Organic Syntheses

Discussion Addendum for: Preparation of (*R*,*R*)-1,2:4,5-Diepoxypentane

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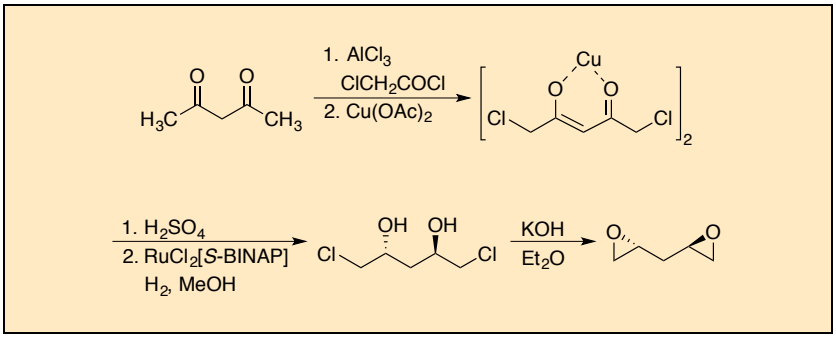
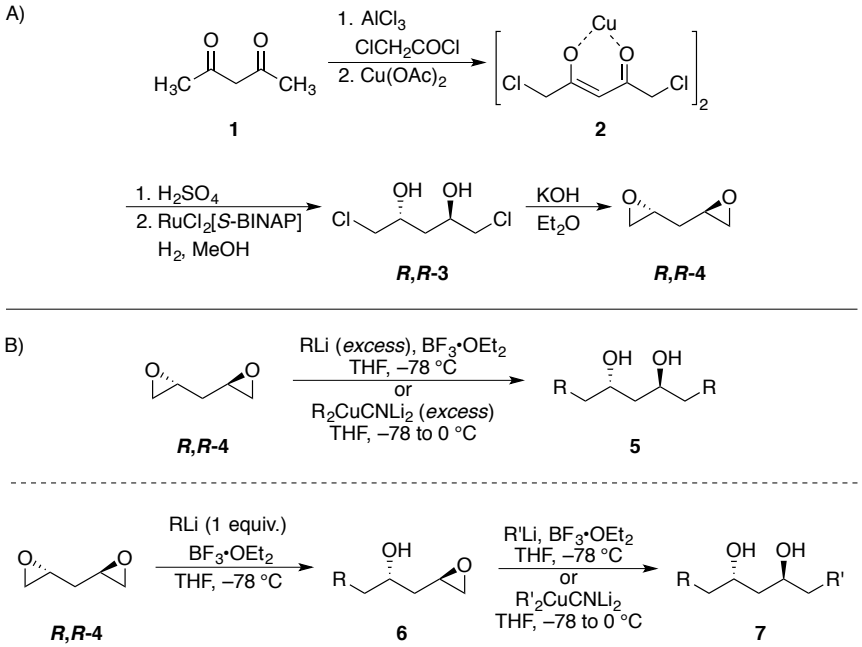


Enantiopure 1,2:4,5-diepoxypentanes and their dichlorodiol precursors have proven to be useful intermediates in the synthesis of complex natural products. Since 2000, the *Organic Syntheses* article[2] and the primary reference[3] have been cited over 100 times. While these C2 symmetric bis-electrophiles have most commonly been employed in the installation of *anti*-1,3 diol motifs, they have also recently been leveraged in development of new methods and utilized in the synthesis of chiral building blocks. These applications, as well as the use of these materials in the context of the total synthesis of complex natural products, will be discussed.

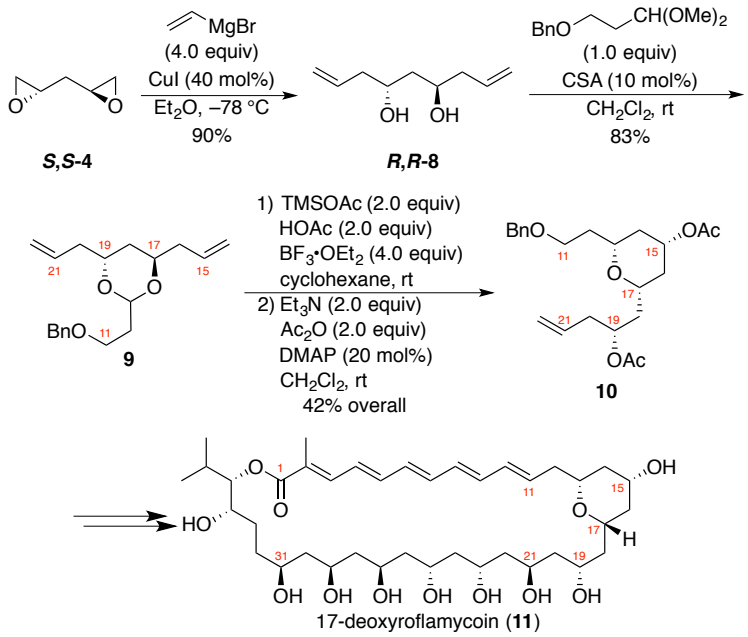
The original procedure (Scheme 1A) utilizes a reversible acyl transfer reaction of acetylacetone (**1**) using aluminum trichloride and chloroacetyl chloride.[4] The reaction is driven forward through removal of acetyl chloride by distillation and the resulting dichlorodione is isolated (57–58% yield) as

copper complex **2**. The dione is then liberated from the metal under acidic conditions and subjected to Noyori asymmetric hydrogenation[5–9] under high pressure to give dichlorodiol ***R,R*-3** in 40% yield after recrystallization, which undergoes double cyclization under basic conditions to form bis-epoxide ***R,R*-4** (92% yield; >97% ee). The initial report also demonstrates the title compound's utility in synthesizing 1,3-diol motifs (Scheme 1B).[3] Treatment of bis-epoxide **4** with unhindered nucleophiles affords symmetric *anti*-1,3-diols (**5**) in high yields (61–96%). Controlled monoadditions to bis-epoxide **4** using organolithium species at low temperatures in the presence of BF_3•OEt_2 [10] provide epoxy alcohols (**6**) in good yields (56–79%). These epoxy alcohols can be efficiently converted to differentially substituted *anti*-1,3-diols (**7**) upon treatment with a second nuceophile (63–89% yields), or converted to *syn*-1,3-diols through Mitsunobu inversion[11,12] of the free hydroxyl. Early applications of these *anti*-1,3-diol strategies are highlighted in the synthesis of 17-deoxyroflamycoin[13] and roflamycoin.[14]



