significant effort from the synthetic community. This review highlights the synthetic approaches to these targets with an emphasis on the strategy for incorporating the requisite stereogenic centers.

Key words phyllanthocin, breynolide, total synthesis, stereochemically linear, stereochemically convergent

Phyllanthoside (**1**) and breynin A (**2**) are structurally similar spiroketal glycoside natural products with diverse and exciting biological activities. Due to their activity and novel architecture, these two natural products have attracted significant attention from the organic community culminating in a number of synthetic approaches to and total syntheses of these agents[1,2] and their corresponding aglycones, phyllanthocin (**3**) and breynolide (**4**). Our focus within this review is not to detail each synthesis, but instead to highlight the synthetic approaches with a particular emphasis on the incorporation of the requisite stereochemistry. The utility of stereochemically linear and convergent approaches will be discussed with an emphasis on the stereochemically linear strategies, as this approach has received limited attention within the chemical literature.

Phyllanthoside was first isolated by Kupchan and colleagues from the roots of the Central American tree *Phyllanthus acuminatus* Vahl.[3] Methanolysis of **1** furnished (+)-phyllanthocin (**3**), the structure of which was elucidated in 1977 *via* single-crystal X-ray analysis.[3] The structure of **1** however, was not determined until 1982 when Pettit deduced the structure.[4—6] Biological interest in phyllanthoside stems from the discovery that it is a potent inhibitor of several NCI tumor cell lines, including human breast cancer and B16 carcinomas.[7,8] The structurally-related breynin A (**2**) was isolated[9—12] in the early 1970s from the Taiwanese woody shrub *Breynia officinalis* Hemsl. Exhaustive hydrolysis afforded breynolide (**4**) along with D- glucose, L-rhamnose and *p*-hydroxybenzoic acid.[11] The structure of **4** was secured by Sasaki and Hirata[9,10] through single-crystal X-ray analysis. The complete trisaccharide structure of **2** and the structure of breynin A (**2**) were deduced independently by Smith *et al.*[13] and Ohkuma *et al.*[14] Interestingly, the medicinal utility of **2** is unrelated to **1** and is based on its potent oral hypocholesterolemic activity.[15]

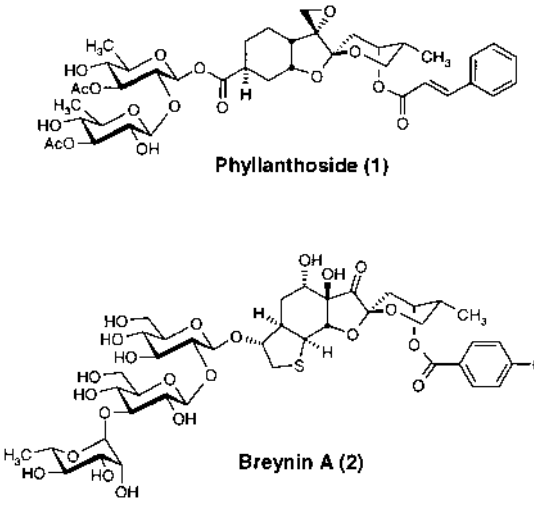

Fig. 1

Phyllanthocin

Eight approaches to phyllanthocin have been reported. Despite the sizable synthetic effort, there is significant diversity among the strategies towards this natural product. Two of these have employed a stereochemically linear approach while six have adopted a stereochemically convergent strategy.

Phyllanthocin: Stereochemically Linear Approaches

An integral part of our work directed towards the synthesis of phyllanthocin (**3**)[16—18] and breynolide (**4**)[19,20] was the development of a strategy in which a single stereochemical center (or multiple centers generated in one transformation)

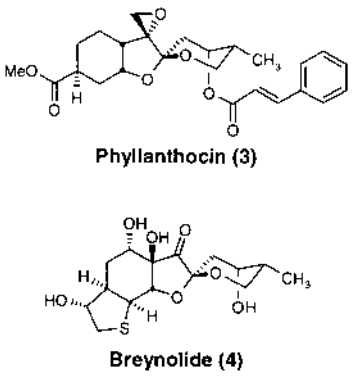

Fig. 2

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introduced early in the synthetic scheme is used to induce the remaining relative stereocenters within these molecules with a high degree of stereoselectivity. Thus the entire stereochemical problem within these molecules is reduced to the introduction of one stereogenic center. In the case of a chiral nonracemic synthetic target, this approach induces the correct relative and absolute stereochemistry. We have coined this approach a 'stereochemically linear strategy'. The underlying basis and criteria for success of this approach is a synthetic analysis which exploits the stereochemical biases induced from an initial stereogenic center in conjunction with substrate control to set all the subsequent stereocenters within the molecule.

