Polypropionate Synthesis

Functionality Propagation by Alkylative Oxidation of Cross-Conjugated Cycloheptadienyl Sulfones**

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Chemists routinely adopt multiply convergent syntheses that combine stereochemically defined, functionality-rich segments. Yet this strategy alone does not guarantee an efficient synthesis. Rather, the selection of easily scaled segments primarily determines the success of a synthetic project. Catalytic processes for the preparation of enantiopure segments have intrinsic advantages over the stoichiometric use of enantiopure auxiliaries or reagents, as these "high-overhead" strategies generate added time and expense. Even successful syntheses that adopt the latter approach may be limited with respect to potential scale-up.

All syntheses that target a single enantiomer must be related ultimately to one or more substances in the chiral pool.[1] Syntheses that generate their asymmetry by means of a chiral catalyst are highly desirable because one molecule of catalyst is responsible for the creation of a multitude of new chiral progeny.

Over the past five years we have been developing cross-conjugated six- and seven-membered dienyl sulfones to

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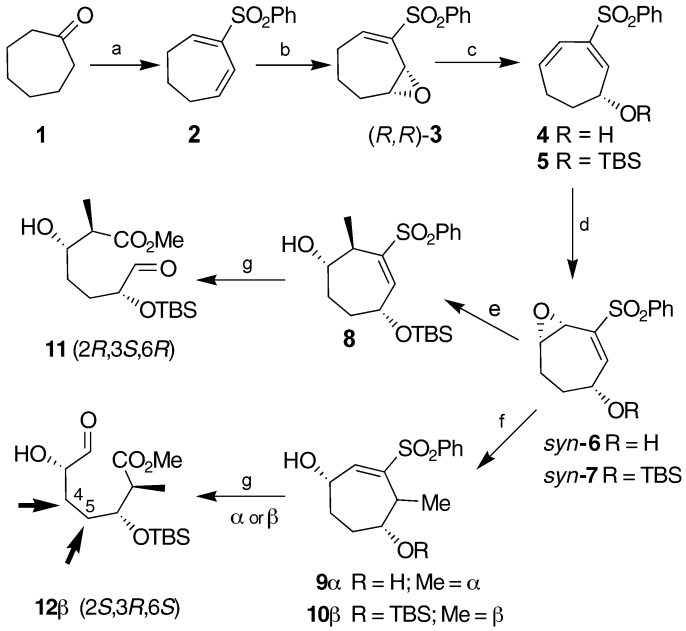
generate a collection of termini-differentiated acyclic arrays bearing two to five stereocenters.[2] Jacobsen asymmetric epoxidation of dienyl sulfone **2** with ca. 1% catalyst loading gives either epoxide (*R*,*R*)-**3** or (*S*,*S*)-**3** in >80% yield and >97% *ee* (Scheme 1).[3,4] When the same protocol was applied to **5**, double stereoselection (>12:1) resulted and the individual isomers of **6** and **7** were isolated as crystalline products in >75% yield and >97% *de*.[5,6]

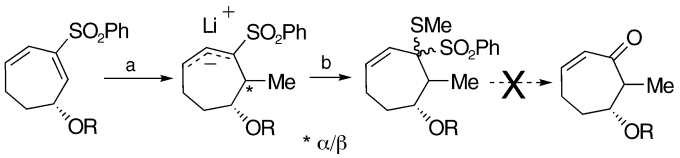
The complementary reactions of trimethylaluminum and dimethylcuprate with silyl ether *syn*-**7** gave alcohols **8** and **10β**, respectively (Scheme 1). Alternatively, when alcohol



Scheme 1. Preparation of acyclic arrays. For reaction conditions, see refs. [3–6]. TBS = *tert*-butyldimethylsilyl.

syn-**6** was treated with methyllithium, methylation occurred on the α-face of the vinyl sulfone, providing product **9α**. While cleavage of the vinyl sulfones **8** and **10β** gave the pseudoenantiomers (enantiomers with protecting group reversal) **11** and **12β**, respectively, it is apparent that further evolution of these compounds in order to access polypropionates with functional groups at C4 and C5 (marked with arrows in compound **12β**, Scheme 1) would not be easily accomplished.