Scheme 1. Synthesis of (*R,R*)-1,2:4,5-diepoxypentane; double addition and sequential addition to the bis-epoxide with organometallic nucleophiles

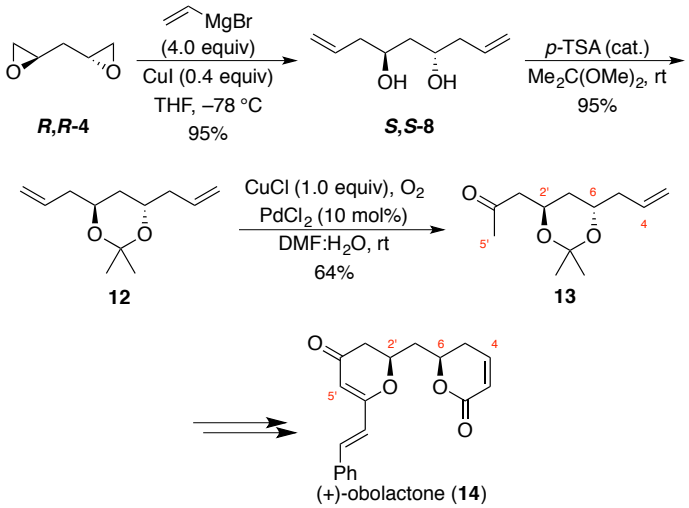
In Rychnovsky and co-worker's synthesis of 17-deoxyroflamycoin (**11**, Scheme 2), the ethereal tetrahydropyran (THP) ring provided a natural application of the double addition strategy.[13] Treatment of bis-epoxide ***S,S*-4** with an excess of vinylmagnesium bromide in the presence of a catalytic amount of CuI at –78 °C provided bis-homoallylic diol ***R,R*-8** in 90% yield. Diol **8** underwent an acid-catalyzed transacetalization to afford high yields of acetal **9**. The C2 symmetric acetal was then poised to undergo an intramolecular Prins cyclization[15]/desymmetrization with concomitant acetate trapping to provide THP-diacetate **10** in 42% overall yield. This noteworthy sequence leveraged the symmetry of the bis-epoxide to correctly install the 2,4,6-*cis*-THP stereochemistry, as well as the C19 stereocenter. The bis-homoallylic diol (**8**) generated by this double addition strategy has proven useful in a number of other synthetic programs.



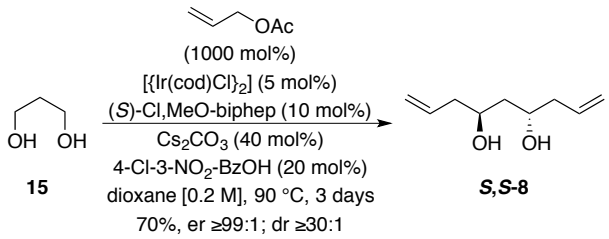
Scheme 2. Rychnovsky's synthesis of 17-deoxyroflamycoin

The synthesis of (+)-obolactone (**14**, Scheme 3) by Brückner and Walleser employed the same conditions from the synthesis of 17-deoxyroflamycoin to

transform bis-epoxide ***R,R*-4** to bis-homoallylic diol ***S,S*-8**.[16] Diol **8** was then protected using 2,2-dimethoxypropane under acidic conditions to provide acetonide **12** in 95% yield. One of the alkene functional groups of the C2-symmetric acetal underwent a subsequent symmetry-breaking Wacker oxidation.[17–19] Treatment of acetonide **12** with catalytic $PdCl_2$ under an atmosphere of oxygen using CuCl as the stoichiometric oxidant afforded a 64% yield of methyl ketone **13**, with over-oxidation to the diketone also observed (18% yield). The methyl ketone functionality of **13** was critical for the installation of the dihydro-γ-pyranone moiety in the natural product, while the *syn*-orientation of the C–O bonds was achieved through Mitsunobu inversion of the lactone stereocenter. Brückner and Walleser specifically mention that while Krische and co-workers have reported on an impressive single-step procedure for the catalytic enantioselective synthesis of bis-homoallylic diol (***S,S*-4**) from 1,3-propanediol (Scheme 4),[20] and have used this method extensively in the synthesis of polyketide natural products,[21,22] the high cost of catalyst and ligand precluded their use on scale in this case.

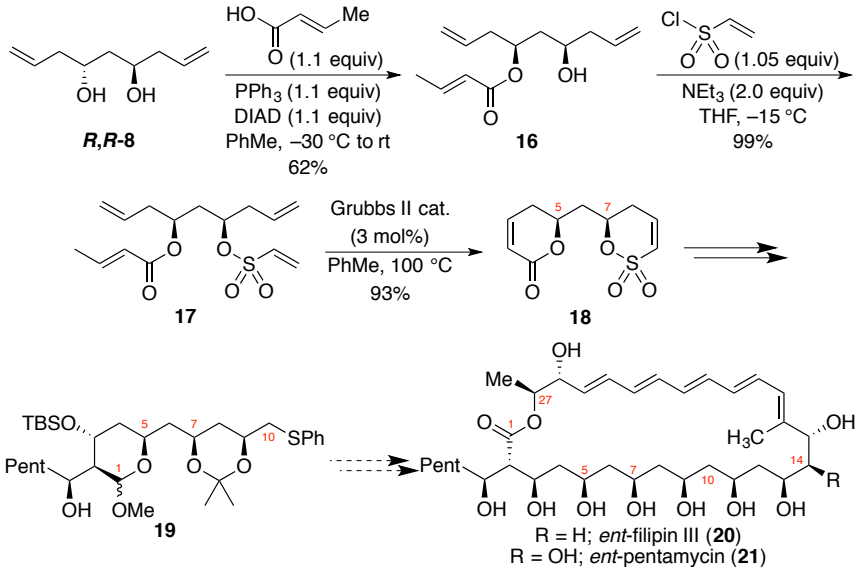


Scheme 3. Brückner and Walleser's synthesis of (+)-obolactone



Scheme 4. Krische's one-step synthesis of *S,S*-8.