The advantages of such an approach are twofold a) that diastereomeric mixtures are not introduced late in a synthetic sequence, and b) for the preparation of an enantiomerically pure product, only a single resolution, asymmetric induction, or resort to the pool of chiral substrates is required. This approach may lead to a synthetic scheme involving an increased number of synthetic steps vis-a-vis a convergent approach, nonetheless overall efficiency may be enhanced and cost reduced as only a single chiral substrate is required.

A stereochemically linear approach may not be appropriate in all cases and the advantages of a convergent synthetic approach are well appreciated within the synthetic community. For example, the preparation of a disaccharide where individual sugar moieties are readily available and inexpensive is most efficiently prepared in a convergent approach. This approach has been utilized successfully within the spiroketal glycoside arena (vide infra). A stereochemically linear approach can, however, have advantages in the arena of complex natural product synthesis. Indeed we found this to be the case for the synthesis of the spiroketal fused bicyclic targets phyllanthocin (**3**) and breynolide (**4**).

Our approach to phyllanthocin (**3**) (Table 1) was based on the conjecture that the stereochemistry at the C(8) spirogenetic center could be set late in the synthetic scheme by taking advantage of the thermodynamic preference, as a manifestation of the anomeric effect,[21,22] of the desired spiroketal configuration in **5a** compared to that in **5b**. Specifically, the anomeric interactions of the furanone and pyranone oxygens, in conjunction with the rigidity of the perhydrobenzofuranone system would blend together to stabilize **5a**, under equilibrating conditions, relative to the C(8) epimer. The necessary stereogenicity of the methyl group at C(11) again was envisioned to be controllable under equilibrating conditions, by taking advantage of the undesirable 1,3-diaxial interactions which are known to thermodynamically favor the equatorial configuration. Therefore, we reasoned that the C(11) methyl stereocenter need not be predetermined prior to the generation of **5**, but could be set late in the synthetic scheme. This would enable the use of racemic **8** during the coupling to aldehyde **6** (Table 1). Methylenation at C(7) and reduction of the C(10) carbonyl were anticipated to be under substrate-control which would provide the desired stereogenicity at both of these positions needed to prepare phyllanthocin (**3**).

Aldehyde **6** in turn was expected to arise via a stereoselective intramolecular ene reaction of **7**, followed by ozonolysis. The preferred chair transition state for the ene reaction, with the benzyloxy substituent occupying an equatorial position, dictates the relative stereochemistry of the C(5) and C(6) centers of **6**. The absolute configuration of **6** is determined by the absolute configuration at the C(3) position in the ene precursor **7**. Therefore, the entire stereochemical problem of (+)-phyllanthocin (**3**) reduces, due to the stereochemical linearity of the strategy, to the preparation of **7** possessing the

Amos B. Smith, III was born in Lewisburg, PA. In 1966 he was awarded Bucknell University's first combined four-year B.S.-M.S. degree in Chemistry under the direction of Harold W. Heine. After a year in medical school (University of Pennsylvania), he earned his Ph. D. degree (1972) and completed a year as a Research Associate at Rockefeller University with Professor William C. Agosta. In 1973, he joined the Department of Chemistry at the University of Pennsylvania; currently, he is the Rhodes-Thompson Professor of Chemistry and Member of the Monell Chemical Senses Center and the Laboratory for Research on the Structure of Matter (LRSM), two interdisciplinary lnstitutes on the Penn Campus. From 1988 to 1996 he served as Chairman of the Department. In addition, he is a Visiting Director at the Kitasato Institute (Tokyo, Japan). He has served as research director to over 200 graduate students and postdoctoral associates, including more than 30 from Japan. More than 375 publications have emanated from his research program at the University of Pennsylvania. Currently he is Editor-in-Chief of Organic Letters.

