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1,5-Polyols: Challenging motifs for configurational assignment and synthesis*

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Abstract: Despite the well-established methods for stereochemical assignments and synthesis of 1,3-diols, the corresponding 1,5-diols and -polyols present specific challenges which remain unsolved. This article highlights some new strategies and methodologies specifically designed for the 1,5-diol motif.

Keywords: alcohols; asymmetric synthesis; coupling reactions; natural products; polyketides.

INTRODUCTION

Chiral 1,5-polyol substructures are found within many diverse classes of biologically active natural products. In these structures, one or more 1,5-diol units, consisting usually of secondary alcohols, may be present in *syn* or *anti* relative configurations, and are often accompanied by intervening alkenes (Fig. 1). Despite their frequent occurrence, only a few reports deal with methodologies or strategies designed especially for structural assignment and synthesis of the 1,5-polyol motifs. Of course, existing strategies designed for 1,3-diols and related polyketide structures may also be applicable to some 1,5-polyols, but more direct, efficient, and versatile means may be envisioned to specifically target 1,5-polyols.

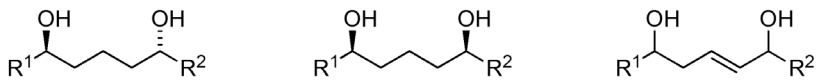

Fig. 1 Representative 1,5-diol structures.

Structural assignments, and particularly issues of stereochemistry, are complicated in 1,5-polyols because the stereogenic centers are relatively remote from each other. While 1,3-polyols are commonly synthesized through biomimetic polyketide assembly strategies or other aldol-based bond constructions [1], there are some significant problems with adapting these strategies to 1,5-polyols: First, many 1,5-polyol targets are unbranched, i.e., composed of acetate aldol units, which offer continuing challenges at the limits of asymmetric synthesis methodology [2]. Second, any such polyacetate constructs would still require modifications, post-C–C bond construction, in order to regioselectively remove alternating hydroxyl functions. Third, as complexity of the growing polyol chain builds, the stereocontrol in the aldol reaction becomes more prone to deviate from predictions, so some ambiguity will accompany

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the generation of each stereocenter. Syntheses according to this strategy would confront challenging configurational assignments.

In view of these concerns, new strategies and methods have begun to emerge in order to specifically address the 1,5-polyol problems, both in structural analysis and synthesis. The goal of this brief review is to highlight selected developments at the forefront of this new area.

SELECTED NATURAL PRODUCTS WITH 1,5-POLYOL MOTIFS

Natural products incorporating 1,5-diol and 1,5-polyol motifs exhibit a wide range of interesting structures and diverse biological activities. Tetrafibricin (**1**, Fig. 2), a fibrinogen receptor antagonist, was iso-

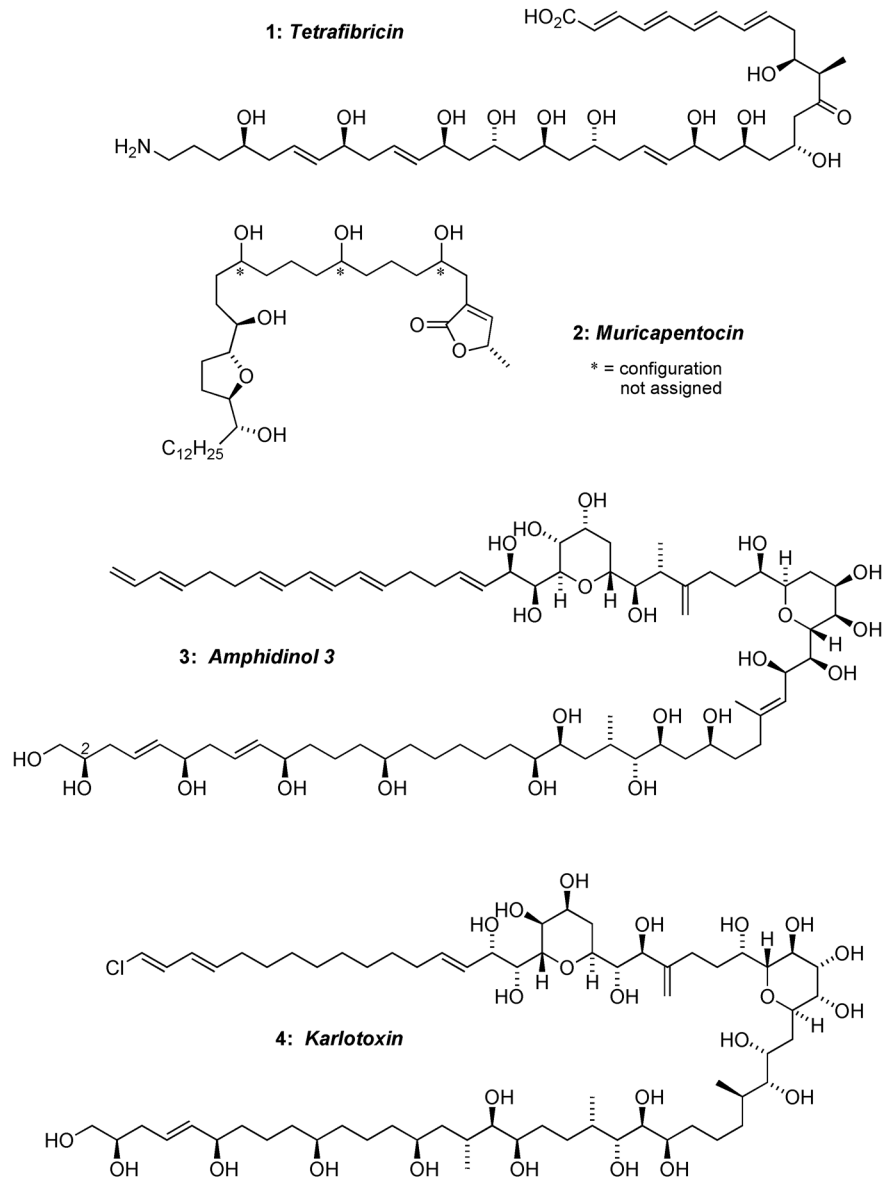
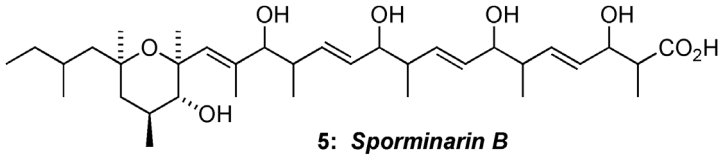


Fig. 2 Structures of selected 1,5-polyol-containing natural products.

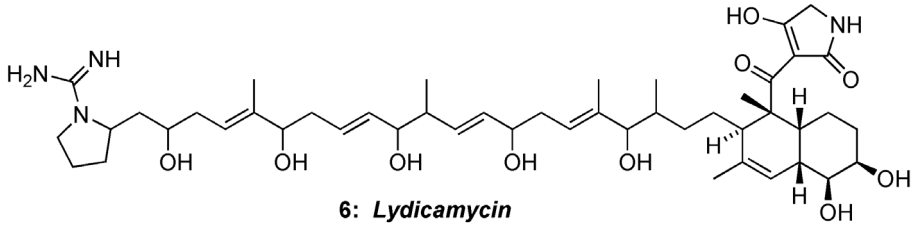
lated from a *Streptomyces* culture broth, and combines polyene, 1,3-polyol, and 1,5-polyol structures, along with amino acid functionality divided between the termini [3]. Muricapentocin (**2**), isolated from the leaves of the soursop tree (*Annona muricata*) [4], is a 1,5-polyol from the annonaceous acetogenin family of natural products, which are inhibitors of the mitochondrial complex I (NADH:ubiquinone oxidoreductase) and may induce apoptosis [5]. Here the 1,5-polyol motif is combined with the γ-lactone and 2,5-bis(hydroxyalkyl)tetrahydrofuran substructures characteristic of the acetogenin family.