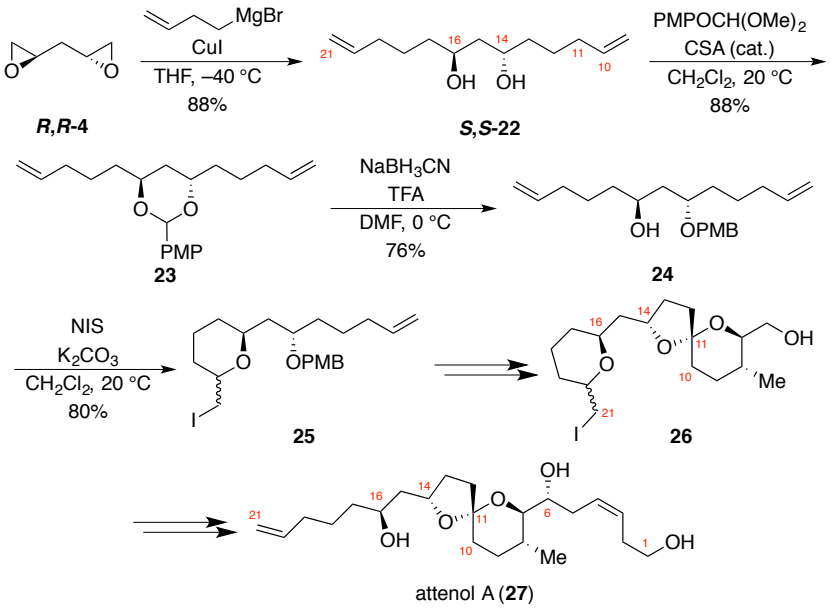
Brückner and Walleser also used bis-homoallylic diol ***R,R*-8** as the starting point for their work on a unified synthetic strategy toward *ent*-filipin III and *ent*-pentamycin (**20** & **21**), as shown in Scheme 5.[23] Symmetry-breaking Mitsunobu inversion of bis-homoallylic diol ***R,R*-8** was achieved by treatment with crotonic acid, triphenyl phosphine and diisopropyl azodicarboxylate (DIAD) in toluene to give monoester **16** in 62% yield. The free hydroxyl group of **16** was then converted to sulfonate ester **17** in high yield using vinylsulfonyl chloride and triethylamine. Tetraene **17** was subjected to double ring closing metathesis using Grubbs II catalyst[24] in toluene at 100 °C to afford bicyclic intermediate **18**. This bicyclic lactone was



Scheme 5. Brückner and Walleser's approach to *ent*-filipin and *ent*-pentamycin

further elaborated to acetonide **19** constituting a synthesis of the C1–C10 or "southwestern" portion of the polyketides.

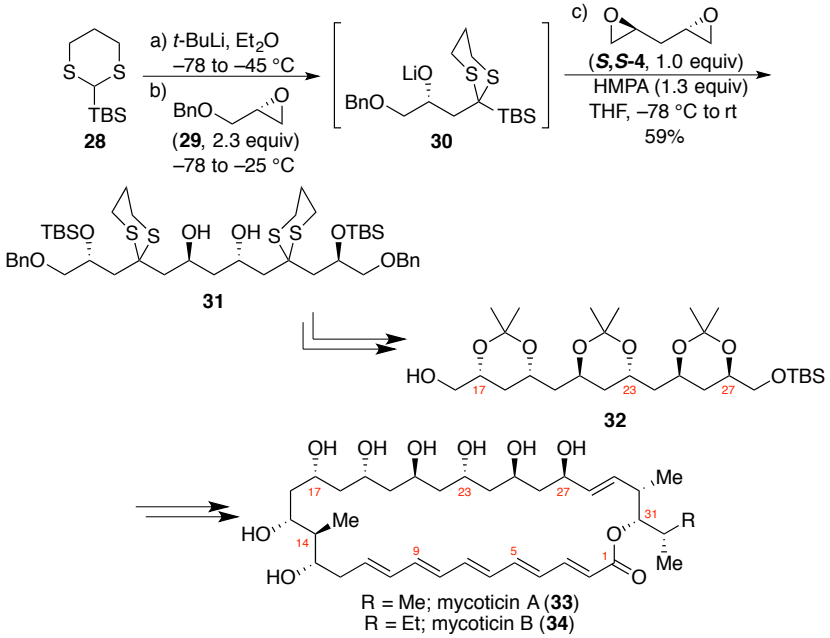
Another example of double addition using an organomagnesium nucleophile was utilized in Eustache and co-workers synthesis of attenol A (**27**, Scheme 6).[25] Treatment of bis-epoxide ***R,R*-4** with 3-butenylmagnesium bromide in the presence of CuI at –40 °C provided diene diol ***S,S*-22** in 88% yield. Diol ***S,S*-22** was then converted to PMP-acetal **23** in high yield (88%) through acid-catalyzed transacetalization. Reductive cleavage of the benzylic C–O bond by the action of sodium cyanoborohydride under acidic conditions afforded PMB ether **24** in 76% yield. The free hydroxyl group of mono-protected diol **24** was then poised for intermolecular iodoetherification when treated with *N*-iodosuccinimide (NIS) in the presence of potassium carbonate. The resulting differentially protected diol derivative **25** was obtained in 80% yield and carried forward as inconsequential mixture of diastereomers to access spiroketal **26** en route to attentol A.