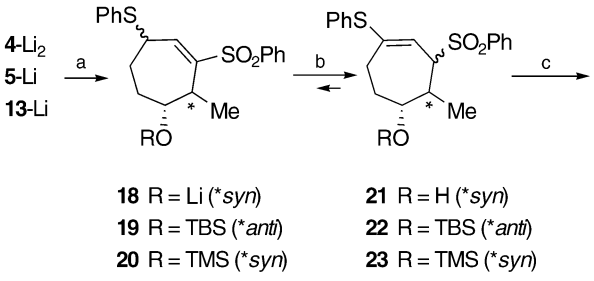
Our new protocol for functionalizing the remaining two centers began by treating compounds **4** and **5** with methyllithium to generate allyl sulfonyl anions **4**-Li_2 and **5**-Li, respectively (Scheme 2). Quenching of these anions at low temperature delivered **14α** and **15β** (as mixtures of sulfone diastereomers) in >85% yield. HPLC analysis revealed that methylation of both intermediates occurred with complementary >10:1 diastereoselectivity. Unfortunately, sulfenylation with dimethyl disulfide or methyl thiolsulfonate gave a complicated mixture of products, which appeared to result from both α- and γ-sulfenylation of the intermediate allylic

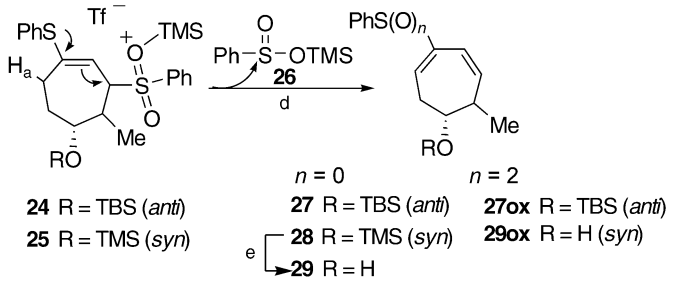


Scheme 2. Initial sulfenylation attempts. a) MeLi, THF, −78°C, b) Me_2S. TMS = trimethylsilyl.

anions. Attempted hydrolysis of these mixtures to enones **16** or **17** was unrewarding.

A subsequent experiment showed that reaction of the allylic anions **4**-Li_2 and **5**-Li with the sterically more demanding diphenyl disulfide suffered regiospecific quenching at the γ-position, initially affording *syn*-**18** and *anti*-**19** as a mixture of sulfide diastereomers (Scheme 3). We monitored the reaction to find that the intermediate vinyl sulfones *syn*-**18** and *anti*-**19** isomerize to allyl sulfones *syn*-**21** and *anti*-**22** under the basic reaction conditions. While ionization of the γ-phenylsulfonyl moiety of acyclic vinyl ethers and vinyl sulfides is known to generate enones and enals, the corresponding reaction for cyclic substrates is far less common.[7,8] After considerable experimentation we found that reaction of allyl sulfones *syn*-**21** and *anti*-**22** with TMS triflate and triethylamine in methylene chloride at reflux effected regiospecific elimination to dienylsulfides *syn*-**29** and *anti*-**27**. This transformation relies upon the unique amphoteric nature of the sulfone moiety.[9] While sulfones are commonly used as electron-withdrawing groups to polarize olefins and inductively stabilize anions, it is the