Amphidinol 3 (**3**, Fig. 2), a secondary metabolite from the dinoflagellate *Amphidinium klebsii*, offers hemolytic and antifungal activity along with intriguing structural complexity; along with interesting polyene and C-glycoside architectures is a 1,5-polyol motif at C2–C14 [6]. The dinoflagellate *Karlodinium veneficum* produces karlotoxins (**4**), a family of water-soluble toxins associated with fish kills from dinoflagellate blooms [7]. Hamann et al. recently assigned the complete stereostructure of karlotoxin 2 [8], which closely resembles that of amphidinol 3, adding a chlorinated diene to the structural diversity accompanying 1,5-polyol motifs.

Although the 1,5-polyol portions of the natural products discussed above have the unbranched carbon chains typical of acetate-derived polyketides, the 1,5-polyol subunits of sporminarin B [9] (**5**, Fig. 3) and lydicamycin (**6**) [10] are decorated with methyl substituents characteristic of propionate-derived polyketides. Both structures lack stereochemical assignments in their 1,5-polyol sectors. Lydicamycin is an antibiotic, active against multidrug-resistant strains, and sporminarin possesses antifungal activity.



5: *Sporminarin B*

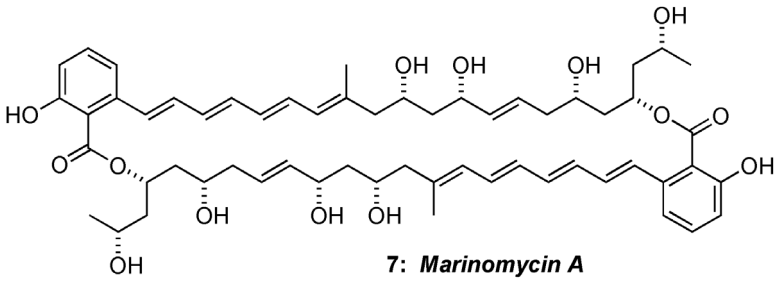


6: *Lydicamycin*

Fig. 3 Structures of 1,5-polyols bearing methyl substituents.

Cultures of the marine actinomycete *Marinispora* strain CNQ-140 afforded marinomycin A [11] (**7**, Fig. 4) and marinisporolide A (**8**), which exhibit a mixed 1,5-diol along with extensive 1,3-oxygenation [12]. The marinomycins showed antibiotic activity against methicillin- and vancomycin-resistant strains, as well as selective cytotoxicity toward melanoma cell lines in the NCI panel.

The brief survey of selected 1,5-polyol natural products described here offers a representative view of the diversity of natural sources, range of biological activities, and variety of fascinating hybrid architectures associated with the 1,5-polyol motifs. Clearly such structures offer an abundance of opportunities for intriguing new research questions.



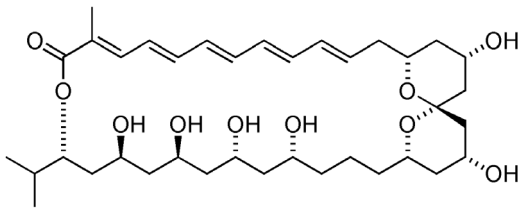


Fig. 4 Structures of *Marinispora* metabolites.

METHODS OF CONFIGURATIONAL ASSIGNMENT

The stereocenters in 1,5-polyols are isolated from each other and poorly suited for standard tools like coupling constant analysis or examination of cyclic derivatives as in Rychnovsky's acetonide method [13]. Furthermore, Mosher ester analysis may not differentiate all isomers [14].

The hybrid 1,3- and 1,5-polyol structure of mediomycin B [15] (**9**, Fig. 5) illustrates the difficulty in stereochemical analysis of the 1,5-polyols, in which the stereochemical arrays are isolated from each other. Although relative configurations *within* the 1,3-diols at C33–C35, C39–C43, C47–C49, and C53–C55 could all be assigned using an NMR database method using chemical shifts obtained in achiral solvents [16], the intervening 1,5-diol relationships *between* each of the stereochemical arrays are more challenging to address. In mediomycin, these 1,5 relationships were left unassigned due to the limitations of the data obtained in achiral solvents.

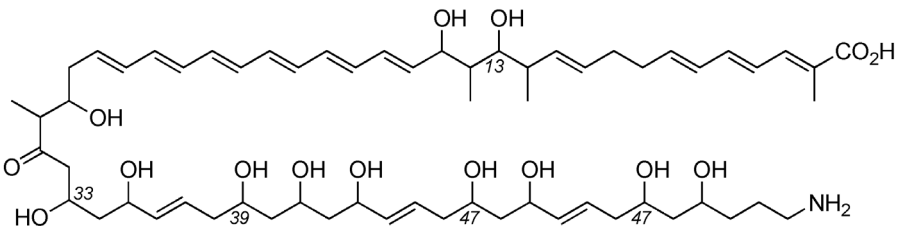


Fig. 5 Structure of mediomycin.

NMR analysis of ester derivatives from chiral acids

Assignment of the individual hydroxyl groups may be manageable in modified Mosher ester analysis, using ester derivatives prepared from certain chiral acids [17]. Predictable through-space magnetic anisotropy leads to chemical shift differences between esters prepared from the enantiomeric chiral

acids, and the analysis reveals configuration of the secondary alcohol. This depends on appropriately resolved absorbances, which is by no means assured in 1,5-polyols. Modifications of the classical Mosher method were applied to the 1,5-polyol portions of karlotoxin [18] and amphidinol 3 [19]. Degradation of karlotoxin by sequential treatment with periodic acid and $NaBH_4$ afforded a C2–C17 polyol fragment, which was then converted to (*R*)- and (*S*)-α-methoxyphenylacetate derivatives **10a** and **10b** (Fig. 6).

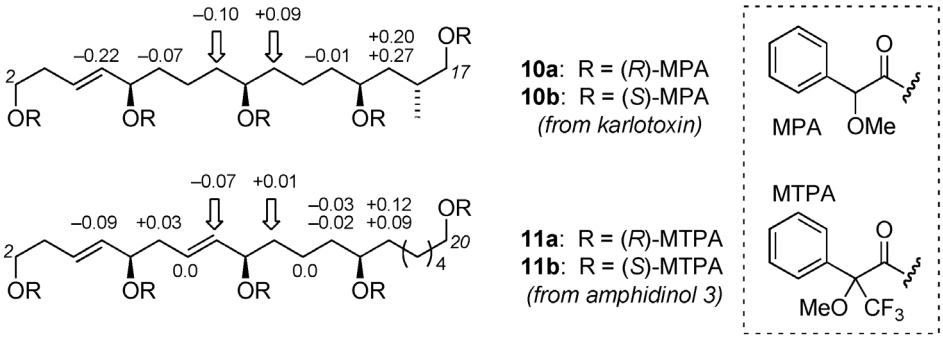


Fig. 6 Chemical shift difference (Δδ) data from configurational analysis of karlotoxin and amphidinol 3.

Still, 1,5-polyols exhibit deviations from the normal behavior of secondary alcohols. Closer examination of the Δδ data from amphidinol derivatives **11a** and **11b** (Fig. 6) shows unusually small changes in chemical shift for selected hydrogens located at positions equidistant from the hydroxyls, presumably due to interference from the MTPA groups at neighboring alcohols. In compounds **11a** and **11b**, the Δδ data for hydrogens at C8 and C12 go to zero due to this interference. While this can be rationalized using conformational analysis to predict the relative orientations of the nearest neighbor MTPA or MPA aromatic rings and the effects of their magnetic anisotropy, these assignments are less straightforward than those of typical secondary alcohols.

