A Versatile Enantioselective Strategy Toward L-*C*-Nucleosides: A Total Synthesis of L-Showdomycin

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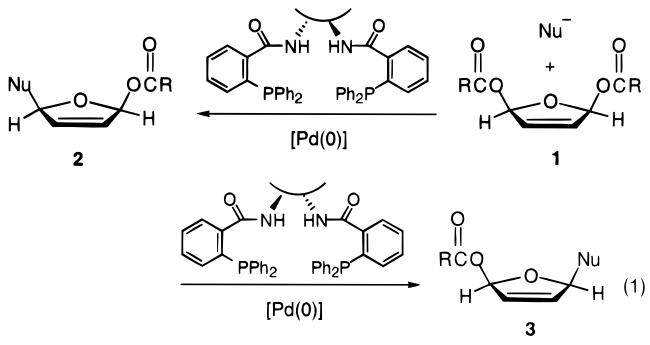
Strategies for the synthesis of nucleosides that can provide either L or D isomers become more important as a result of the increasing number of such compounds that are therapeutically useful. The lower toxicity and reduced susceptibility toward metabolism of the L isomers make them particularly interesting. A strategy toward the *C*-nucleoside analogues has been explored in the context of the synthesis of L-showdomycin. The route involves an asymmetric desymmetrization using palladium catalysis of *cis*-2,5-diacyloxy-2,5-dihydrofurans available in one step from furan, with carbon nucleophiles. Nucleophilic synthons for a maleimide unit and a methoxycarbonyl unit have been designed. Two sequential palladium-catalyzed reactions introduce both substituents with excellent chemo-, regio-, diastereo-, and enantioselectivity. The presence of a double bond in this doubly alkylated compound at C-3 and C-4 allows easy structural variation. The use of an ester as a hydroxymethyl precursor also introduces a diversity element as well as having importance in its own right. The successful completion of a synthesis of L-showdomycin validates this approach as a viable strategy to *C*-nucleosides.

The therapeutic value of nucleosides and their analogues have drawn attention to the need for new strategic approaches to their synthesis. Furthermore, easy access to both enantiomeric series is proving more important as the therapeutic advantages for the L-series compared to the D-series are being increasingly demonstrated.[1−3] Reduced tendency for enzymatic metabolism can increase bioavailability and, thus, potency. Further, the potential for higher specificity of mammalian enzymes for processing of nucleic acids may also reduce toxicity. Such benefits have been demonstrated for the treatment of the human immunodeficiency virus (HIV) with the L-nucleoside analogues L-3TC[2] and L-ddC.[3] The recent work with the C-nucleosides L-9-deazaadenosine and the dideoxy analogue indicate the growing interest in this area,[4] particularly with respect to *C*- rather than *O*-glycosylation reactions.

In developing a new strategy for the synthesis of nucleosides, we focused on the ability to generate either enantiomer equally well. Our strategy derives from the development of asymmetric palladium-catalyzed reactions[5] and is based upon the desymmetrization of *cis*-2,5-diacyloxy-2,5-dihydrofuran (**1**), available in one step by oxidation of furan.[7] Simply by choice of ligand, substitution of either prochiral leaving group leading to either enantiomeric series, **2** or **3**, may be accomplished (eq 1).[8]



(1)

By choosing appropriate nucleophiles, nucleosides may be readily accessed. For example, by using purine or pyrimidine bases, both D- and L-nucleosides have been prepared.[6] It should be pointed out that desymmetrization of diesters such as **1** with hydrolytic enzymes does not work due to instability of the lactol product.

The applicability of this strategy to C-nucleosides would expand its scope significantly. We chose showdomycin (**4**) because of its interesting biological activity as an antibiotic and antitumor agent, yet its development is, in part, limited by its toxicity.[9] Thus, access to

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(4) (a) Lee, C. S.; Du, J.; Chu, C. K. *Nucleosides Nucleotides* **1996**, *15*, 1223. (b) Liang, C.; Ma, T.; Cooperwood, J. S.; Du, J.; Chu, C. K. *Carbohydr. Res.* **1997**, *303*, 33.