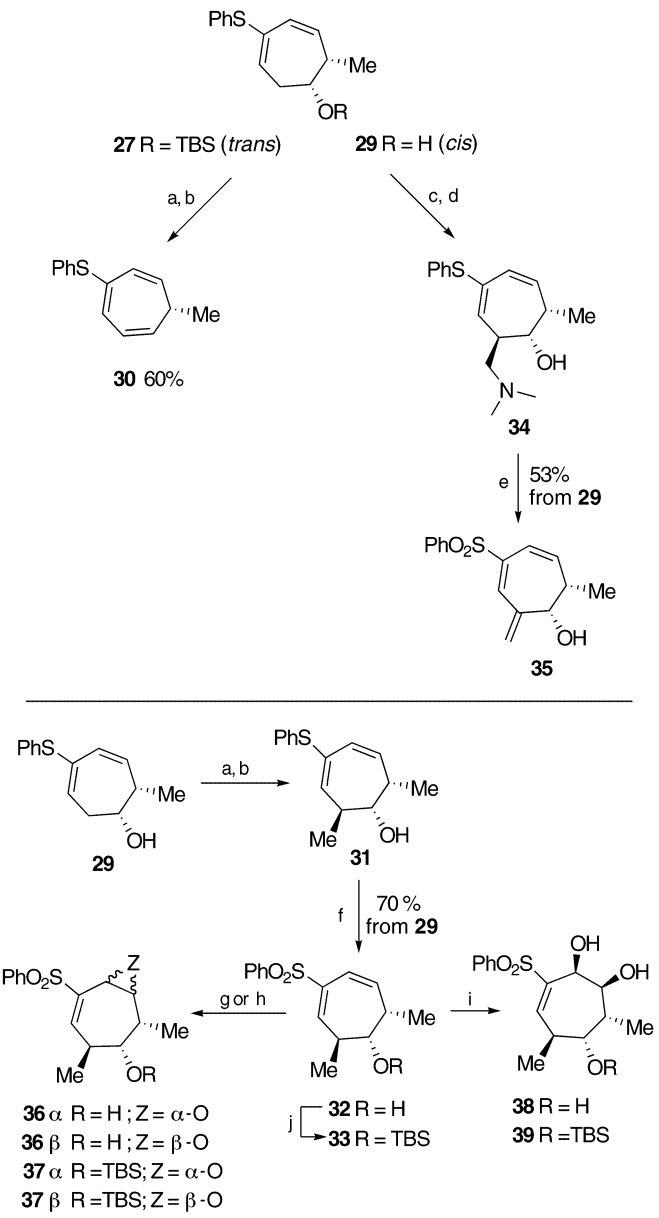
Scheme 3. γ-Sulfenylation and diene transposition. a) 1. MeLi, THF, −78°C, 2. Ph_2S_2; b) warm to RT, c) TMSOTf, Et_3N, CH_2Cl_2, d) reflux. RT = room temperature, Tf = trifluoromethanesulfonyl.

leaving group ability of phenyl sulfinic acid ($pK_a = 7.1$), which enables the lone pair of phenylvinyl sulfide group to expel sulfinate.[10] Presumably the silyl triflate serves to activate the sulfone moiety by forming silyl ethers **24** and **25** reversibly, thereby also preventing readdition of silyl sulfinate **26** once the vinyl thionium ion loses the proximal proton H_a.[11] Compounds **27** and **29** can be oxidized to the key dienyl sulfones **27ox** and **29ox** simply by addition of *m*CPBA to the crude reaction mixture. This two-operation sequence enables stereoselective methylation with simultaneous establishment of a new, transposed diene (Scheme 3). The enantiopure stereodiads **27** and **29** are obtained in five operations from cycloheptanone **1** (overall yields are >40% on a 40-g scale). These key substrates can serve as progenitors to compounds bearing up to five stereocenters, thereby potentially enabling synthesis of an entire collection of enantiopure diastereomers from catalytically generated epoxide **3** (or *ent*-**3**). Elimination of the sulfone moiety from the TMS ether **13** afforded the unexpected *syn*-**28** (Scheme 3). *syn*-Addition directed by OLi groups has been demonstrated on many occasions, but since the oxygen atom in silyloxy groups is generally not thought to be accessible for coordination, it appeared possible that more subtle conformational effects were involved.[12] Conformational modeling shows that in the preferred conformation of the TMS derivative of **19** the silyl ether function is equatorial, which places the TMS group away from the α-face of the vinyl sulfone, providing unencumbered access for conjugate addition.

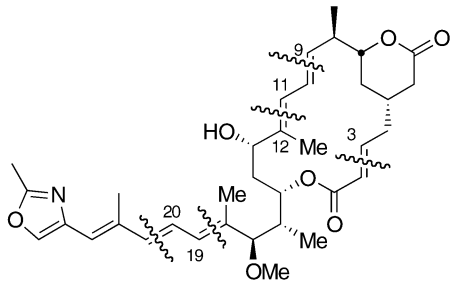
To demonstrate the value of enantiopure *anti* and *syn* stereodiads **27** and **29**, we have explored the preparation of a group of termini-differentiated seven-carbon segments projected to be of use in the synthesis of bioactive polypropionate-derived natural products. Initially, the syntheses of the highest priority targets relied on *syn* intermediates **21**, **23**, and **29** as starting materials; however, recent (unpublished) results indicate that the *anti* intermediates **19**, **22**, and **27** are equally useful (Scheme 4). Further functionalization of these substrates gives cycloheptenyl sulfones, which afford termini-differentiated aldehyde segments after oxidative cleavage.[13] For example, direct methylation of the dianion of alcohol **29** produces dienylsulfide **31** (Scheme 4, structure confirmed by X-ray diffraction analysis).[14] Oxidation of **31** provides dienyl sulfone **32** in 70% overall yield from **29**. The necessity of "protecting" the hydroxy group as an oxido anion is apparent from attempted alkylation of **27**, which suffers β-elimination to give trienylsulfide **30**, as expected. Treatment of the dianion of **29** with Eschenmoser's salt ($H_2C{=}N(CH_3)_2I$) gives amine **34**, which undergoes smooth trisoxidation to afford trienylsulfone **35** upon exposure to excess *m*CPBA.[15] Oxidation of dienyl sulfones **32** and **33** with *m*CPBA was unselective, but **36**–**39** could be obtained with high diastereoselectivity when molybdenum, manganese, and osmium complexes were used to catalyze the oxidizations (Scheme 4).