NMR database comparisons

Diagnostic chemical shifts and coupling constants of a variety of polyketide structural fragments in chiral and achiral solvents have been compiled into NMR databases, resulting in predictive tools for various stereochemical relationships [20]. This approach by Kishi et al. makes it possible to assign configurations of stereochemical arrays such as 1,3-diols and 2-methyl-1,3-diols without derivatization, and even isolated secondary alcohols without neighboring functionality have been assigned by this database method. As noted for mediomycin (Fig. 5), the stereochemical relationships in 1,5-diols are more difficult to address. However, by employing NMR spectra obtained in a chiral solvent BMBA-*p*-Me (**13**, Fig. 7), the configurations in the 1,5-polyol sector of tetrafibricin could be assigned [21]. For this analysis, the natural product was reduced at the ketone function to afford two epimers **12α** and **12β**. The ^{13}C NMR resonances in the 1,5-polyol segment, for positions adjacent to each alcohol carbon, fit the trends of database structures, enabling the configurational assignments shown.

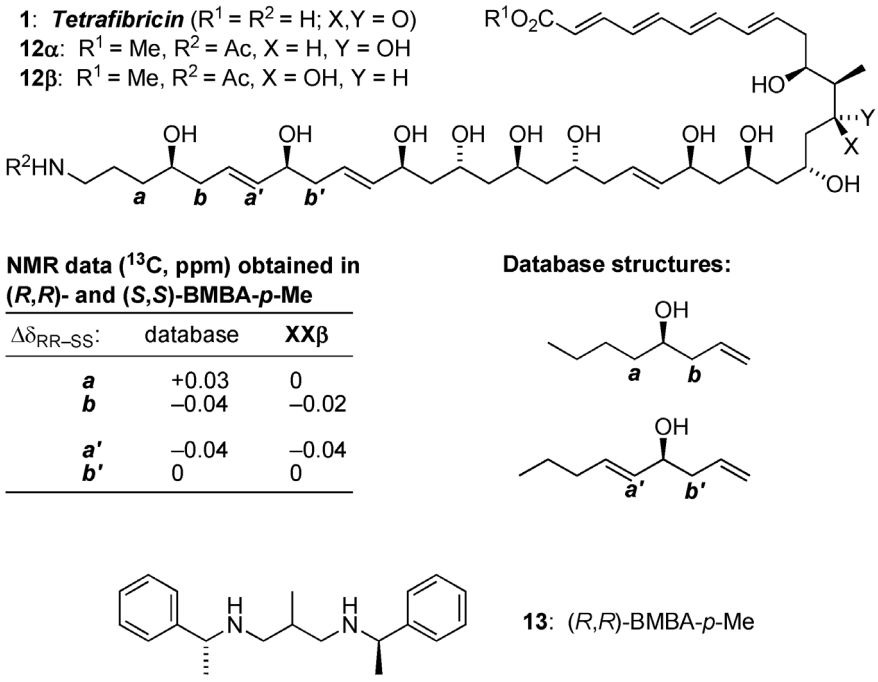


Fig. 7 Configurational analysis of tetrafibricin derivatives.

Liposomal circular dichroism

A unique liposomal circular dichroism spectroscopic solution was introduced by Molinski to address the 1,5-diol configurational analysis problem [22]. A 1,5-diol such as **14** is functionalized as porphyrin carboxylate diester **15** (Fig. 8) and incorporated into liposomes, where the dipoles of the chromophores exhibit nonaveraged orientations. Thus, the rotational freedom intervening between remote functional groups is mitigated, and transmission of stereochemical information is possible between those remote centers. Circular dichroism spectra then become diagnostic for relative and absolute configuration. The *syn* and *anti* relative configurations of 1,5-, 1,7-, and 1,9-diols were all distinguishable by this method. The liposomal ordering concept has also been successful with other remote stereochemical relationships [23].

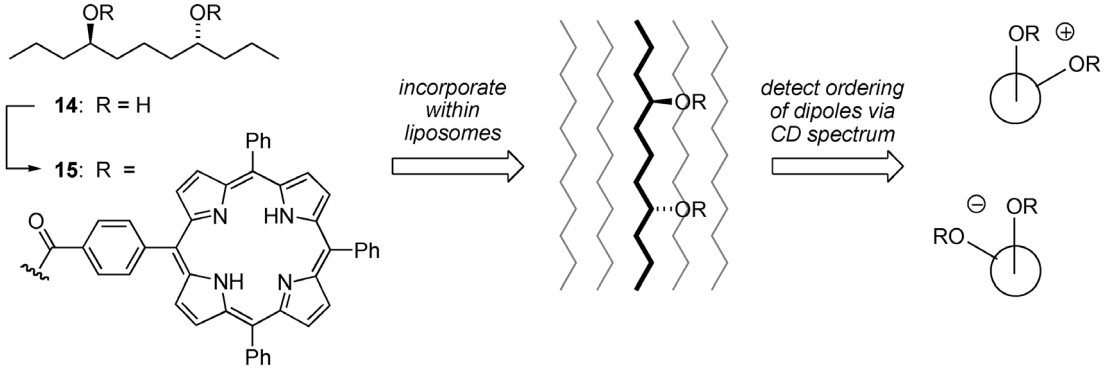


Fig. 8 Schematic view of the liposomal CD analysis method.

SYNTHETIC STRATEGIES AND METHODOLOGIES

Complementing the existing methods for polyketide synthesis, several new synthetic methods and strategies have been employed to address the special circumstances associated with stereocontrolled synthesis of 1,5-diols and -polyols. In particular, the longer-range relative stereochemical relationships pose a significant problem, not only for structure determination as noted above, but also for stereocontrol. Some selected approaches to this problem are outlined below.

C–C bond constructions at the stereogenic centers

Additions of alkoxy-substituted allylstannanes

The problem of 1,5-stereocontrol has been addressed by Thomas using allylstannane reagents bearing protected hydroxyl groups adjacent to the allylstannane (Fig. 9) [24]. The allylstannane reagents are prepared in a 9-step synthesis from glycidol, and are useful in generating 1,5-polyols. Thus, $SnCl_4$-promoted addition of δ-alkoxyallylstannane **16a** to isobutyraldehyde afforded (*Z*)-2-ene-1,5-diol **17** in 75 % yield and high diastereoselectivity (dr 95:5). After transforming the terminal alkene to an aldehyde, the addition of allylstannane **16b** followed by hydrogenation then furnished saturated 1,5,9,13-tetraol **20**. Along with Thomas' other seminal efforts with chiral allylstannanes, this defined an interesting new mode of 1,5-stereocontrol.

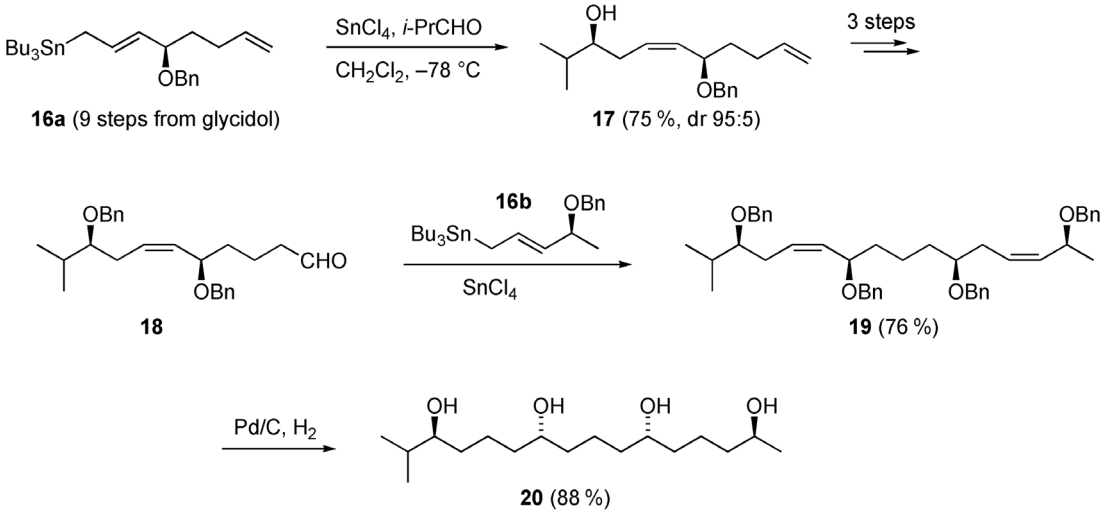


Fig. 9 δ-Alkoxyallylstannane additions with 1,5-stereocontrol.