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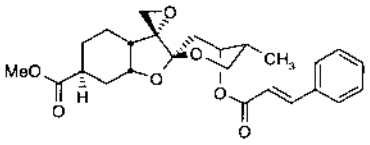
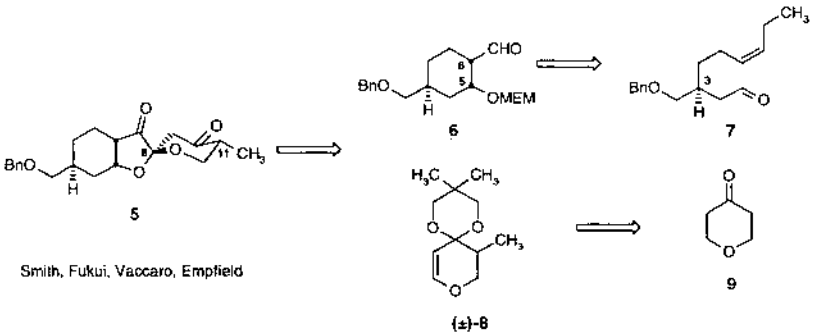
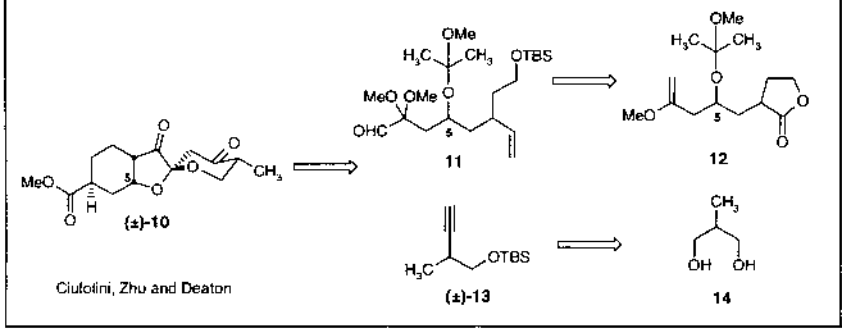
James R. Empfield was born in Everett. PA in 1961. He received his B. S. in Chemistry degree in 1983 from Lebanon Valley College. In 1985 he earned his M. S. in Chemistry degree from Bucknell University where he investigated the reactivity of o-quinone monoimides under the direction of Harold W. Heine. He then continued his education at the University of Pennsylvania where he obtained his Ph. D. degree while completing the total synthesis of (±)-breynolide under the guidance of Amos B. Smith, III. Currently, he is a Principal Chemist within the Wilmington Medicinal Chemistry Department at Astra Zeneca.

Table 1. Stereochemically Linear Approaches to (+)- and (±)-Phyllanthocin (**3**)



Retrosynthetic Analysis	Total Synthetic Steps[a]	Overall Efficiency[b]
 Smith, Fukui, Vaccaro, Empfield	26 21 14	5.5% 7.8%
 Ciufolini, Zhu and Deaton	27 23 19	0.8% 0.8%

a) Total number of steps listed first followed by the number of synthetic sequences through each synthetic route from commercially available starting materials. *b*) Total overall yield (percent incorporation of starting material into final product, phyllanthocin (**3**)) through each synthetic pathway.

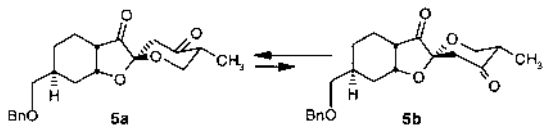


Fig. 3

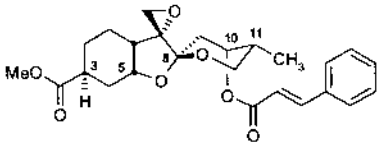
correct absolute stereochemistry as shown. We introduced the requisite stereogenicity at C(3) *via* an Evans aldol reaction[23] utilizing the oxazolidinone derived from 5-octynoic acid as the substrate. This approach has yielded a relatively short (26 total steps, 21 steps *via* the longest linear sequence) and efficient (5.5% overall yield) total synthesis of (+)-phyllanthocin (**3**) employing only one asymmetric induction.