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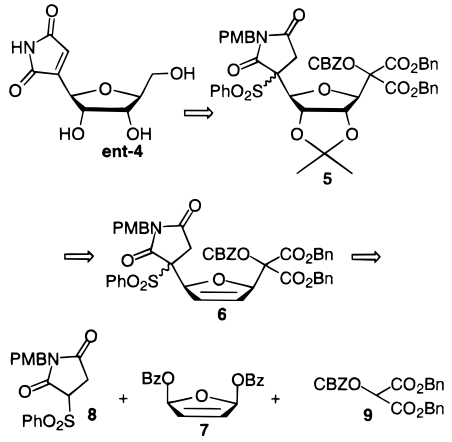
L-showdomycin (***ent*-4**) would provide the ability to evaluate the biological properties of its mirror image. Showdomycin demonstrated a broad range of inhibitory effects toward the growth of Gram-positive and Gram-negative bacteria.[9] In *E. coli*, showdomycin inhibits growth by obstructing the membrane transport of nutrients.[10] Showdomycin has also demonstrated antitumor activity. It inhibits the growth of Ehrlich ascites tumor cells in vivo and HeLa cells in vitro.[11] Showdomycin expressed a 2-fold selective toxicity for L1210 leukemia cells over bone marrow progenitor cells. This selectivity was enhanced by the addition of cytidine, a nontoxic competitive substrate.[12]

Several studies have been done to elucidate showdomycin's specific mechanism of action as an antibiotic and antitumor agent. The growth-inhibiting properties of showdomycin on *E. coli* were reversed by preincubation with RNA, DNA, and thiols but not other biologically relevant compounds.[10] Since these results imply that the alkylating ability of the maleimide aglycon is important for activity, it was postulated that showdomycin inactivates membrane proteins by alkylating available thiols,[6,13] although this theory has been challenged.[14,15] Further studies will be necessary to clarify the mechanism(s) of showdomycin's biological activity.

The interesting biological activity of showdomycin has inspired multiple synthetic studies; both racemic[16] and enantiomerically pure[17−19] showdomycin have been synthesized. Most synthetic approaches build upon the biogenetic precursor, D-ribose, by forming a diastereoselective anomeric carbon−carbon bond.[17] Although some very short syntheses of showdomycin have been realized by this method, few analogues can be prepared in this manner. Alternatively, the total synthesis of showdomycin from noncarbohydrate starting materials provides access to a broader range of analogues. The only method to date in which the enantioselectivity was introduced catalytically to synthesize showdomycin from noncarbohydrate starting materials was an enzymatic desymmetrization in which the enantiomeric excess was moderate.[19] In this paper, we report a short and versatile synthesis of (−)-showdomycin predicated on the highly selective palladium-catalyzed desymmetrization of eq 1. Since the absolute stereochemistry is set by the chiral ligand, either enantiomer of the final product is equally accessible simply by choosing the correct enantiomer of the ligand. Thus, a synthesis of *ent*-showdomycin also constitutes a strategy for the synthesis of the natural enantiomer as well. Proceeding through a 2,5-dihydrofuran intermediate also provides easy access to numerous analogues similar to the types of structural modifications found in several clinically important antiviral nucleoside analogues.

Scheme 1. Retrosynthetic Analysis



Synthetic Strategy

Scheme 1 outlines the retrosynthetic analysis wherein the 2,5-dihydrofuran **6** is a key intermediate derived from the dibenzoate **7** and the two side chain fragments that evolve from **8** and **9**. The latter has previously been shown by us to provide access to a carboxylic acid function that can be reduced to a hydroxymethyl unit.[6] The maleimide fragment of showdomycin can derive by elimination of the elements of benzenesulfinic acid from **8**. Therein also lies the problem—the ease of this elimination since the sulfone stabilized anion must be able to be generated and serve as a nucleophile prior to any elimination. In principle, either unit, **8** or **9**, can be introduced in either order. The lability of **8** toward elimination suggests it should be introduced later rather than earlier, but both protocols were examined.

Allylic Alkylation

Maleimide synthon **8** was prepared to investigate its utility as a carbon nucleophile for allylic alkylation reactions. It was decided to protect the imide nitrogen with the *p*-methoxybenzyl group to prevent N-alkylation, a side reaction observed in the unprotected case. As shown in Scheme 2, thiophenol underwent smooth conjugate addition to maleimide. Oxidation with hydrogen peroxide in acetic acid generated the desired sulfone **10** in 83% yield for the two steps. To reduce the number of steps, a Michael addition with sodium benzenesulfinate to maleimide was explored (Scheme 2). Though this reaction is reversible, the reaction is driven by the precipitation of **10** in a buffered aqueous medium. After filtration and drying, no further purification of **10** was necessary. Protection of the imide with an alkyl group without undue elimination was successful utilizing Mit-

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(16) (a) Just, G.; Liak, T. J.; Lim, M.-I.; Potvin, P.; Tsantrizos, Y. S. *Can. J. Chem.* **1980**, *58*, 2024. (b) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1981**, *103*, 3923.