Rhizoxin, the bisepoxide of rhizoxin D (**40**, Scheme 5), was isolated by Okuda et al. from rice seedlings infected with *Rhizopus chinensis*.[16–18] Eight total and/or formal syntheses of rhizoxin (four via rhizoxin D) have been reported.[19]

Our strategy for the synthesis of rhizoxin D (**40**) was to develop a one- or two-pot method for sequentially linking a pair of carbonyl compounds through a two-carbon unit that would be the the C–C single bond in a butadienyl unit in the final compound (Scheme 5). In the event, acylation of *ent*-**21** followed by hydrolysis gave β-sulfonyl ketone **41**, which was then transformed into silyl dienyl ether **42**.[20] Addition of singlet oxygen to **42** effected stereospecific formation of stable bicyclic peroxide **43** (the OTIPS group was necessary for selective addition (>95%) to the β-face).[21] Epoxidation of silyl enol ether **43** with dimethyl dioxirane (DMDO)

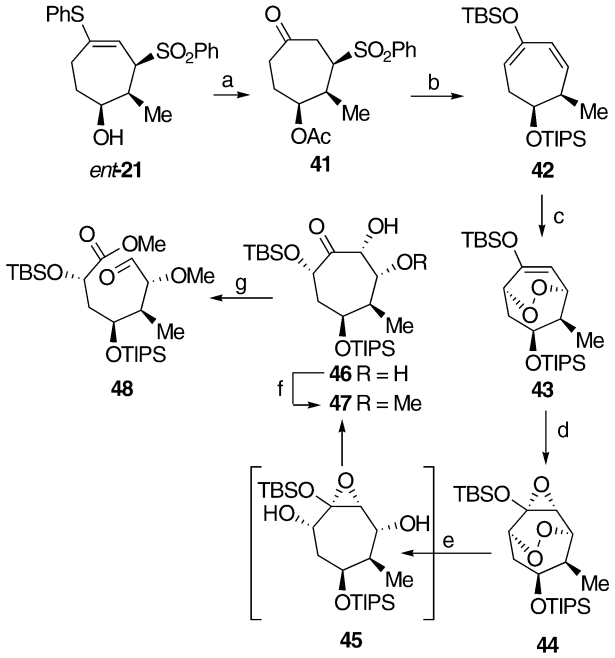


Scheme 4. Preparation of stereopentad progenitors. a) 2.2 equiv *n*BuLi, THF −78°C to −7°C; b) 5 equiv MeI, −90° to −50°C; c) 2.2 equiv *n*BuLi, THF, −78°C to −5°C, 90 min; d) 2.5 equiv $H_2C{=}N(CH_3)_2I$, THF, −70°C to 0°C, 1.5 h; e) 4 equiv *m*CPBA, CH_2Cl_2, 25°C, 1 h; f) 2.2 equiv *m*CPBA, CH_2Cl_2, 25°C, 30 min; g) TBHP, 5%[$Mo(CO)_6$], 88%, >15:1 α/β; h) 10% [(*R*,*R*)-Mn(salen)Cl], H_2O_2, 1 equiv NH_4OAc, 83%, <1:20 α/β; i) cat. OsO_4, >80%, single diastereomer. j) 1.2 equiv TBSOTf, 2 equiv lutidine, CH_2Cl_2, 25°C, 2 h. *m*CPBA = *meta*-chloroperbenzoic acid, TBHP = *tert*-butyl hydroperoxide.