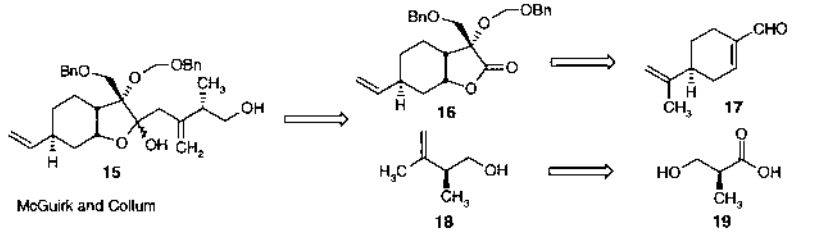
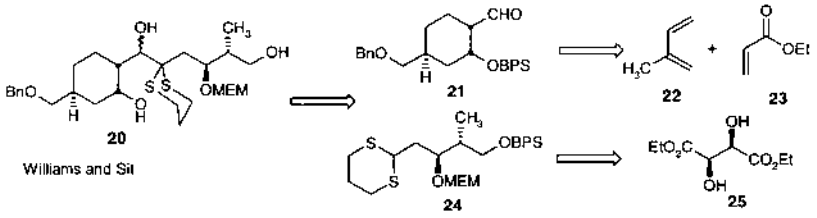
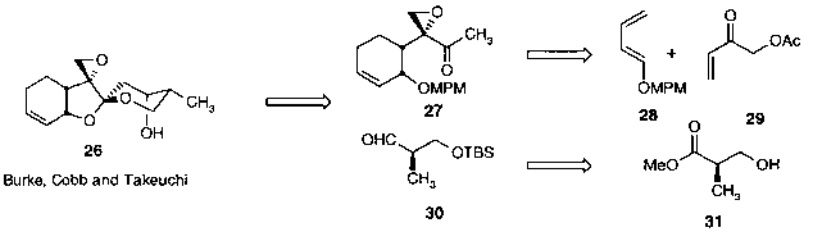
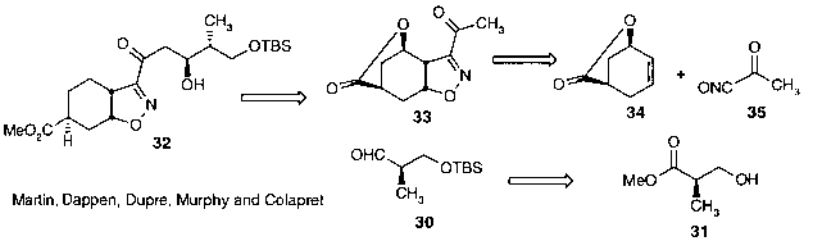
More recently, Ciufolini and coworkers[24,25] adopted a similar approach in that they employed a single stereogenic center to relay the relative stereochemistry throughout (±)-phyllanthocin (**3**). Specifically, they designed a synthetic route *via* diketone, (±)-**10**, in which the stereocenter at C(5) is the sole nonepimerizable center in the entire molecule. They reasoned that all of the remaining centers could be controlled thermodynamically and that the relative stereochemistry could be relayed through C(5). In fact this proved to be the case. Furthermore, the key stereocenter at C(5) was generated through an ene-like reaction of (±)-**12** and 2-methoxypropene, exploiting methodology developed in their laboratory.[26] Further elaboration of the ene product provided aldehyde **11** as a mixture of isomers which was coupled with the anion of racemic acetylene **13**. This adduct was then transformed into **10** as an almost equal mixture of four isomers, which upon treatment with DBU provided racemic **10** as the major product confirming the original hypothesis that the remaining stereocenters, other than C(5), indeed could be equilibrated to the requisite stereogenicity necessary to complete phyllanthocin (**3**).

Phyllanthocin (3): Stereochemical Convergent Approaches

A number of research groups have utilized a stereochemically convergent approach for the synthesis of phyllanthocin (**3**). The basic retrosynthetic disconnections to the key chiral components for these approaches are shown in Table 2. The first total synthesis of phyllanthocin (**3**) was reported by Collum and McGuirk[27] in 1982. The synthesis also established the absolute configuration of phyllanthocin (**3**). The key transformation involved coupling the dianion of **18** to lactone **16** to provide advance intermediate **15**. Equally important was the realization that **16** could be accessed *via* the complex and commercially available (*S*)-(−)-perilla aldehyde (**17**) while the deceptively simple **18** was available from (*S*)-(+)-3-hydroxy-2-methyl propanoic acid (**19**), which in turn is

Table 2. Stereochemically Convergent Approaches to (+)-Phyllanthocin (**3**)