Scheme 6. Eustache's synthesis of attenol A

Perhaps the most complex example of simultaneous double addition is seen in Smith and Pitrem's synthesis of the Schrieber trisacetonide in their synthesis of mycoticins A and B (**33** & **34**, Scheme 7).[26,27] This single-pot, five-

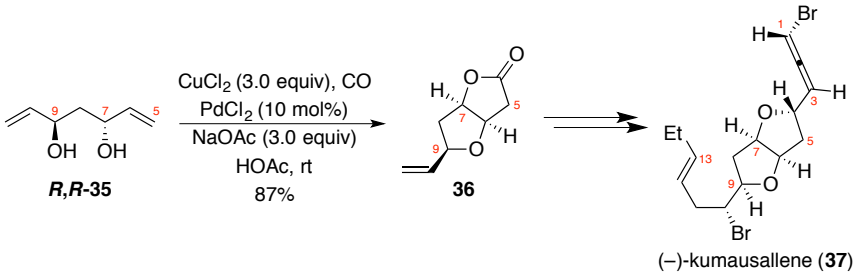
component linchpin coupling strategy utilized bis-epoxide ***S,S*-4** as the central five carbon piece of the C16–C28 fragment of the natural products. The sequence began with lithiation of silyl dithiane **28**, which opened the epoxide of (–)-benzyl glycidyl ether **29** to give alkoxide **30**. Upon warming, the transient intermediate underwent an intramolecular [1,4]-Brook rearrangement[28,29] to generate an organolithium poised for double addition into bis-epoxide ***S,S*-4** to afford diol **31** in 59% overall yield. This remarkable sequence forged four C–C bonds and provided the entire carbon framework of the C16–C28 fragment in a single operation.



Scheme 7. Smith's synthesis of mycoticin A and B

In an interesting example of post-double addition functionalization, Tang and Werness were able to exploit the C_2-symmetry of bis-epoxide ***R,R*-4** to synthesize the 2,5-*cis*-disubstituted tetrahydrofuran (THF) core of the marine sesquiterpene (–)-kumausallene (**37**, Scheme 8).[30] Their strategy employed bis-allylic diol ***R,R*-35**, which was accessed through a protocol developed by Hanson and co-workers (*vide infra*). Treatment of diol **35** with a catalytic amount of $PdCl_2$ in the presence of CO and NaOAc using $CuCl_2$ as the stoichiometric oxidant initiated a carbonylative cascade reaction[31,32] to

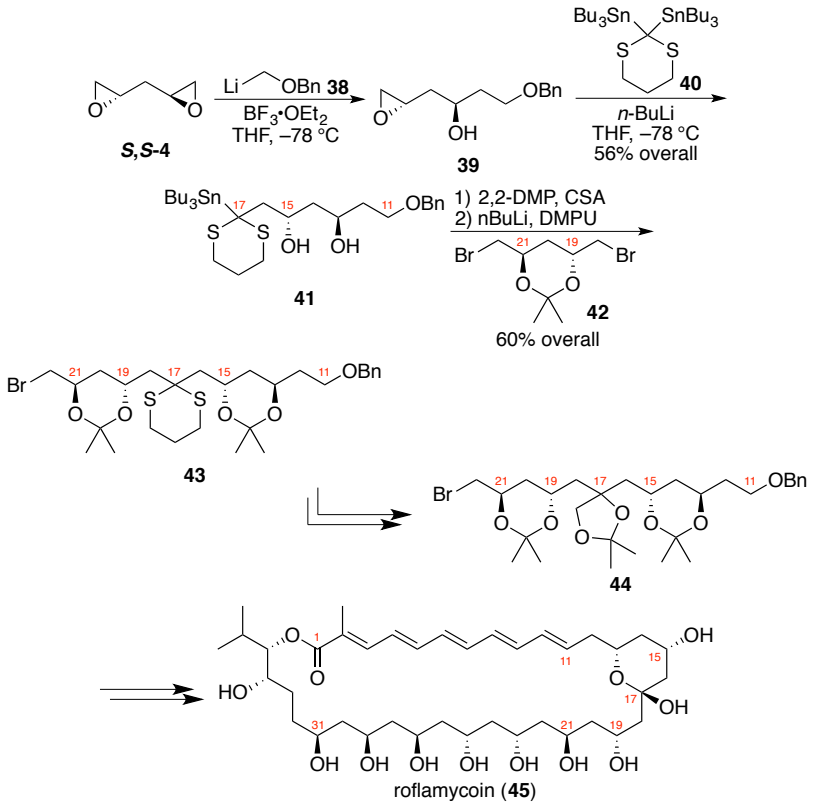
provide bicyclic lactone **36** in 87% yield. This key transformation installed the requisite stereochemistry of the central portion of the natural product, as well as appropriate synthetic handles for further functionalization.