40: rhizoxin D

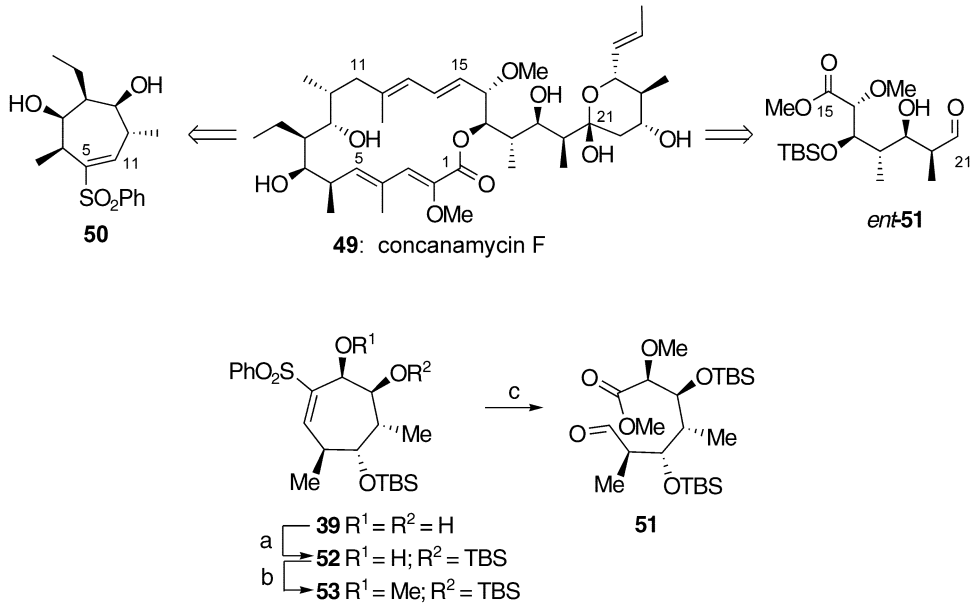
Scheme 5. Synthesis of C12–C18 of rhizoxin D (**40**). a) 1. Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 0.5 h, 2. $HgCl_2$, TMSCl, NaI, H_2O, CH_3CN, RT, 16 h, 85% from *ent*-**21**; b) 1. DBU, toluene, RT, 2 h, 2. TBDMSOTf, *i*Pr_2EtN, CH_2Cl_2, RT, 1 h, 3. KOH, MeOH, RT, 10 min, 4. TIPSOTf, Et_3N, CH_2Cl_2, RT, 1 h, 68% overall from **41**; c) $^1O_2$, TPP, CH_2Cl_2, −78 °C, 30 min; d) DMDO, CH_2Cl_2, 0 °C, 2 h; e) H_2, Pd/C, $NaHCO_3$, MeOH, RT, 20 min, 53% from 42; f) cat. Me_2SnCl_2, MeOTf, K_2CO_3, CH_2Cl_2, 17–20 °C, 8 h, 88%; g) $Pb(OAc)_4$, pyridine, MeOH/C_6H_6, 0 °C, 1.5 h, 85%. DMAP = dimethylaminopyridine, DMDO = dimethyldioxirane, TBDMS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine.



provided the isolable α-epoxysilyl ether **44**.[22] Hydrogenation of **44** proceeded, as desired, with silicon migration to give diol **46** in 83% yield. Methylation of the keto-diol **46** absolutely required the dimethyltin chloride catalyst to effect regiospecific O-methylation at the more electron-rich distal hydroxy group, rapidly providing ketone **47** in high yield. (This is the first example for a 1-keto-2,3-diol).[23] Methylation or silylation without the tin catalyst was very slow and strongly favored functionalization of the opposite hydroxy group. Cleavage of **47** in methanol with lead tetraacetate completed the synthesis of enantiopure aldehyde ester **48** (Scheme 5).[24]

Concanamycin F (**49**), also called concanolide A, is the most intricate parent aglycone of a series of related macrocyclic lactones bearing considerable structural homology (Scheme 6). This family also includes biafilomycin A and hygrolidin.[25–27] Concanamycin F (**49**) has been synthesized by the groups of Paterson in 2000 and Toshima in 2001 in 44 and 53 steps, respectively.[28,29]