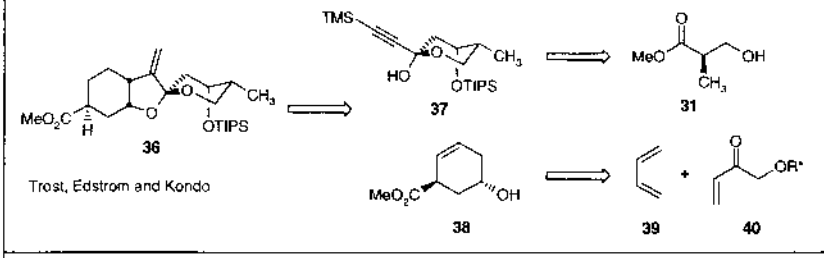
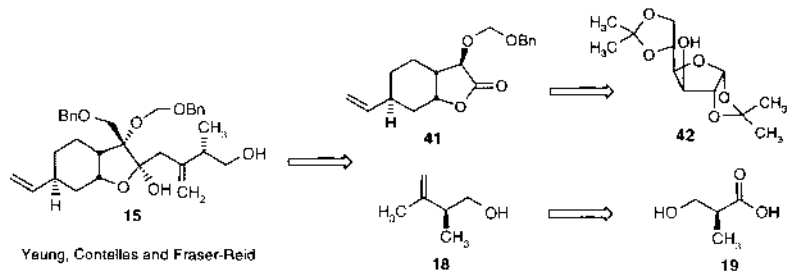
Retrosynthetic Analysis	Total Synthetic Steps[a]	Overall Efficiency[b]
 McGuirk and Collum	26 17 18	8.4% 5.7%
 Williams and Sit	33 19 25	1.1% 2.2%
 Burke, Cobb and Takeuchi	18 15 13	2.0% 15.7%
 Martin, Dappen, Dupre, Murphy and Colapret	18 15 13	1.4% 2.8%

available in 48% yield from isobutyric acid via bacterial oxidation.[28] This highly efficient approach to (+)-phyllanthocin (**3**) highlights the value of well conceived stereochemically convergent approaches to complex natural products.

A different approach utilizing the dithiane **24** as the pyranone precursor was employed by Williams *et al.*[29] to prepare (+)-phyllanthocin (**3**). Anion formation followed by addition to aldehyde **21** provided the highly functionalized intermediate **20** which was converted into (+)-phyllanthocin (**3**) in 10 steps. The stereocenters of **24**, and therefore those of the pyranone ring, arose from diethyl L-(−)-tartrate. The coupling partner, aldehyde **21**, was prepared *via* Diels-Alder reaction followed by a subsequent resolution to provide optically pure material. Interestingly the resolution of the alcohol precursor to **21** could be avoided as **24** was shown to facilitate the resolution of (±)-**21** following dithiane coupling. In this way, Williams has demonstrated the advantage of employing a stereochemically convergent approach.

The Burke,[30—33] Martin[34,35] and Trost[36—39] groups have reported the total synthesis of (+)-phyllanthocin (**3**) employing (*R*)-(−)-methyl 3-hydroxy-2-methyl propionate (**31**) as the source for the C(11) methyl stereocenter. (As an interesting aside, Collum employed the corresponding acid as the source of the C(11) stereocenter but used the opposite antipode!) Despite utilizing the same source of chirality, each of the three approaches to (+)-phyllanthocin (**3**) differs significantly. Nonetheless, the Burke and Martin approaches do employ an anion coupling to the same aldehyde **30**. However, the anion substrates differ significantly, other than the nucleophilic carbon in each case becomes the C(9) center in the

Table 2. (continued)

Retrosynthetic Analysis	Total Synthetic Steps[a]	Overall Efficiency[b]
 Trost, Edstrom and Kondo	24 17 15	10.2% 9.9%
 Yeung, Contellas and Fraser-Reid	33 25 17	0.8% 11.8%

a) Total number of steps listed first followed by the number of synthetic sequences through each synthetic route from commercially available starting materials. *b*) Total overall yield (percent incorporation of starting material into final product, phyllanthocin (**3**)) through each synthetic pathway.