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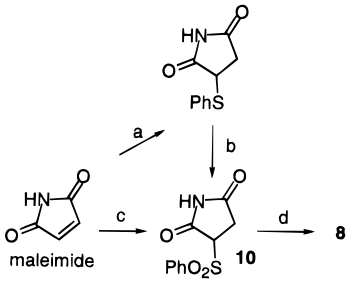
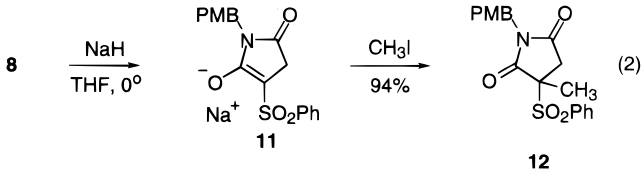
(19) Ito, Y.; Shibata, T.; Arita, M.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 6739.

Scheme 2. Synthesis of Nucleophilic Maleimide Synthon



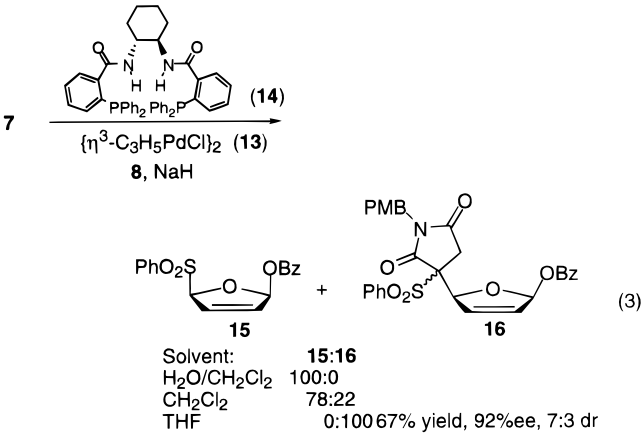
sunobu conditions.[20] In this way, sulfonylsuccinimide **8** was prepared in three steps in 50% overall yield or in two steps in an overall 46% yield.

To test the viability of using sulfone **8** as a nucleophile, it was treated with sodium hydride in THF at 0 °C. After 10 min, a white solid precipitated (eq 2). To establish the



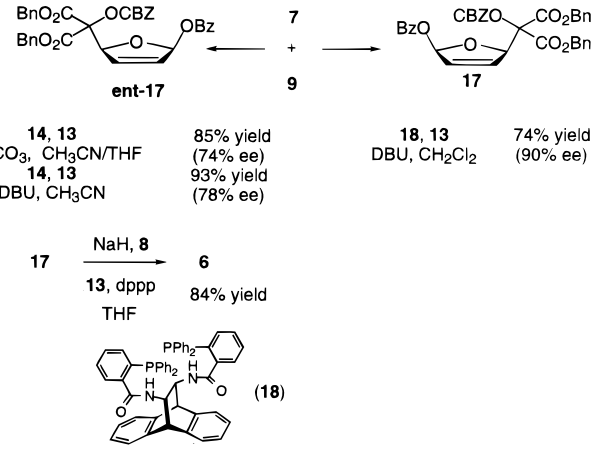
identity of this solid, in particular to explore whether it was sodium benzenesulfinate or the desired anion **11**, it was exposed to methyl iodide. Indeed, the desired methylated product **12** was isolated in excellent yield.

The heterocyclic substrate **7**[6,7] was reacted with nucleophile **11** using a catalyst derived from palladium complex **13** and the *R*,*R* configuration of chiral ligand **14**.[8] A strong solvent effect was discovered. Using a biphasic mixture, the only product was determined to be the sulfone adduct **15** (eq 3). This indicates that the polar



protic solvent facilitated proton exchange, which led to the thermodynamically favorable elimination of sulfinate. The latter then serves as a nucleophile in the palladium-catalyzed desymmetrization. Sodium benzenesulfinate has been shown previously to be a good nucleophile in allylic alkylation reactions.[21] The same reaction was repeated in methylene chloride to give both **15** and the

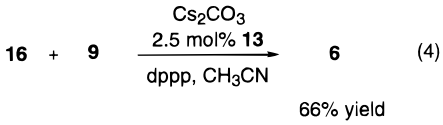
Scheme 3. Alternative Synthesis of Key Dihydrofuran Intermediate



desired carbon adduct **16**. By changing the solvent to THF, **16** was formed exclusively.