Our analysis of concanamycin F (**49**) envisages the construction of a pair of stereopentads derived from vinyl sulfones **50** and **53** (Scheme 6). While synthesis of compound **50** is not yet complete, we have been able to make good use of the diol **39** for generation of stereopentad **51**. Silylation of **39**



Scheme 6. Synthesis of the *ent*-C15–C21 fragment of concanomycin F (**49**). a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h, 99%; b) KOH/MeI/DMSO, 25 °C, 5 min, 94%; c) O_3, CH_2Cl_2/MeOH (1:2), $NaHCO_3$, −78 °C, 15 min, then PPh_3, 92%.

provided vinyl sulfone **52** in near-quantitative yield, which was directly methylated in DMSO to give vinyl sulfone **53** in 94% yield. Ozonolysis of **53** afforded ester aldehyde **51** in 92% yield. Compound **51** is the enantiomer of the C15–C21 stereopentad of concanamycin F (**49**, Scheme 6).

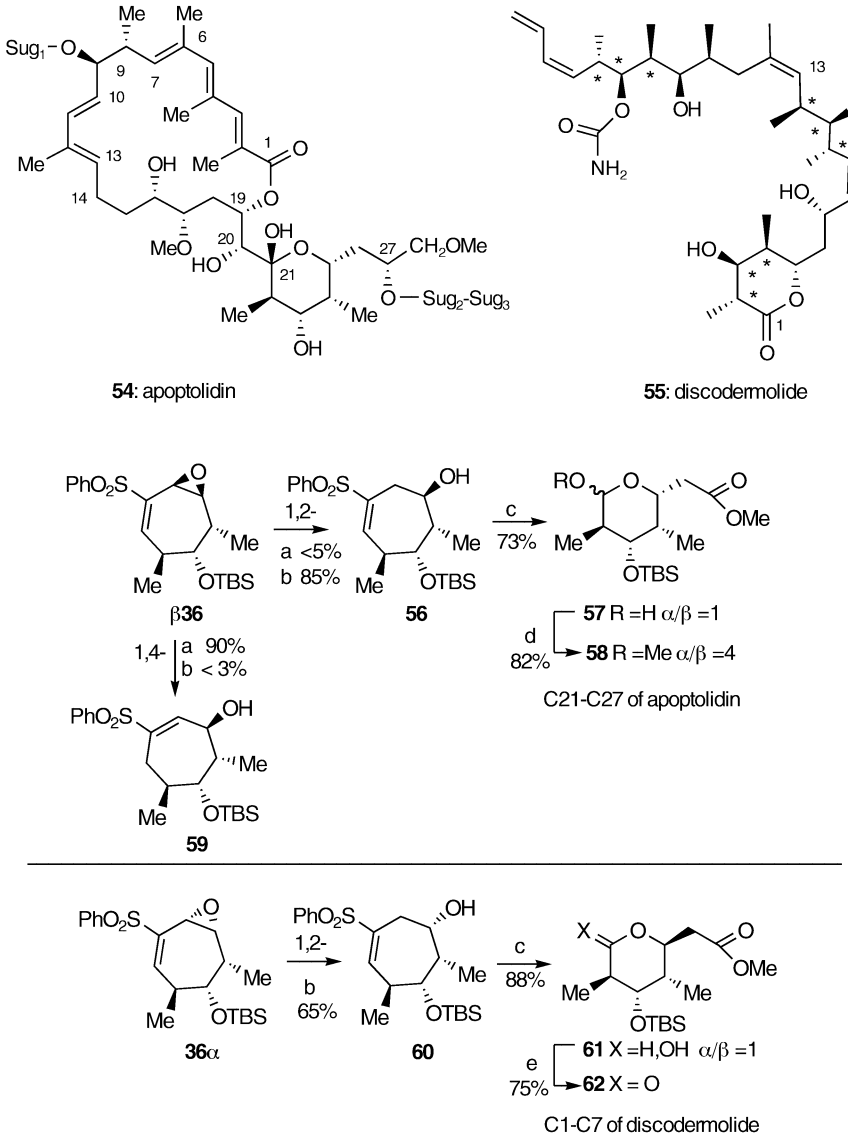
Apoptolidin (**54**) is a 20-membered macrocyclic lactone isolated from *Norcardiopsis* sp. (Scheme 7).[30] "Apoptolidin induced apoptotic cell death in rat gila cells transformed with the E1A oncogene at 11 ng mL^{-1} but did not cause cell death in normal gila cells or fibroblasts at >100 g mL^{-1}."[30f–g,31] The group of K. C. Nicolaou provided the first total synthesis of apoptolidin (**54**) in ca. 90 steps.[30f–g,31]