Scheme 8. Tang's synthesis of (–)-kumausallene

Sequential Double Addition Strategies in Natural Product Synthesis

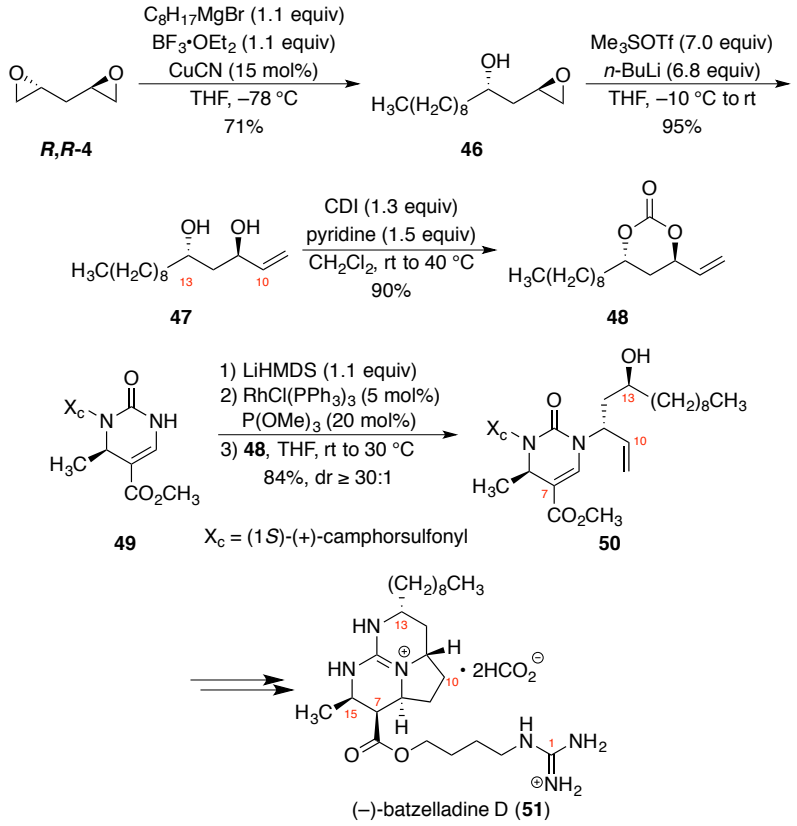
For Rychnovsky and co-worker's synthesis of roflamycoin (**45**), the hemiketal-pyran linkage required differential substitution (Scheme 9) and demonstrated the power of the sequential double addition strategy.[14] Treatment of bis-epoxide ***S,S*-4** with a stoichiometric amount of (benzyloxy)methyllithium **38** and BF_3•OEt_2 in THF at –78 °C provided mono-addition adduct **39**, which was then treated with the organolithium formed from transmetallation of 2,2-bis-(tributyltin)dithiane **40**. This single-pot procedure afforded dithiane diol **41** in 56% overall yield. Subsequent acetonide formation and transmetallation provided a competent nucleophile for direct displacement of dibromide **42**, which itself was derived from dichlorodiol ***R,R*-3**. The resulting bis-acetonide (**43**) was obtained in 60% overall yield and provided a rapid access to tris-acetonide **44**, a key intermediate for the synthesis of the hemiketal-pyran moiety of **45**. Similar sequential addition strategies have proven to be useful as well.



Scheme 9. Rychnovsky's synthesis of roflamycoin

Though most commonly used in the synthesis of polyketide natural products, Evans and co-workers were able to employ bis-epoxide ***R,R*-4** in the synthesis of polycyclic guanidinium alkaloid (–)-batzelladine D (**51**, Scheme 10).[33] Addition of the transiently formed cuprate derived from catalytic CuCN and octyl Grignard reagent in the presence of BF_3•OEt_2 in THF at –78 °C led to formation of mono-addition adduct **46** in 71% yield. The resulting epoxy alcohol (**46**) was then treated with the ylide generated from the *in situ* deprotonation of trimethylsulfonium triflate to afford 95% yield of *anti*-1,3-diol **47**. Conversion of diol **47** to cyclic carbonate **48** was achieved in 90% yield by treatment with 1,1′-carbonyldiimidazole (CDI) and pyridine. Cyclic carbonate **48** was then employed as the electrophile in a rhodium-catalyzed allylic amination.[34] The LiHMDS-mediated deprotonation of dihydropyrimidinone **49** provided a nucleophile, which in the presence of

Wilkinson's catalyst and trimethyl phosphite displaced the allylic carbonate to forge the C–N bond of **50** in high conversion and selectivity (84% yield; dr ≥ 30:1). This sequence rapidly provided the required stereochemistry for the bicyclic guanidinium portion of (–)-batzelladine D.

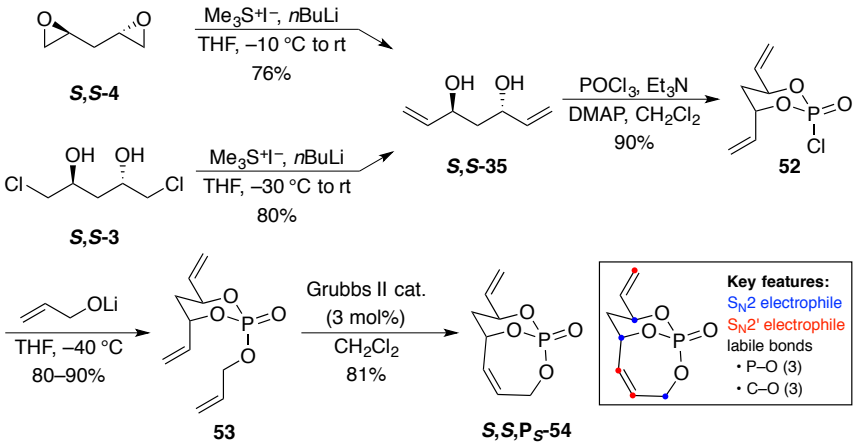


Scheme 10. Evan's synthesis of (–)-batzelladine D

Hanson's synthesis of chiral bicyclo[4.3.1]phosphate triester building blocks

While Mioskowski's conversion of epoxides to homologated allylic alcohols[35] was used in Evans' synthesis of (–)-batzelladine D, the use of this transformation as it pertains to 1,2:4,5-diepoxypentanes was pioneered by Hanson and co-workers for their research in synthesis of phosphate triester building blocks.[36] The simultaneous double addition of sulfonium ylides onto either chiral bis-epoxide ***S,S*-4** or dichlorodiol ***S,S*-3** to give the corresponding

bis-allylic diol ***S,S*-35** proceeded in high yields (76% and 80% yield, respectively) (Scheme 11).[37] This was a critical reaction in the synthesis of chiral phosphate triesters. Condensation of diol **35** onto $POCl_3$ in the presence of Et_3N and DMAP provided cyclic chlorophosphate diester **52**. Final chloride displacement was carried out with lithium allyloxide in THF at –40 °C to afford triene **53**, which underwent a ring-closing metathesis reaction in the presence of Grubbs II catalyst[24] to provide phosphate triester ***S,S,P*$_S$-54**.