Iterative allyltitanium addition and cross-metathesis

In contrast to the substrate control approach shown above, the Duthaler chiral allyltitanium reagent **21** [25] (Fig. 10) transfers its stereochemical information, but not the stereocontrol element itself, during allyl addition to aldehydes. BouzBouz and Cossy reported a combination of this ligand-controlled allyltitanium addition with olefin cross-metathesis using catalyst **22** to achieve an iterative assembly of 1,5-polyols [26]. Each iteration consists of allyl addition to an aldehyde, cross-metathesis with acrolein, and introduction of a protecting group. When more than one alkene is present, selection of the protecting group is important for regioselection in the cross-metathesis; either a sterically hindered silyl group or an acetate can allow for control. The sequence is illustrated en route to the C27–C40 fragment of tetrafibricin [27]; reaction of **21** with difunctional aldehyde **23** proceeded in >95 % ee, and was fol-

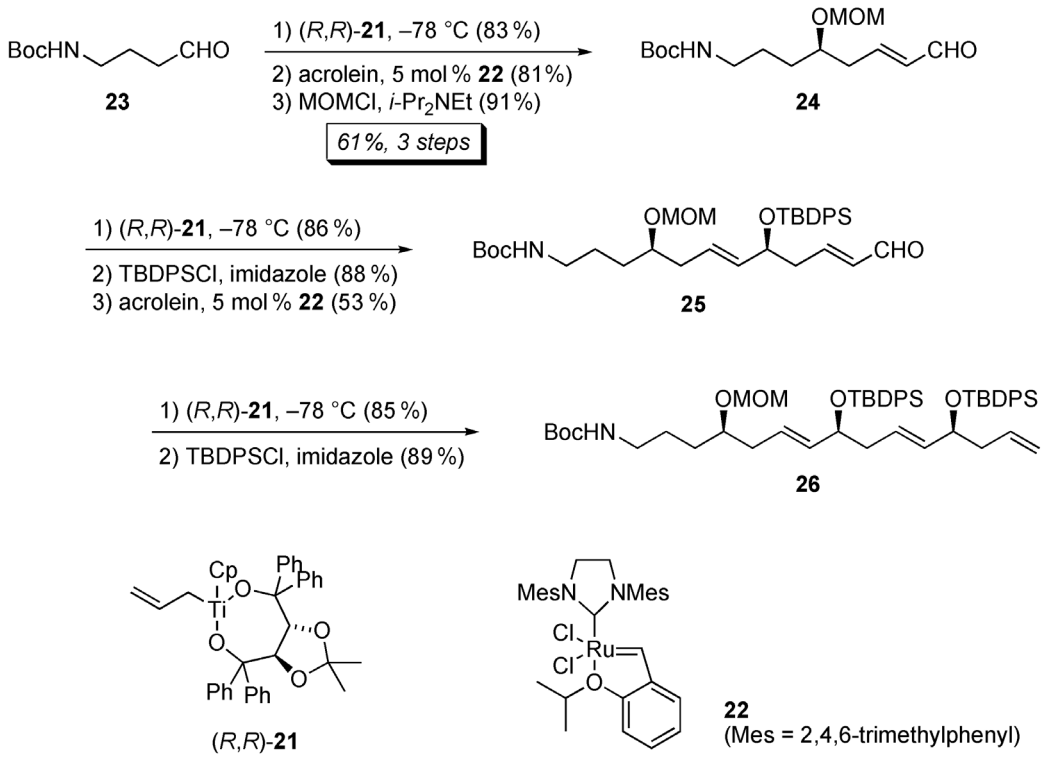


Fig. 10 Application of allyltitanation and cross-metathesis to tetrafibricin.

lowed sequentially by cross-metathesis and protection, affording aldehyde **24** in overall 61 % yield for the complete 3-step interation. After allylation of aldehyde **24**, steric differentiation of the alkenes (*tert*-butyldiphenylsilyl protection) and cross-metathesis led to a 53 % yield of 1,5-diol **25**. Addition of a third equivalent of (*R*,*R*)-**21** afforded allyl adduct **26**, which corresponds to the C27–C40 fragment of tetrafibricin. The second iteration exhibited diminished yield (40 % over 3 steps), mainly due to the cross-metathesis stage; this is also observed in the same authors' application of this approach to amphidinol 3 [26].

Bidirectional double allylboration

Allylborane reagents have been exploited extensively for enantioselective additions to aldehydes since the pioneering efforts of Brown with allylboranes bearing isopinocampheyl groups as stereocontrol elements [28]. Roush also introduced tartrate-derived allylboronates for this purpose [29].

Pietruszka has examined sequential coupling of allylboronate derivatives with two different aldehydes [30]. First, a chiral allylboronate **27** (Fig. 11) bearing methanesulfonate functionality was subjected to Pd-catalyzed allylstannation of an aldehyde to yield a new functionalized allylboronate **28** through the proposed transition state **A**. This then coupled to a second aldehyde, and after treatment with $LiAlH_4$ to remove the boron, 1,5-diol products **29a** and **29b** were obtained. Among several examples reported, the diastereoselectivities were generally moderate in both stages, but the 1,5-diol isomers **29** were generally obtained in >95 % ee.

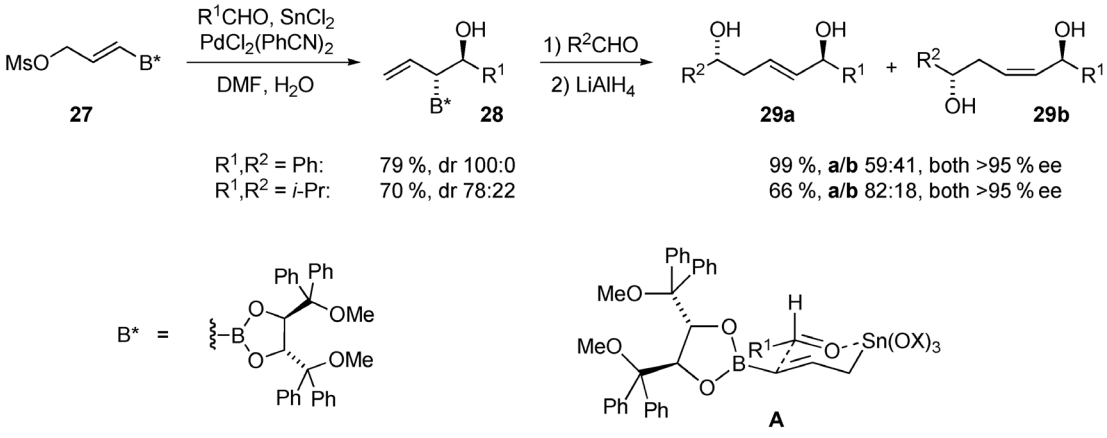


Fig. 11 Tin-mediated double allylboration.