final natural product. For the coupling, the Burke approach employs methyl ketone **27** which has the requisite epoxide in tact but has the C(3) ester functionality masked as an olefin poised for hydroformylation. Compound **27** in turn was prepared in enantiomerically pure form by employing a Diels-Alder approach followed by application of the Sharpless asymmetric epoxidation.[40] The Martin approach involved the use of isoxazoline methyl ketone, **33**, as the nucleophilic partner for aldehyde **30**. This isoxazoline **33** was prepared by dipolar cycloaddition of nitrile oxide **35** with cyclohexene lactone **34**. The latter was in turn prepared in enantiomerically pure form *via* the asymmetric [4+2] cycloaddition of 1,3-butadiene with the acrylate ester of 8-phenylmenthol. Thus the Martin approach utilized two cycloaddition reactions, followed by coupling the anion of **33** to aldehyde **30** to generate advanced substrate **32**. The latent hydroxyketone **32** was then unmasked and cyclized to provide a late stage intermediate employed in the Williams synthesis. Both the Burke and Martin approaches led to short (18 total steps) synthetic schemes to (+)-phyllanthocin (**3**).

The Trost approach, while slightly longer in synthetic steps than the Burke and Martin syntheses, provided a highly efficient route to (+)-phyllanthocin (**3**). As stated above, (*R*)-(−)-methyl 3-hydroxy-2-methyl propionate (**31**) was employed as the source of the C(11) stereocenter. Unlike all other approaches, **31** was converted to the tetrahydropyran **37** prior to coupling with the cyclohexyl portion of the molecule. The coupling partner, **38** was prepared by a series of manipulations following the asymmetric [4+2] cycloaddition of 1,3-butadiene with the acrylate ester of (*R*)-(−)-pantolactone, which introduced the stereogenic center at C(3). Coupling of **37** and **38** was achieved employing K10 montmorillonite clay to generate a ketal intermediate poised to take advantage of the reductive cyclization of enynes developed in the Trost group; **36** was thus available in very good yield. Ozonolysis then provided a late stage substrate that is common in many of the syntheses of **3**.

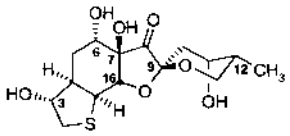
A key intermediate in the Collum synthesis, namely **41**, was prepared by Fraser-Reid[41] by an approach employing a radical cyclization to generate the cyclohexyl ring system. This approach differs from others in that the tetrahydrofuran ring was prepared prior to the cyclohexyl ring and that it was generated from a sugar derivative, namely diacetone glucose (**42**). In this strategy the stereogenicity at C(5) and C(6) is translated through the glucose sugar.

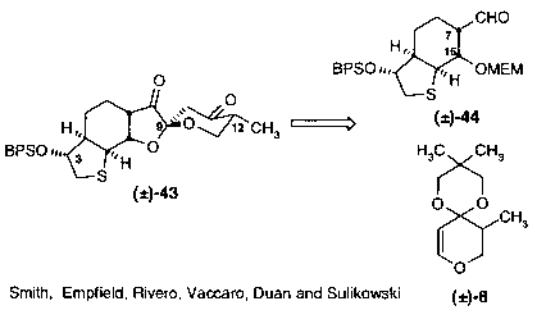
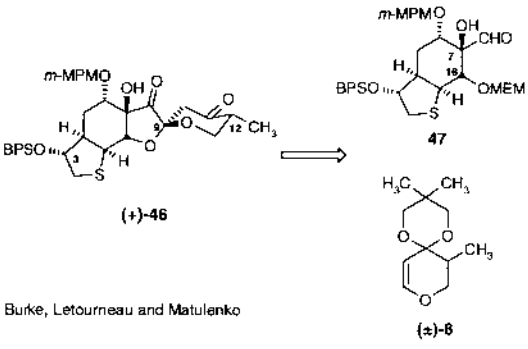
As highlighted here, a variety of synthetic approaches have culminated in the total synthesis of phyllanthocin (**3**). A number of the approaches proved to be very efficient. That is to say they have yielded synthetic routes that provide a high conversion of the commercially available starting material into the desired product. Importantly, there is not a direct correlation between the number of synthetic steps and the overall efficiency. It must however be stressed that the cost of the starting materials and the human cost in time are two factors that have not been considered here. In regard to the former, employing a stereochemically linear approach which requires only one chiral building block may be more cost effective than utilizing a stereochemically convergent approach which requires at least two, even if it leads to a longer synthetic route. Additionally, preparation of chiral building blocks *via* resolution can be costly in regards to time.

Breynolide

To date there have been three total syntheses of breynolide (**4**) and one synthesis of breynolide sulfone. As most of these efforts arose from groups with experience with phyllanthocin (**3**), the lessons learned have been incorporated into the breynolide strategies.