Discodermolide (**55**), like paclitaxel (taxol), has been shown to stabilize microtubules but is more potent and inhibits the growth of paclitaxel-resistant cells.[32,33] The material is in high demand for clinical trials, and synthesis is the only viable source. Five total syntheses and related synthetic approaches all based on aldol-based stereoselection strategies with acyclic substrates have been reported which begin with enantiopure 3-hydroxy 2-methylpropionate.[34] The second-generation synthesis by Smith et al. utilized a total of 34 steps with a linear supply line of only 24 operations and provided the first gram of (+)-discodermolide (**55**). The overall yield was 6%.[35]

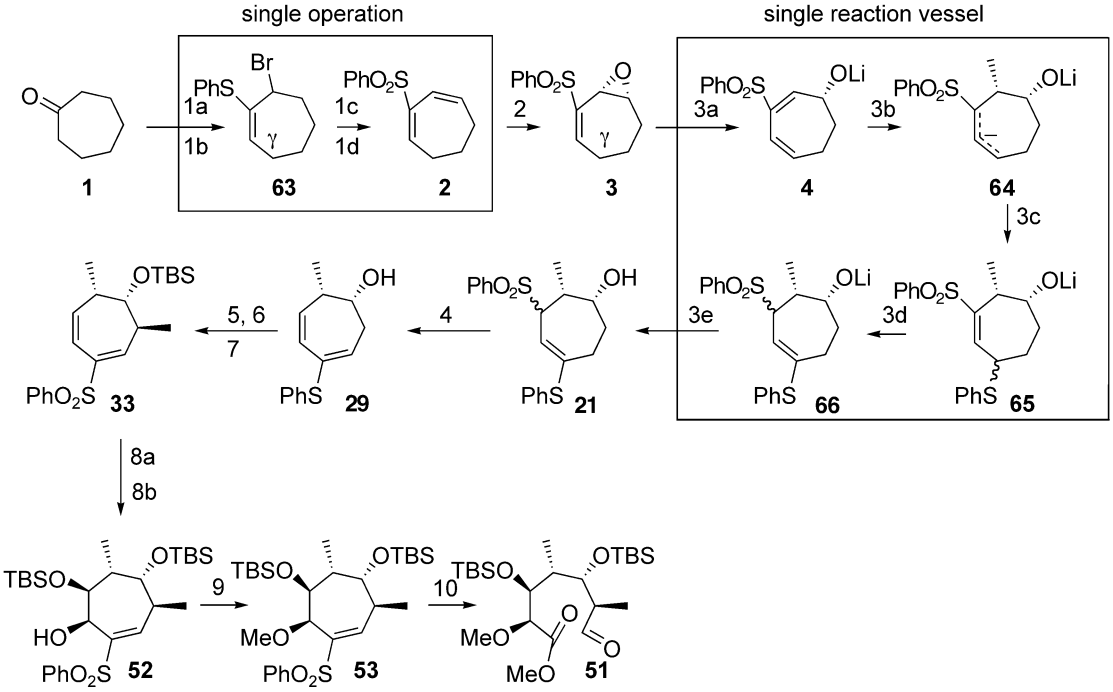
Our approach to apoptolidin (**54**) and discodermolide (**55**) makes use of the central stereotriads **32** and **33** as precursors to the key epoxides **36α** and **36β**, respectively. Preparation of the C21–C27 segment of apoptolidin (**54**) is accomplished from epoxide **36β** beginning with selective 1,2-reduction with DIBAL-H to provide alcohol **56**. The complementary 1,4-reduction to produce alcohol **59** can be achieved selectively with borane–THF. Completing the synthesis of the apoptolidin segment simply requires ozonolysis of **56** to give a δ-hydroxy aldehyde intermediate, which cyclizes to hemiacetal **57**. Protection of **57** as acetal **58** gave a 4:1 mixture of anomers, which can be separated easily by chromatography (Scheme 7). Acetal **58** is also the C20–26 segment of phorboxazole (not shown).[36]

In parallel fashion to the synthesis of **58**, we prepared the C1–C7 segment of discodermolide (**55**) by employing epoxide **36α** for 1,2-reduction with DIBAL-H. This afforded alcohol **60** in 65% yield. Subsequent ozonolysis afforded hemiacetal **61**, which smoothly underwent PDC oxidation to give lactone ester **62** in 75% yield (Scheme 7).