To combine both of the aldehyde additions into a double allylboration sequence, Roush applied Brown's γ-borylallylboronates, prepared from 1,3-propanediol (**30a**) or 1,1,2,2-tetraphenylethane-1,2-diol (**30b**). Conversion of the diol into a cyclic chloroboronic ester by reaction with BCl_3 (Fig. 12a),

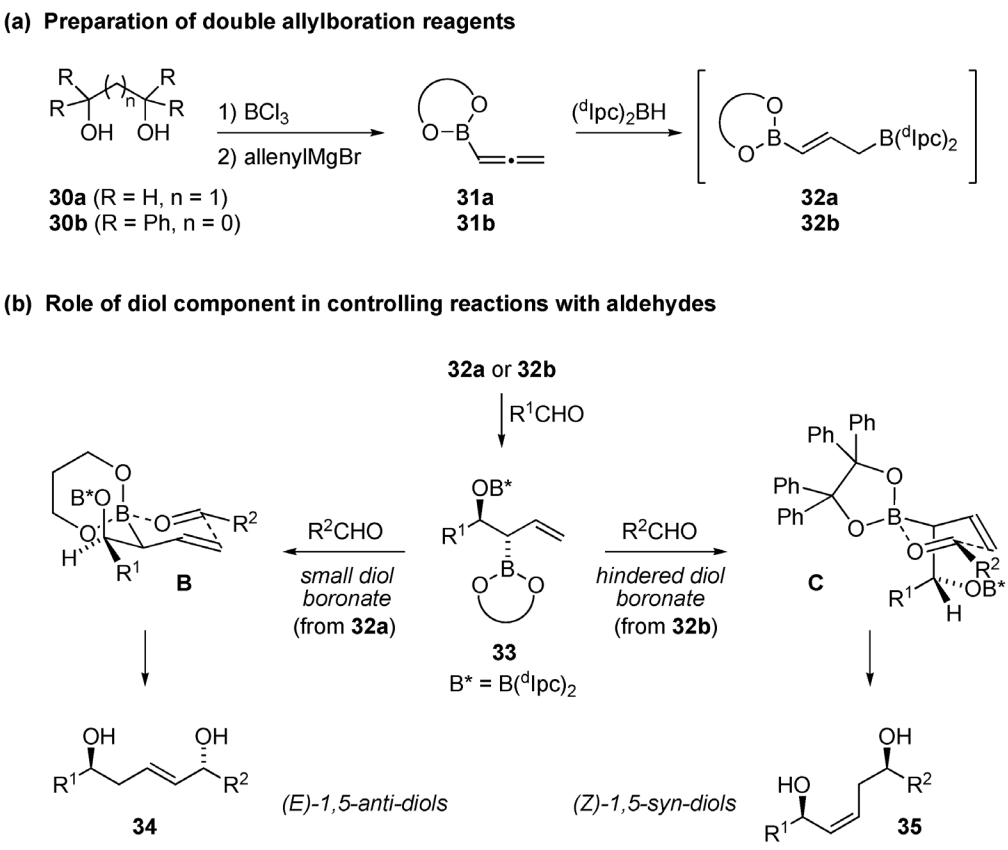
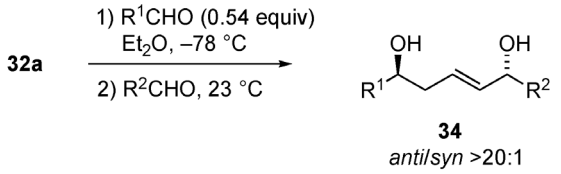


Fig. 12 Double allylboration reagents and modes of stereocontrol.

followed by substitution with allenyl Grignard, afforded allenylboronates **31a** and **31b**. Hydroboration with diisopinocampheylborane then produced the double allylboration reagents **32a** and **32b**. The former had already been shown by Brown to generate intermediate **33** (Fig. 12b) on addition to an aldehyde [31]; in Roush's work, these were then subjected to reaction with a second aldehyde to achieve the bidirectional synthesis of 1,5-diols **34** or **35** [32]. In these reactions, the steric bulk of the diol used in preparing the boronate derivatives **32a** and **32b** is critical to the outcome in the second allylboration: The smaller boronate is presumed to proceed through a chair-equatorial transition state **B** to afford (*E*)-1,5-*anti*-diol **34**, while the larger boronate may enforce an axial orientation of the $R^1CH(OH^*)$ substituent in transition state **C**, proceeding to (*Z*)-*syn*-1,5-diol **35**.

A variety of aliphatic and aromatic aldehyde combinations were employed to clarify the scope of the double allylboration (Fig. 13). The complementary methods led to adduct **34** with >20:1 1,5-*anti* diastereoselection, or to adduct **35** with >14:1 1,5-*syn* diastereoselection. Both variants showed high enantioselectivities, although yields were significantly higher for the route to (*Z*)-1,5-*syn*-diol **35**.

(a) (*E*)-1,5-*anti*-diols

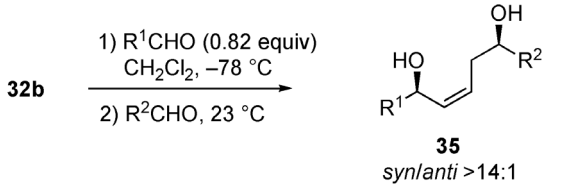


34
anti/*syn* >20:1

R^1	R^2	yield[a] (% ee)
i-Pr	$PhCH_2CH_2$	69 % (92)
$PhCH_2CH_2$	Ph	83 % (89)
C_6H_{11}	Ph	74 % (96)
Ph	*t*-Bu	65 % (95)

[a]Yield based on R^1CHO as limiting reagent

(b) (*Z*)-1,5-*syn*-diols



35
syn/*anti* >14:1

R^1	R^2	yield (% ee)
i-Pr	$PhCH_2CH_2$	95 % (95)
$PhCH_2CH_2$	*i*-Pr	92 % (94)
i-Pr	Ph	88 % (92)
Ph	$PhCH_2CH_2$	95 % (95)

[a]Yield based on R^1CHO as limiting reagent

Fig. 13 Scope and selectivities of double allylborations.

Despite lacking access to the naturally occuring (*E*)-syn isomer, the Roush methodology has been applied to access *syn* relative configuration in a special case where the olefin geometry is unimportant. Roush has applied two successive bidirectional allylborations to the synthesis of an epimer of the C1–C25 portion of amphidinol 3 [33]. In the first coupling, the Brown borylallylborane reagent **32a** coupled with two aldehydes **36** and **37** to furnish (*E*)-1,5-*anti*-diol **38** in 73 % yield with good enantioselectivity (Fig. 14). After several steps to access α,β-unsaturated aldehyde **39**, allylboration using the more hindered reagent **32b** established the C6–C10 *syn* relationship via chiral borane reagent control, and introduction of the C14–C25 aldehyde (not shown) afforded the C10–C14 *syn* relationship through transition state **C** to produce the (*Z*)-1,5-*syn*-diol relationship in adduct **40**. Since the C11–C12 olefin would eventually be reduced, its geometry was unimportant, conveniently allowing the Roush double allylboration to fit the requirements of amphidinol 3. The 1,5,9,13-tetraol **40** was obtained in an overall yield of 14 % over 11 steps from commercial materials. It was subsequently shown by Oishi that the natural product configuration was epimeric at C2 [34].