Table 3. Stereochemically Linear Approaches to (+)- and (±)-Breynolide (**4**)



Retrosynthetic Analysis	Total Synthetic Steps[a]	Overall Efficiency[b]
 Smith, Empfield, Rivero, Vaccaro, Duan and Sulikowski	37 32 16	1.0% 3.6%
 Burke, Letourneau and Matulenko	39 34 14	1.7% 3.8%

a) Total number of steps listed first followed by the number of synthetic sequences through each synthetic route from commercially available starting materials. *b*) Total overall yield (percent incorporation of starting material into final product, breynolide (**4**)) through each synthetic pathway.

Breynolide: Stereochemically Linear Strategies

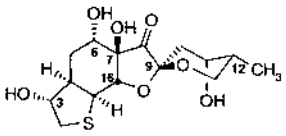
Two stereochemically linear approaches towards breynolide (**4**) have successfully culminated in total syntheses. The first of these accomplished in our laboratory.[19,20] takes advantage, as in our phyllanthocin approach, that the requisite stereochemistry of the C(9) and C(12) centers can be controlled thermodynamically. Thus, racemic **8** can be utilized as the coupling partner with aldehyde **44**, which following functional group manipulation and spiroketalization with equilibration, provided (±)-**43**. Note that although both coupling components, **8** and **44** are racemic, following thermodynamic equilibration only one of the possible diastereomers, **43**, is isolated, albeit in racemic form. Thus a stereochemically linear approach has utility not only for a chiral synthesis but also in the racemic case in that it minimizes the formation of unwanted diastereomers. In this approach the stereochemistry at C(7) is initially set *via* a Diels-Alder reaction leading to **45** in which the bridgehead carbon α to the carbonyl becomes the C(7) center. It is the structure-based control of bicyclic **45** that enables the remaining stereocenters of **44** to be incorporated efficiently.

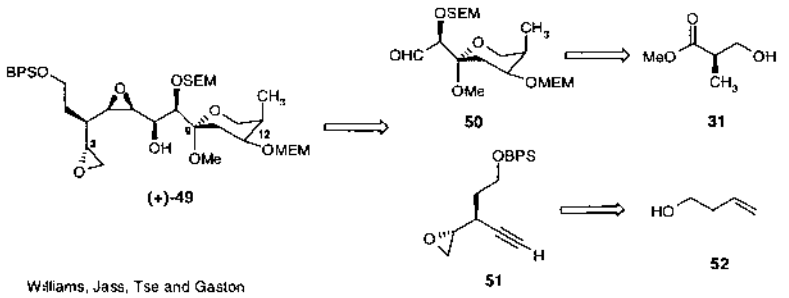
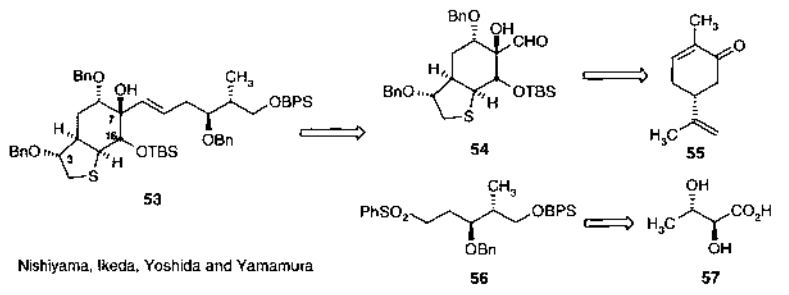
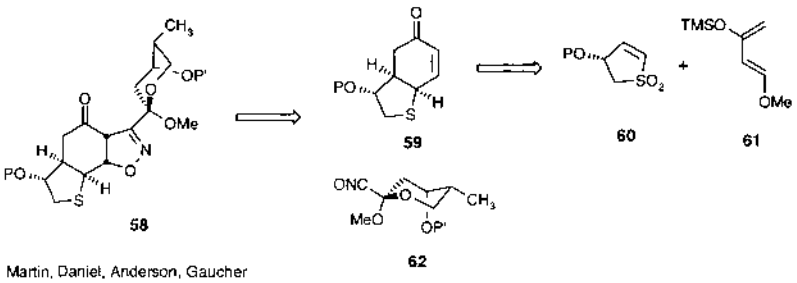
More recently, Burke and coworkers[42] utilized a similar approach by employing the coupling of (±)-**8** with aldehyde **47**, with the notable exception that **47** is homochiral. Following the Smith protocol then led to the highly functionalized spiroketal (+)-**46** which was converted to (+)-breynolide (**4**) in four steps. The center at C(6) was the first stereocenter introduced, accomplished by asymmetric reduction of 2-bromo-2-cyclohexenone. Dehalogenation, epoxidation and alcohol protection provided **48**, thus setting the correct absolute configuration at C(6) and C(7).