The absolute stereochemistry of product **16** was predicted on the basis of precedence and subsequently verified by completion of the synthesis.[8] For both the major and minor diastereomers, the enantiomeric excess was determined to be 92% by chiral HPLC. This high enantioselectivity was obtained without optimization. The diastereoselectivity does not affect the synthesis of showdomycin because this stereocenter will be lost when the sulfone is eliminated. Nevertheless, it is of some interest since induction of chirality at the prostereogenic center of a nucleophile is an important dimension of asymmetric palladium-catalyzed reactions.[22]

A second regio- and diastereoselective allylic alkylation reaction of **16** with the known protected tartronic acid **9**[6] was explored. Since the chiral product is formed through a chirality transfer, an achiral ligand can be used for this reaction. As shown in eq 4, the reaction proceeded



to introduce the tartronate forming the key intermediate **6** with complete regio- and diastereocontrol. The yield may reflect sensitivity of the substrate and/or product to base catalyzed eliminations.

To make the synthesis more general for all *C*-nucleosides, we were also interested in using **9** in the desymmetrization step (see Scheme 3). With the initial conditions of using **14** as the ligand and cesium carbonate as the base, a high yield (85%) of product *ent*-**17** of 74% ee was obtained. The enantioselectivity improved to 78% (93% yield) upon switching the base to DBU with similar results being obtained in both acetonitrile and methylene chloride. On the other hand, by utilizing ligand **18**,[8] which we believe creates a tighter pocket, the ee jumped to 90% using DBU in methylene chloride to give **17**.

The alkylated product **17** was a good substrate for a second allylic alkylation reaction with the sulfonylsuccinimide **8**. The conditions employed were the same as those previously developed except that the achiral bis-

(20) Mitsunobu, O.; Wada, M.; Sano T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(21) Trost, B. M.; Organ, M. O.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

(22) (a) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. (b) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635.

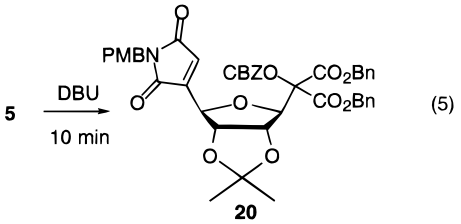
(diphenylphosphino)propane (dppp) was substituted as the ligand. With the dppp ligand, the rate of the allylic alkylation reaction was faster and the yield was higher than the corresponding reaction with the chiral ligand. Part of the reason may derive from the smaller steric demand of the achiral ligand.

Either of the two carbon nucleophiles shown can be introduced with good enantioselectivity (≥90%) in the desymmetrization of *cis*-diester **1**. Also, either enantiomer of the product can be accessed based on the choice of ligand stereochemistry. It appears that the palladium-catalyzed allylic alkylation offers an improvement in enantioselectivity over an alternative enzymatic strategy previously published for the synthesis of D-showdomycin.[19]

Completion of the Synthesis

cis-Dihydroxylation of **6** with osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO) as the co-oxidant was low yielding because the *N*-methylmorpholine byproduct proved basic enough to eliminate some of the sulfone from product **19**. This complication arose partly because the dihydroxylation was exceptionally slow for this substrate. By experimenting with buffered conditions and higher catalyst loading (20 mol %), the dihydroxylation was achieved efficiently (Scheme 4). The substrate-controlled dihydroxylation occurred with complete diastereoselectivity; the anti configuration was inferred on the basis of steric predictions, precedent,[6] and by the observed low vicinal coupling constant between the protons at C-4 and C-5 ($J = 1.7$ Hz). Protection of diol as the acetonide to form **5** proceeded straightforwardly.