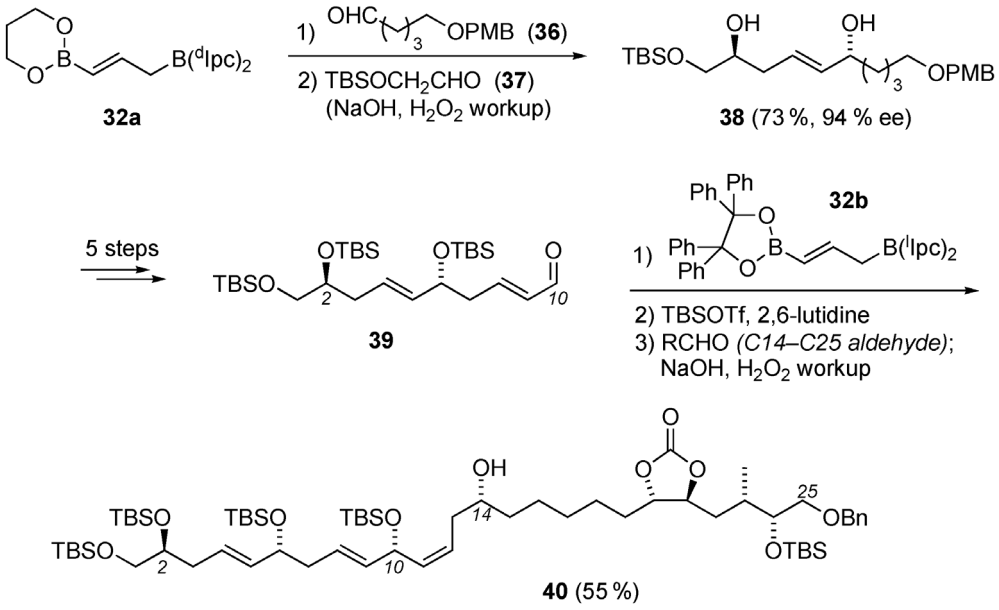


Fig. 14 Application of double allylboration to amphidinol 3.

Roush has developed methods for further functionalization of the alkene moiety produced in the double allylboration in order to access 1,3,5-triol functionality, with application in a route to the C1–C19 fragment of tetrafibricin [35]. A similar bidirectional strategy has also been reported by Morken, who reported Ni-catalyzed borylation for coupling of a diene with two aldehydes, leading to a 1,6-diol [36].

Carbon–carbon bond constructions independent of alcohol functionality

A synthetic strategy which establishes the configuration of each hydroxyl group independently from the C–C coupling reaction would be quite valuable, avoiding the challenges of stereochemical assignments and surmounting the limited accessibility of certain stereochemical relationships in other methods. Ideally, all stereochemical permutations would be easily synthesized with no need for alternative reagents or specialized methods, facilitating applications to total syntheses and stereochemical assignments of a variety of 1,5-polyol natural products.

Julia–Kocienski coupling of subunits from the chiral pool

The isolated stereogenic centers of 1,5-polyols may be derived from the pool of natural chiral materials, such as α-hydroxy acids. In efforts directed toward synthesis of amphidinol 3, Paquette employed this approach; individual chiral alcohols **41** and **42** bearing a single stereogenic center were prepared from enantiopure malic acid. Two efficient Julia–Kocienski couplings were employed to furnish the 1,5,9-triol subunit found in the C2–C10 locale [37]. The first coupling afforded **43** in high yield (Fig. 15), and was followed by a seven-step sequence to prepare sulfone **47** for the second coupling event with C9–C30 aldehyde **48**, affording C1–C30 fragment **49**. This has an undesired configuration at C2 as the natural product configuration was later revised, as discussed below. The sequence involving the 1,5-polyol construction entailed 13 steps from dimethyl (*S*)-malate.

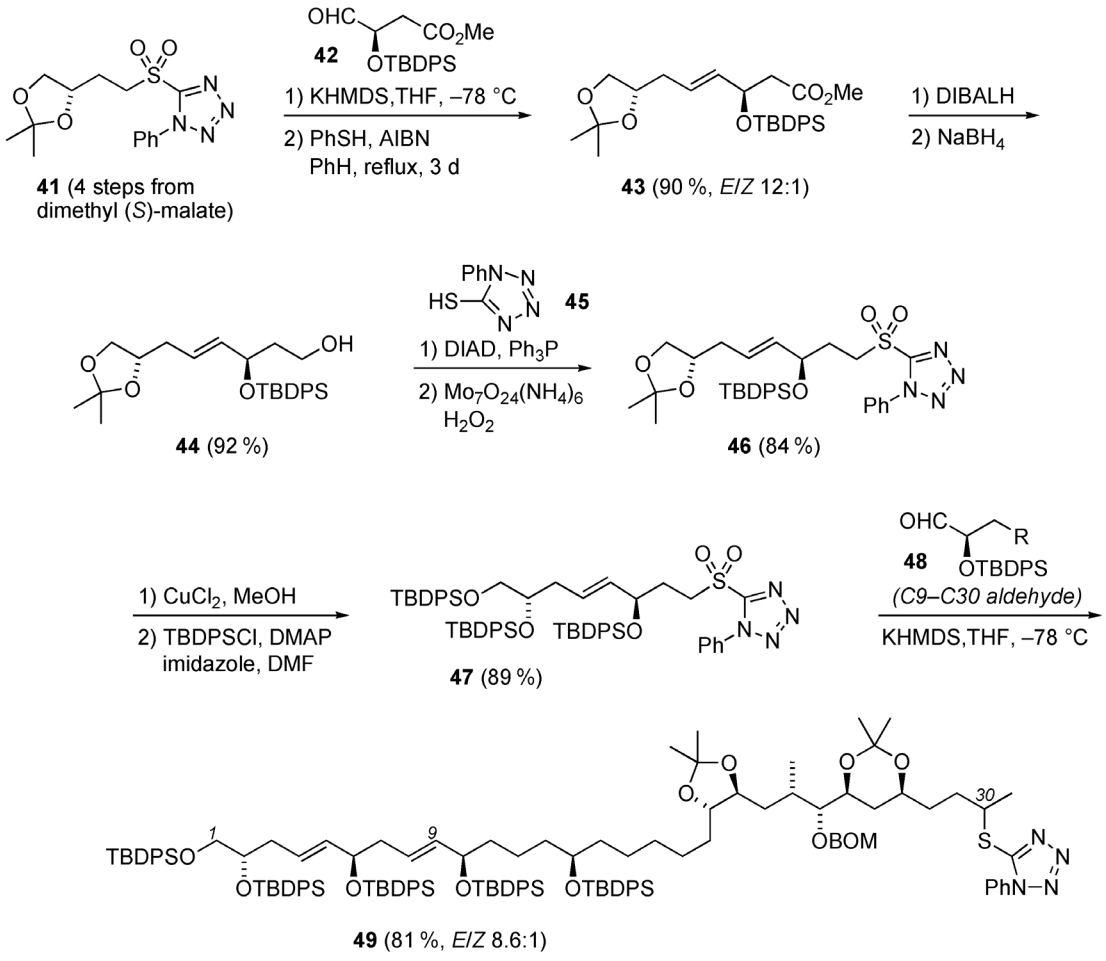


Fig. 15 Paquette approach to amphidinol 3.

In a route toward tetrafibricin, Curran also applied a convergent Julia–Kocienski coupling strategy [38]. Here, in addition to malic acid, another source of asymmetry was epoxide **50** (Fig. 16), obtained via Jacobsen hydrolytic kinetic resolution. From **50** and **51** were obtained coupling partners **52** and **53**, which were linked via Julia–Kocienski coupling to afford 1,5-diol **54**. After oxidation of the sulfide to sulfone, a subsequent Julia–Kocienski coupling with the C21–C30 aldehyde (not shown) afforded the C21–C40 fragment of tetrafibricin **55** in a total of 13 steps for the longest linear sequence from pent-4-en-1-ol.