Breynolide: Stereochemically Convergent Strategies

The first total synthesis of breynolide (**4**) was reported in 1990 by Williams *et al*.[43] Their approach involved the incorporation of the thioether late in the synthetic scheme, after the necessary hydroxyl functionality had been installed. Towards this end, the highly oxygenated **49** was prepared and successfully employed as the breynolide precursor. This advanced intermediate arose, following further manipulations, including the coupling of aldehyde **50** with the anion of **51**. Interestingly, both coupling partners are derived from asymmetric epoxidations of allylic alcohols. The initial stereocenter of **50** arises from (*R*)-(−)-methyl 3-hydroxy-2-methyl propionate (**31**) and becomes the C(12) center. The C(11) stereocenter was then introduced *via* asymmetric Sharpless epoxidation.[40] Epoxy acetylene **51** arose in a similar fashion from an allylic alcohol derived from 3-buten-1-ol. In this regard, Williams is able to employ an achiral starting material and convert it in high yield to a chiral component utilizing

Table 4. Stereochemically Convergent Approaches to (+)-Breynolide and Breynolide Sulfone



Retrosynthetic Analysis	Total Synthetic Steps[a]	Overall Efficiency[b]
 Williams, Jass, Tse and Gaston	33 26 17	9.2% 6.5%
 Nishiyama, Ikeda, Yoshida and Yamamura	40 33 17	2.1% 8.5%
 Martin, Daniel, Anderson, Gaucher		

a) Total number of steps listed first followed by the number of synthetic sequences through each synthetic route from commercially available starting materials. *b*) Total overall yield (percent incorporation of starting material into final product, breynolide (**4**)) through each synthetic pathway.

the Sharpless methodology.[40] This approach has led to an efficient route to breynolide (**4**).

The first reported synthetic studies towards breynolide (**4**) came from Yamamura *et al*. and culminated in the synthesis of breynolide sulfone.[44,45] The strategy entailed coupling the anion of phenylsulfone **56** (eventually transformed into the tetrahydropyran ring) with the highly functionalized aldehyde **54**. The aldehyde was in turn prepared from L-carvone, while the phenylsulfone was prepared from L-tartaric acid.

More recently, Martin and coworkers[46,47] presented their approach to breynolide (**4**) which involves a similar strategy to that employed in their successful synthesis of phyllanthocin (**3**), namely 1,3-dipolar cycloaddition of a functionalized nitrile oxide (**62**) with an olefin, in this case **59**. The utility of this approach has been established in that **59** has been prepared and shown to add with simplified nitrile oxides. Enone **59** was synthesized *via* a Diels-Alder reaction employing vinyl sulfone **60** and Danishefsky diene (**61**). Thus the stereocenter at C(3) is first introduced into the molecule and used to induce the necessary stereogenicity at C(4) and C(17).

Thus, as shown herein, both stereochemically linear and convergent strategies have proven to be successful in the total synthesis on breynolide (**4**). The most efficient of these coming from the Williams' group involves asymmetric epoxidations employing the methodology developed by Sharpless[40] for the construction of both chiral components.

In summary, when developing a synthetic approach towards stereochemically complex natural products, optimal efficiency can be achieved *via* a chemically convergent strategy. Introduction of stereocenters however, need not be convergent. Herein we have highlighted the utility of both stereochemically linear and convergent approaches to natural product synthesis. Importantly, optimal efficiency is not nec-

essarily correlated with the shortest synthetic routes, but by those that employ high yielding transformations and inexpensive, readily available starting materials. Often this can be accomplished by employing a chemically convergent but stereochemically linear approach (or alternatively by developing an approach which utilizes inexpensive chiral starting materials). The future challenge for the synthetic community continues to be the development of efficient convergent synthetic schemes, and the necessary enabling methodology, which requires a minimum of chiral nonracemic building blocks.

References and Notes

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