The lessons that Trost is teaching about atom economy prompt questions of the strategic validity of the dienyl sulfone methodology since sulfur is not found in the product.[37] We can address this point by briefly examining our synthesis of segment **51**, which begins with cycloheptanone (**1**) The sulfur atoms used in this strategy are essential for the synthesis (Scheme 8). The initial vinyl sulfide activates the olefin for bromination in operation 1b. The sulfone formed by oxidization (operation 1c) activates the allylic position for base-promoted 1,4-elimination in operation 1d to yield dienyl sulfone **2**. The electrophilic double bond in the cross-conjugated dienyl sulfone **2** is flanked by a sterically demanding sp^3-hybridized sulfone moiety, which has been shown to be crucial for the high enantiomeric excess obtained in the Jacobsen epoxidation (operation 2).[5] Once again, in



Scheme 7. Preparation of C21–C27 of apoptolidin (**54**) and C1–C7 of discodermolide (**55**). a) 1.6 equiv BH_3·THF, THF, 0°C warming to 25°C, 12 h; b) 1.5 equiv DIBAL-H, −78°C; c) O_3, CH_2Cl_2/MeOH (1:2), $NaHCO_3$, −78°C, 15 min; d) Ag_2O, MeI, CH_3CN, reflux, 3 h; e) 5 equiv PDC, CH_2Cl_2, 25°C, 10 h. DIBAL-H = diisobutylaluminum hydride.



Scheme 8. Evaluation of the contribution of sulfur functional groups in the synthesis of ester aldehyde **51** (for a discussion of the operations refer to the text).

a 1,4-elimination (operation 3a) epoxy vinyl sulfone **3** is transformed into intermediate **4**, which undergoes conjugate addition with methyllithium (operation 3b) to provide the allyl sulfonyl anion **64**, which is directly sulfenylated to **65** (operation 3c). Vinyl sulfone **65** equilibrates to **66** in operation 3d and is finally protonated to **21** in operation 3e. Vinylogous dioxythioacetal **21** undergoes vinyl-sulfide-promoted loss of sulfinic acid in operation 4 to afford cross-conjugated dienyl sulfide **29** after workup. Methylation of the dianion of **29** (operation 5), followed by oxidation of sulfide, and alcohol protection gives **33**. Catalytic substrate-based dihydroxylation followed by regiospecific silylation of the more available hydroxy group generates alcohol **52**, which undergoes O-methylation to **53**, and finally, cleavage of the vinyl sulfone (operation 10) to deliver the target stereopentad **51**.

In the course of this synthesis we have introduced and ultimately removed two sulfur moieties. While this may be negative from the viewpoint of atom economy, the groups are absolutely essential to the chemistry. The synthesis of **51** via a dienyl sulfone exploits a chiral catalyst, and all further stereochemistry is related to the newly created stereocenter(s). This creates less costly "overhead" than a synthesis employing an enantiopure starting material and then twice using either a chiral reagent or a chiral auxiliary. This difference can be especially significant when reactions are scaled up, since the cost of auxiliaries or reagents cost, recycling, and/or disposal all strongly impact production cost.

In conclusion, it has been shown that a new alkylative sulfenylation–desulfonylation reaction efficiently transforms enantiopure epoxyvinyl sulfone **3** to *syn* and *anti* dienylsulfides **29** and **27** in two operations. This reaction permits the stereospecific functionalization of all seven carbons of a cycloheptyl system, ultimately providing seven-carbon termini-differentiated polypropionate stereotetrads and stereopentads appropriate for natural product synthesis.

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Keywords: epoxidation · polypropionates · stereoselectivity · sulfones · synthetic methods

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[10] Phenyl sulfones are about 10^5 times less reactive than chloride as leaving groups. A. K. Colter, R. E. Miller, *J. Org. Chem.* **1971**, *36*, 1898 – 1903. β-Sulfonyl ketones, homoallyl, homopropargyl, and homobenzyl sulfones, having an allylically activated C–H π bond or α-heteroatom-substituted sulfones are competent leaving groups. The reaction shown in Scheme 3 is a vinylogous example of the latter case.

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