Scheme 11. Hanson's synthesis of tris-allylic phosphate triesters

Hanson and co-workers have shown these tethered phosphate esters to be versatile intermediates for organic synthesis.[36] In addition to synthesis of complex natural products such as those seen in Figure 1,[38–41] recent extensions of this technology include probing the complementary reactivity of the corresponding phosphite–borane tethers.[42,43] While these reports demonstrate the utility of P-tethered building blocks, perhaps none more clearly highlight the versatility of these intermediates than Hanson's approach to dolabelide C.[41] Retrosynthetic analysis of this 24-membered macrolide produced by the sea hare *D. auricularia* (**58**, Scheme 12) divided the macrolactone into two large fragments (**59** and **60**) that can come from the enantiomeric phosphate triesters ***R,R,P*$_R$-54** and ***S,S,P*$_S$-54**.

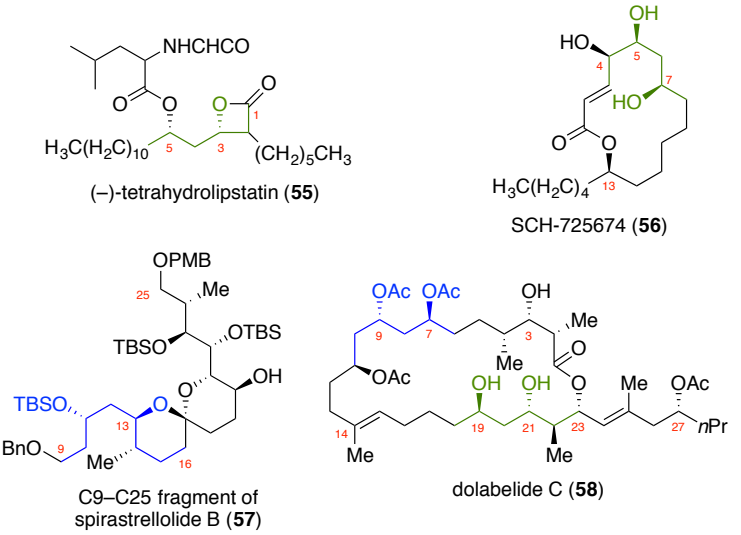
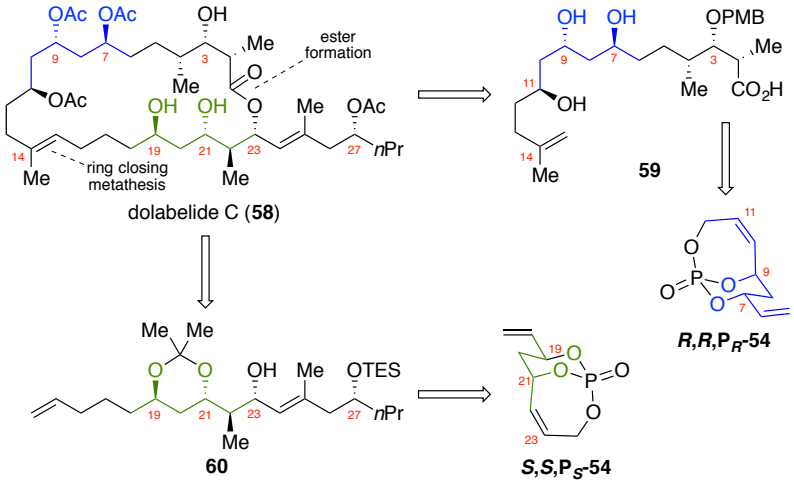


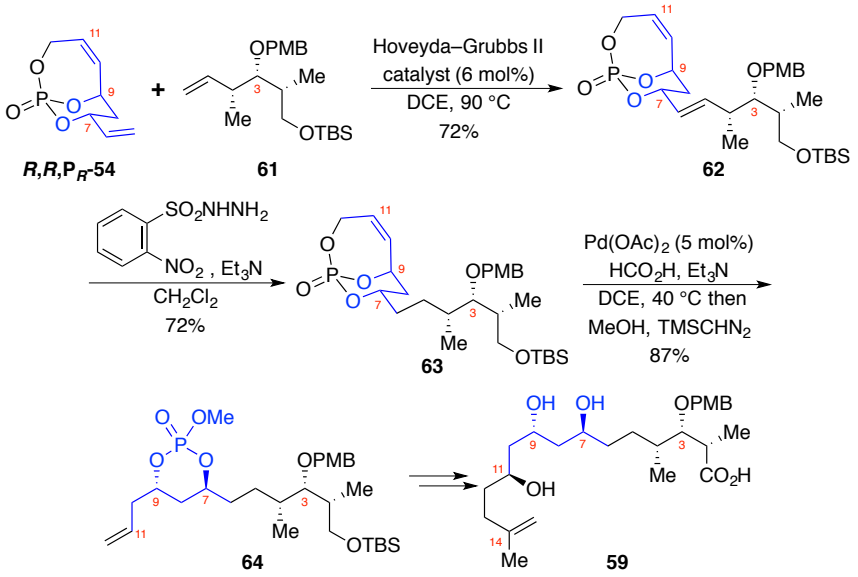
Figure 1. Complex products synthesized using phosphate triester building blocks