Elimination of the sulfone to form an olefin would be desirable as early in the synthetic sequence as possible in order to simplify the mixture of diastereomers. When substrate **5** was reacted with DBU, two different products were observed. The kinetic product **20** had the desired maleimide moiety (eq 5), and the thermodynamic product **21** derived from isomerization of the double bond to the exocyclic position (eq 6).[23] The isomerization is particularly undesirable in our case because the chirality at the furan carbon is lost. Since the isomerization may be difficult to avoid, we decided to retain the sulfone as a "protected olefin" to be removed later in the synthetic sequence.



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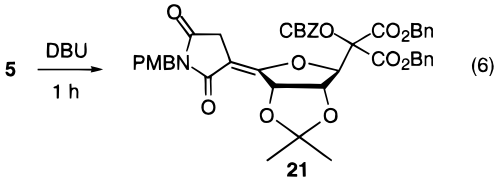
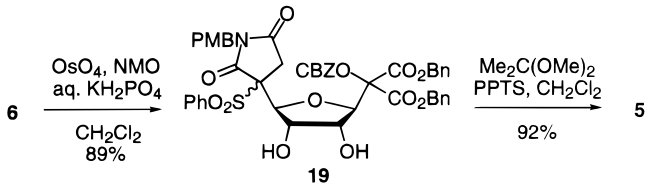


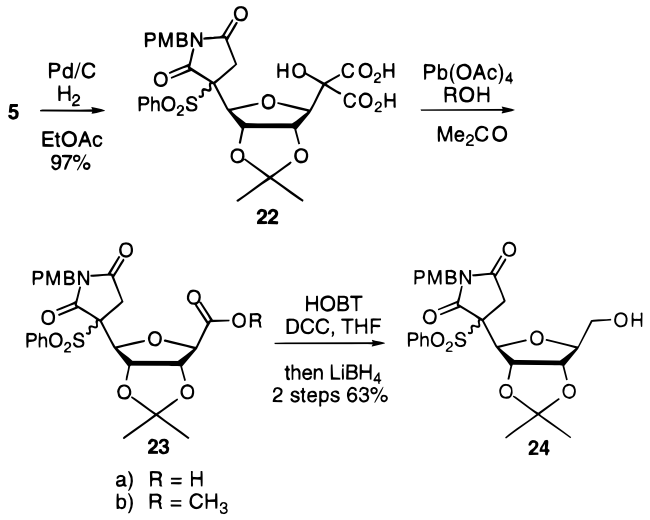
(6)

To remove the benzyl and benzyloxycarbonyl protecting groups from **5**, catalytic hydrogenolysis was employed

Scheme 4



Scheme 5



(see Scheme 5). With ethyl acetate as the solvent, the desired hydroxy diacid **22** was isolated in essentially a quantitative yield. It has been noted previously that alkoxy-substituted benzylamines are inert to hydrogenolysis.[24] Our results also support this observation; the *p*-methoxybenzyl group on the imide nitrogen was not removed under these hydrogenolysis conditions.

A procedure had been previously developed in our laboratory to convert a hydroxy diacid to a hydroxymethyl.[6] This approach could not be used with substrate **22** because triethylamine, a necessary reagent, was able to induce the elimination of the sulfone and isomerize the olefin to the undesired exocyclic position. As an alternative approach, an oxidative decarboxylaton was considered.[25] With a hydroxy diacid, it should be possible to effect a decarboxylation, a hydration, and a second decarboxylation in one pot to give the desired acid **23a**. Sodium periodate did form some of the desired product (35%), but increasing the reaction time or temperature led to decomposition. Using pure ground lead tetraacetate was more successful; acid **23a** was the major compound in the crude extract (65−75% yield). Direct reduction of the resultant acid **23a** via activation as the hydroxybenzotriazole[26] ester worked well. Considering the difficulty of the two steps, a didecarboxylation and reduction in the presence of sensitive functionality, an overall yield of 63% from **5** was very satisfying. Interestingly, performing the oxidative bis-decarboxylation in 2:1 acetone−methanol gave directly the methyl ester **23b** in 69% yield.

The completion of the synthesis of showdomycin from **24** requires removal of the protecting groups. In the elimination of the sulfone, which unmasks a maleimide,

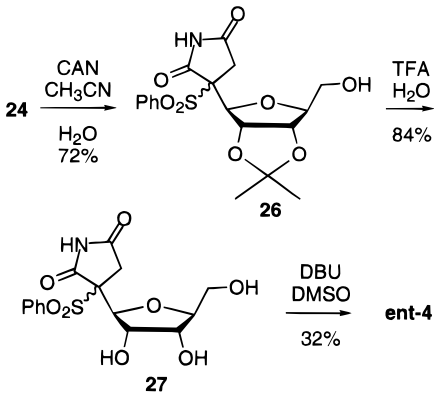
(23) Ozaki, M.; Kariya, T.; Kato, H.; Kimura, T. *Agric. Biol. Chem.* **1972**, *36*, 451−456.