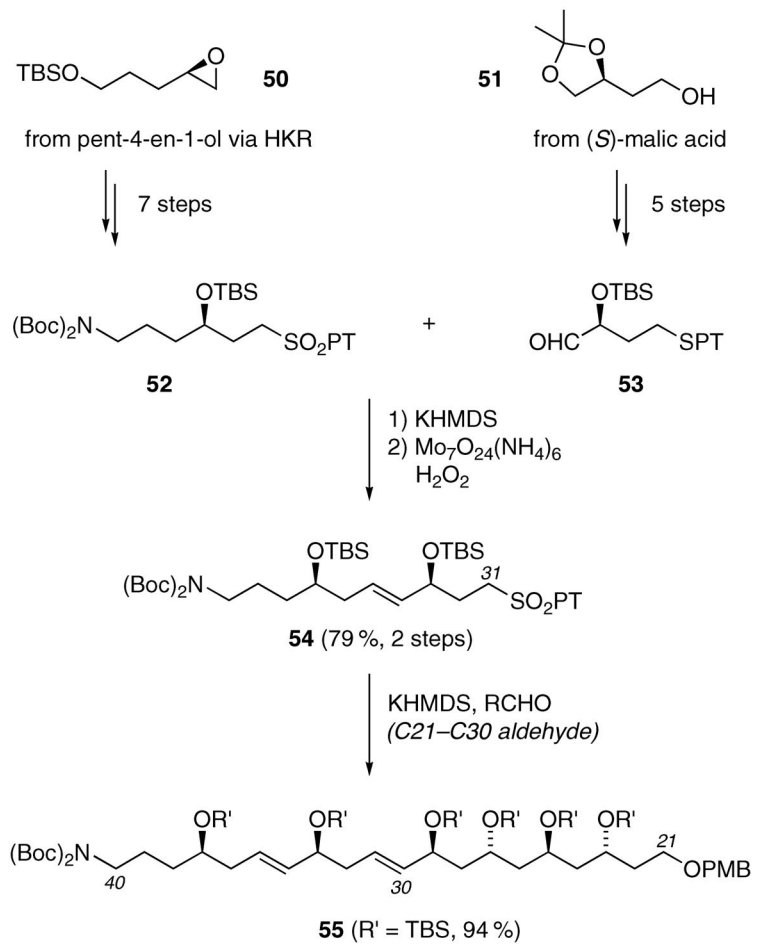


Fig. 16 Curran approach to tetrafibricin.

Iterative configuration-encoded strategy

Recently, we disclosed an alternative strategy which encodes the configuration of each hydroxyl group within a repeating subunit [39]. We hypothesized that an appropriate building block could be designed to enable iterative application of a coupling sequence to build up 1,5-polyols in a programmed manner, not unlike peptide synthesis. For this purpose, we would need a C–C coupling method with well-documented reliability approaching that of peptide bond construction. New coupling chemistry was not the initial aim, but rather, this began as an innovation at the strategy level.

Armed with numerous precedents for efficient couplings exhibiting considerable functional group compatibility, we chose the Julia–Kocienski reaction as the key coupling method [40,41]. For a representative 1,5-polyol bearing intervening alkenes (Fig. 17), Julia–Kocienski disconnection at the alkene bonds according to an iterative strategy suggests a repeat unit bearing sulfone and aldehyde functionalities at the two termini. Oligomer synthesis would then proceed via sequential addition of sulfone building blocks to the aldehyde functionality upon the growing 1,5-polyol chain (Scheme 1). This requires the aldehyde of the building block to be masked, with reactivity orthogonal to both *O*-silyl protection and Julia–Kocienski olefination. This suggested α-silyloxy-γ-sulfononitriles (*R*)-**56** and (*S*)-**56**; after Julia–Kocienski coupling, the nitrile functionality on the growing oligomer could be converted to aldehyde by DIBAL-H reduction.

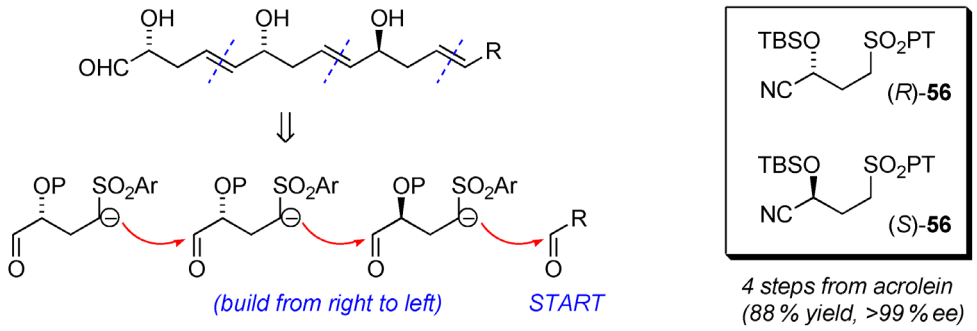


Fig. 17 Disconnection of 1,5-polyol into repeating units.

The sulfononitriles (*R*)-**56** and (*S*)-**56**, prepared in enantiomerically pure form in 4 steps from acrolein, were coupled with a series of α-silyloxyaldehydes, affording high yields of the (*E*)-alkene products **57a**–**f** (Fig. 18). Enantiomeric purity was maintained, despite the potential for metalation adjacent to the nitrile. Both 1,5-*syn*- and 1,5-*anti*-diols **57c** and **57d** were obtained with excellent efficiency. After reduction of **57a** (DIBALH), the resulting aldehyde (91 % yield, not shown) was directly subjected to the coupling with another unit of (*R*)-**56** to afford a 1,5,9-triol **57e**, and 1,5,9,13-tetrol **57f** was obtained in similar fashion.

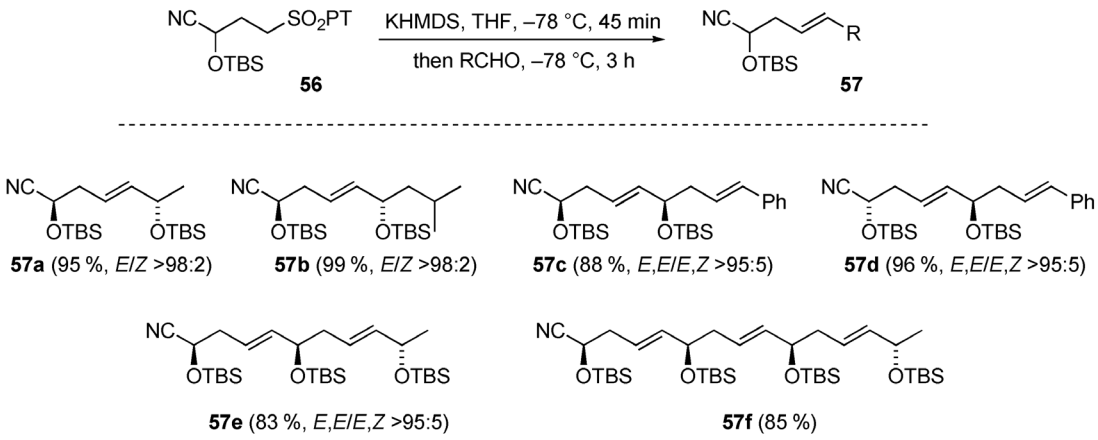


Fig. 18 Examples of Julia–Kocienski couplings of γ-sulfononitrile **56**.

Using the coupling chemistry established above, the preparation of the C27–C40 fragment of tetrafibricin was achieved in a very concise sequence. Two successive iterations of the Julia–Kocienski coupling, beginning with aldehyde **58** (Fig. 19), afforded first *syn*-diol **59**, then the *syn*-*syn*-triol **60**, which was then homologated with a stabilized Wittig reagent to complete the full carbon skeleton and stereochemistry of the C27–C40 fragment of tetrafibricin, with no ambiguity in the relative configurations. Further applications of this efficient assembly of 1,5-polyols are readily envisioned.

In this approach, careful design of the building block with appropriate functionality minimizes the number of steps between coupling events and streamlines the iterative construction process. This would simplify the resurrection of a synthetic route after discovering a mis-assigned configuration. For example, the C2 configuration of amphidinol 3 has been revised *after* Paquette's preparation of compound **49** (Fig. 15); correction of **49** to the natural C2 epimer is nontrivial.