Scheme 12. Hanson's retrosynthetic analysis of dolabelide C

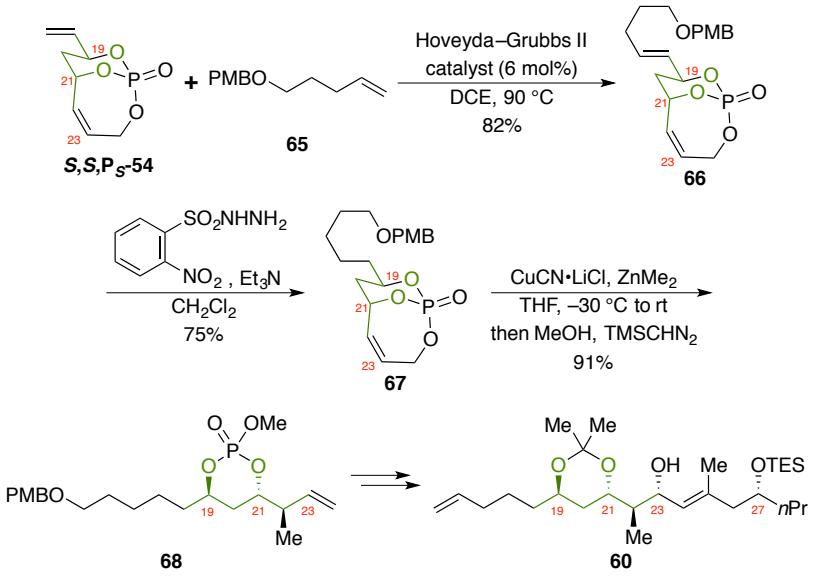
Synthesis of the C1–C14 fragment of dolabelide C, shown in Scheme 13, began with cross metathesis of phosphate triester ***R,R,P*$_R$-54** and alkene **61** in the presence of the 2nd generation Hoveyda–Grubbs catalyst[44–46] to give phosphate diene **62**. Regioselective reduction of the exocyclic alkene in **62**

required treatment with 2-nitrobenzenesulfonyl hydrazine and Et_3N as the phosphate esters are not tolerant of more basic diimide reduction protocols. The resulting cyclic alkene **63** was then subjected to a Pd-catalyzed formate reduction that regioselectively delivered hydride to the C10 position resulting in the desired terminal alkene **64**. With a majority of the northwest coupling fragment assembled, alkene **64** was further elaborated to carboxylic acid **59** in 11 steps.



Scheme 13. Hanson's approach to the C1–C14 fragment of dolabelide C

A similar cross metathesis/reduction strategy was employed for the 2nd generation synthesis of the C15–C30 fragment (Scheme 14) to convert ***S,S,P*$_S$-54** to cyclic alkene **67**. In this case, regio- and diastereoselective methyl cuprate addition proceeded in an S_N2' fashion to afford terminal alkene **68**. This advanced intermediate was carried through another 10 steps to provide southwest fragment **60**. Though containing a problematic MOM protecting group strategy, the 1st generation synthesis of this fragment also demonstrated the phosphate triester moiety's tolerance to both hydroboration/oxidation conditions, as well as an acidic PMB protection protocol.



Scheme 14. Hanson's 2nd generation synthesis of the C15–C30 fragment of dolabelide C

Hanson's chiral phosphate triesters have proven to be useful building blocks for organic synthesis with new modes of reactivity still to be discovered. Advancements in this technology were facilitated by the synthetic route developed for the bis-epoxide and dichlorodiol precursors, which speaks to the reliability of the procedure. In addition to enabling new technologies, these intermediates have also found utility in the context of providing straightforward access to enantioenriched variants of classically important synthetic intermediates.

Aubé's extension through synthesis of valuable chiral building blocks

As shown in Figure 2, 4-hydroxy-2-cyclopentenones (4-HCP) have long been a privileged scaffold in the synthesis of biologically active compounds, including prostaglandins, alkaloids and terpene natural products.[47–49] As such, the ability to access either enantiomer of this class of molecules has been a long standing area of interest for synthetic organic chemists. Aubé and co-workers provided a compelling strategy to synthesize a variety of hydroxyl protected 4-HCP derivatives in enantioenriched forms.[50] The synthetic strategy, shown in Scheme 15, involves using Hanson's protocol to access bis-

allylic diol ***R,R*-35** from dichlorodiol ***R,R*-3**. Monoprotection of C2-symmetric diol ***R,R*-35** proceeded in high yields (66–95%) for a variety of protecting groups. The resulting dienes (**72**) were able to smoothly undergo a RCM reaction using Grubbs I catalyst[51] to give cyclopentenol derivatives (**73**, 88–92% yields), which were then oxidized with pyridium chlorochromate to the corresponding cyclopentenones (**74**) in high yields (92–94%) on gram scale. In addition, this report also provided conditions for further functionalization of both the cyclopentenol derivatives and 4-HCPs.

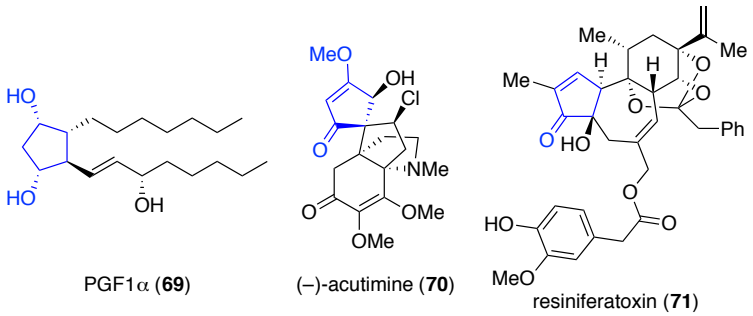
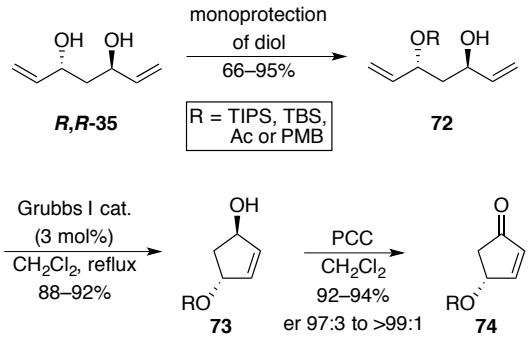