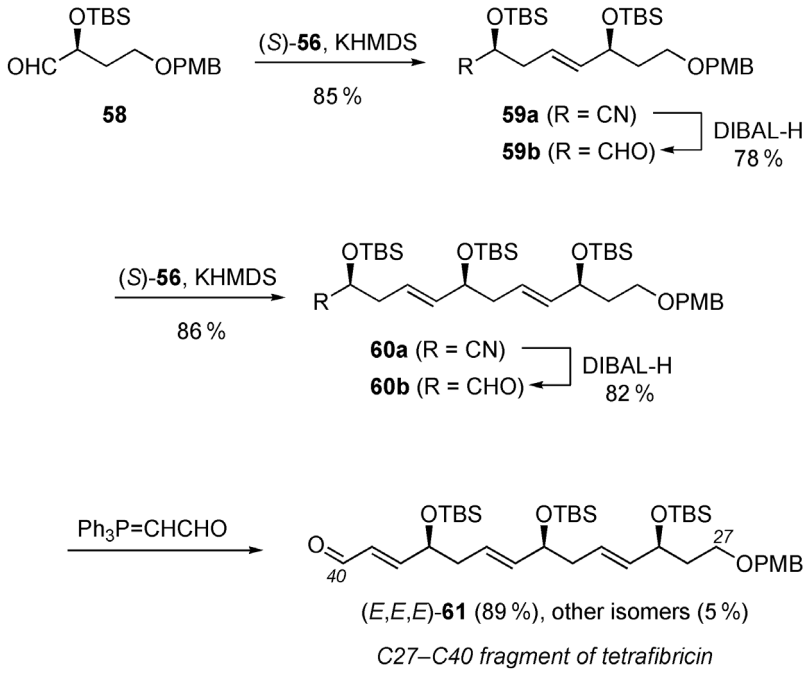


Fig. 19 Iterative configuration-encoded approach to tetrafibricin.

Chemoselective cross-metathesis

In seeking structure-activity correlations of the amphidinols, Oishi and Murata and coworkers synthesized various diastereomers of the C1–C14 fragment of amphidinol 3 [42]. In the course of this work, the configurational assignment at C2 was revised. For the combinatorial synthesis of diastereomers, 1-iodo-1,5-hexadiene-3-ol (**62**, Fig. 20) was constructed and biocatalytically resolved into its silyl-protected antipodes (*R*)-**64** and (*S*)-**64** (6 steps, 27 % yield).

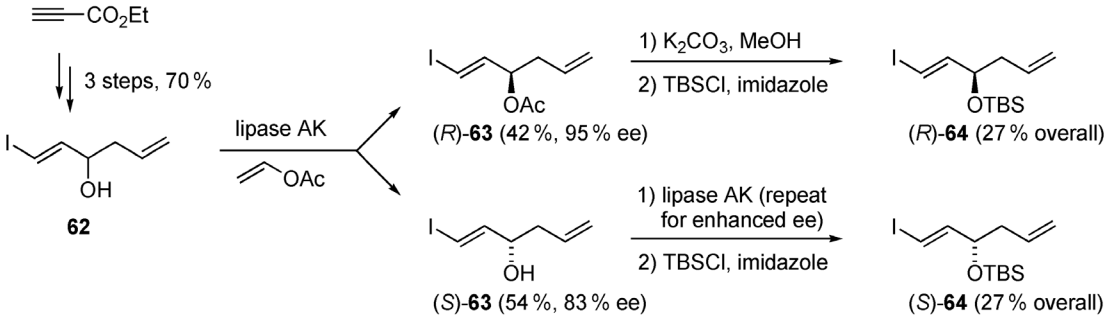


Fig. 20 Preparation of dienes for chemoselective cross-metathesis.

Selective cross-metathesis of (*R*)-**64** and alkene **65**, leaving the iodoalkene intact, afforded alkene **66** (Fig. 21). After Pd-catalyzed reductive deiodination with Bu_3SnH, cross metathesis at the other terminus of **67** with the two enantiomeric alkenes **68a** and **68b** afforded two diastereomeric products **69a** and **69b**. The sequence was repeated with (*S*)-**64** (not shown), affording the C6-epimers. After depro-

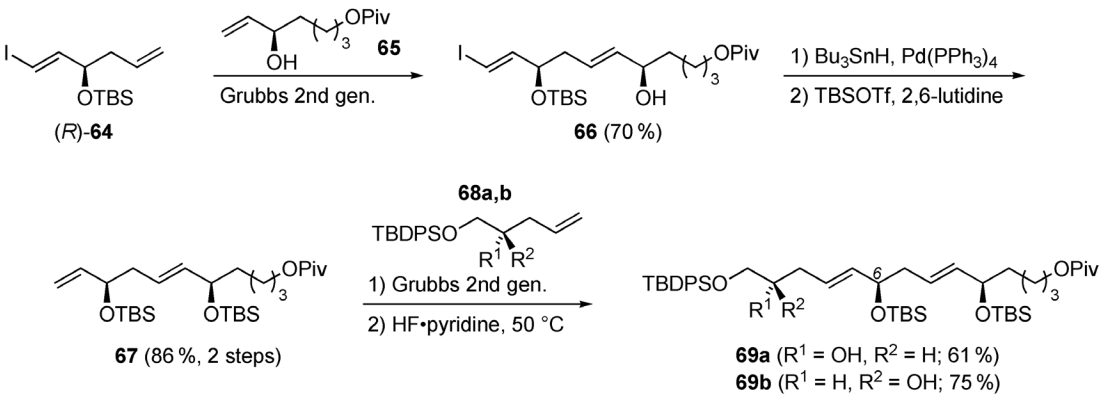


Fig. 21 Chemoselective cross-metathesis for structure revision of amphidinol 3.

tection, analysis of ^{13}C NMR chemical shift differentials identified the *syn-syn* diastereomer **69b** as the best match to the amphidinol 3 spectrum.

CONCLUSION

This review has focused on chemistry designed specifically to access 1,5-polyols. There are a variety of other methods which are potentially applicable to synthesis of 1,5-polyol-containing natural products. While a comprehensive review of these is beyond the scope of this article, a couple of examples are worth noting (Fig. 22). Bäckvall has reported a dynamic kinetic asymmetric transformation which results in enantiopure 1,5-diols bearing additional functionality such as ester or nitrile (e.g., **70**) [43]; this procedure combines kinetic resolution via enzymatic esterification with in situ Ru-catalyzed epimerization of secondary alcohols. Sequential dithiane–epoxide couplings can produce 1,5-diols with great versatility and efficiency, exploiting Brook rearrangement for in situ carbanion relay in a method first introduced by Smith and Boldi [44]. For example, the *anti-anti* 1,5,9-triol relationship in **71** was rapidly established via a three-component coupling [45]. Numerous methods for removal of the dithiane may potentially be applied in order to adapt this anion relay chemistry to 1,5-polyol natural products.

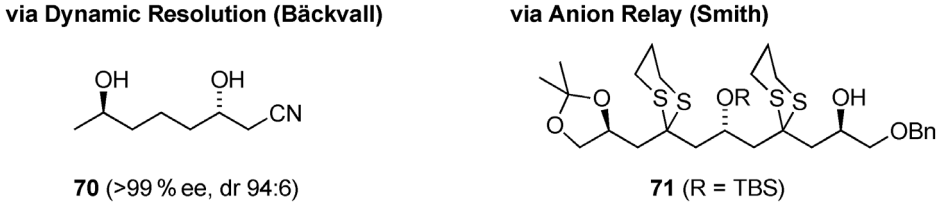


Fig. 22 Other strategies for 1,5-diols.

Further developments along these lines can be expected to further complement the methodology emphasized in this article which has been designed specifically to access 1,5-polyols. A wide range of natural products with various biological activities display 1,5-polyols as part of their structures, uncovering limitations in natural product structure determination and challenging the frontiers of synthetic strategies and methodologies. In the last several years, several lines of inquiry have emerged to address the limitations and challenges inherent to these structures. One can anticipate that the new developments

highlighted here will inspire some creative new insights to further refine the chemical approaches to characterization and synthesis of 1,5-polyols.

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