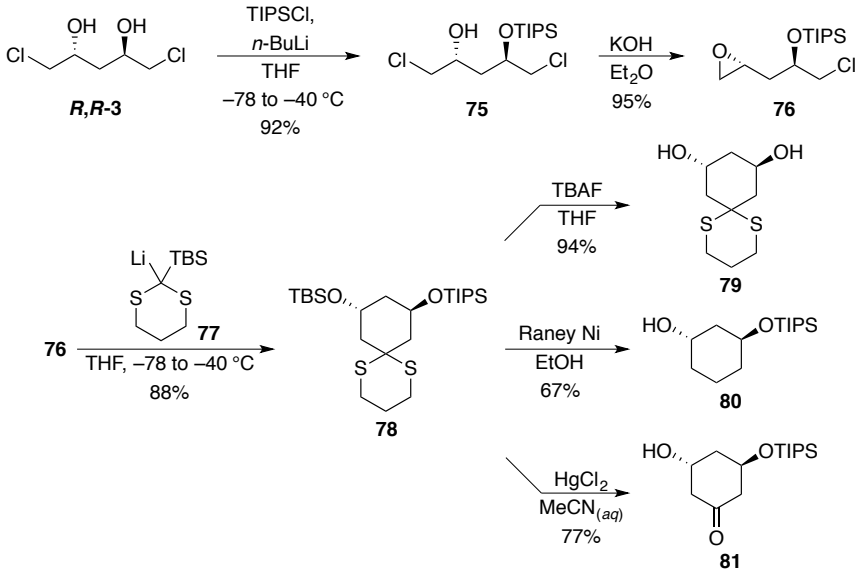
Figure 2. Select examples of natural products synthesized using 4-HCPs



Scheme 15. Aubé's synthesis of enantioenriched 4-HCP derivatives

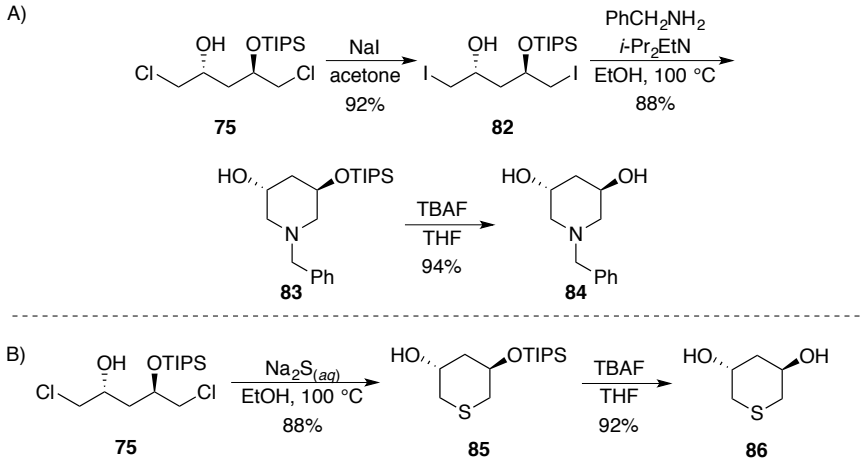
Singh and Aubé used dichlorodiol ***R,R*-3** as a key intermediate in their syntheses of spatially directed cyclohexane-1,3-diols (Scheme 16).[52] Analogous to the monoprotection of bis-allylic diol ***R,R*-35**, dichlorodiol ***R,R*-3** underwent monohydroxyl protection by the action of TIPSCl in the presence of *n*-BuLi to afford dichloride **75** in 92% yield. To synthesize cyclohexyl derivatives, dichloride **75** was then converted to chloroepoxide **76**

in 95% yield under basic conditions. In the presence of Smith's linchpin dithiane **77**, chloroepoxide **76** underwent an epoxide opening/Brook rearrangement sequence. The transient carbanion subsequently displaced the remaining chloride to provide differentially protected cyclohexane **78**, which can be selectively deprotected in a variety of ways. This method is complementary to the work of Linclau *et al.*, who used dithiane linchpin coupling on bis-epoxides (e.g. **4**) to construct cyclopentyl nucleosides.[53,54]



Scheme 16. Singh and Aubé's synthesis of cyclohexyl *trans*-1,3-diols

In addition to cyclohexane-1,3-diols, Singh and Aubé also used dichloride **75** to synthesize piperidine and thiane derivatives as well (Scheme 17). In the case of piperidine derivatives, dichloride **75** was first converted to diiodide **82** through a double Finkelstein reaction.[55,56] This more potent bis-electrophile was primed to undergo a double displacement with benzylamine to give piperidine **83** in 88% yield. The increased nucleophilicity of sulfur meant that dichloride **75** was a competent bis-electrophile for the double displacement and provided thiane **85** in 88% yield when treated with sodium sulfide. These heterocycles also underwent standard silyl group cleavage to give the corresponding 1,3-diols (**84** and **86**) in high yields (94% and 92%, respectively).



Scheme 17. Singh and Aubé's synthesis of piperidinyl and thianyl *trans*-1,3-diols

Concluding Remarks

The enantiopure forms of 1,2:4,5-diepoxypentane (**4**) and dichlorodiol (**3**) have been used by many groups as chiral precursors for organic synthesis. The original procedure is convenient and scalable, providing access to either enantiomer based on readily available and inexpensive chiral BINAP ligands. Displacement at the primary positions lead to a variety of simple enantiopure cyclic and acyclic building blocks. These typically occur either through simultaneous double addition of organometallic nucleophiles to give C2 symmetric diols or sequential double addition to give asymmetric diols. While the resulting 1,3-diol motif has most commonly found utility in the context of polyketide natural product synthesis, applications to alkaloid and terpene natural products have also been described. In addition, this method has provided straightforward access to bicyclo[4.3.1]phosphate triesters and 4-hydroxycyclopentenones derivatives, themselves valuable synthetic intermediates. Based on these recent developments, **4** and **3** will continue to provide synthetic chemists with useful entry points for chiral synthesis and enable new modes of reactivity.

References

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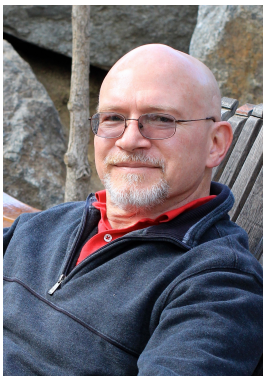

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