(24) Bringmann, G.; Geisler, J.-P.; Geuder, T.; Kunkel, G.; Kinzinger, L. *Liebigs Ann. Chem.* **1990**, 795.

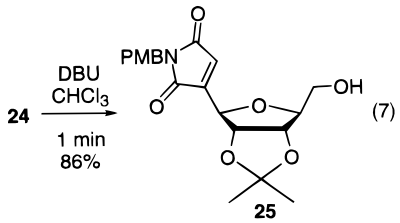
(25) Yanuka, Y.; Katz, R.; Sarel, S. *Tetrahedron Lett.* **1968**, 1725. (b) Baer, E. *J. Am. Chem. Soc.* **1940**, *62*, 1597.

(26) Trost, B. M.; Hipskind, P. A. *Tetrahedron Lett.* **1992**, *33*, 4541.

Scheme 6



one side reaction to keep in mind is the presence of an unprotected hydroxyl group that is also known to undergo an intramolecular Michael addition to form a spirocycle.[27] This Michael addition was observed when following the reaction over time by proton NMR. By adding DBU to the substrate at 0 °C and quenching with monopotassium phosphate buffer after exactly 1 min, a high yield of the desired product **25** was obtained (eq 7).



Removal of the *p*-methoxybenzyl group from **25** proved to be more difficult than had been expected. By treating **25** with trifluoroacetic acid,[28] only the acetonide was removed. Oxidative cleavage methods to remove the *p*-methoxybenzyl group from **25** were also unsuccessful; ceric ammonium nitrate (CAN)[29] decomposed the substrate, and no reaction was observed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). To address the possibility that CAN was decomposing the maleimide functionality, the deprotection of substrate **24** with CAN was tried. Indeed, the removal of the *p*-methoxybenzyl group to give **26** worked well (Scheme 6).

Returning to the issue of a base-induced sulfone elimination, the presence of an unprotected imide in **26** ($pK_a = 9$) slowed the elimination, allowing time for the competing Michael addition. To avoid the Michael addition, the acetonide was removed first since the bicyclic nature of substrate **26** facilitates the Michael addition by bringing the hydroxyl group proximal to the maleimide olefin. Aqueous acid cleaved the acetonide to give diol **27** in a high yield.[30]

The elimination of the sulfone from **27** was followed by proton NMR in DMSO-d_6; showdomycin was the major product, along with a small amount (<10%) of unreacted starting material, the isomerized olefin, and the Michael adduct. Unfortunately, separating the product from the DMSO was difficult, and the collected showdomycin with all the known byproducts only accounted for 51% of the starting material. Recrystallization of the crude material afforded a 32% yield of showdomycin as a white solid. At this time, this last step has not been optimized and would likely proceed in higher yields.

The proton and carbon NMR and IR data of the synthetically prepared showdomycin matched the literature data for the natural product except for the sign of the rotation.[27] The synthesized material had been prepared from a bulk supply of **6**, which was only 70% enantiomerically pure, but enantiopure L-showdomycin was obtained by a recrystallization from acetone/benzene to give a crystalline product that had an optical rotation of −47.8°; this value compares favorably with that of natural showdomycin except being opposite in sign, verifying that we had prepared the enantiomer of the natural product.

Conclusion

L-Showdomycin was prepared in 10 synthetic steps from the know *cis*-diester **1** by using an enantioselective palladium-catalyzed allylic alkylation reaction. We demonstrated that a novel sulfone-substituted succinimide (**8**) could be used as a nucleophile and elaborated into maleimide. The palladium-catalyzed desymmetrization was demonstrated to be efficient with either of two carbon nucleophiles, giving enantiomeric excesses of ≥90%. The remaining stereocenters were efficiently introduced by a regio- and diastereoselective palladium-catalyzed allylic alkylation and a diastereoselective dihydroxylation. An efficient and more general method for the decarboxylation of a hydroxy diacid was developed with lead tetraacetate under neutral conditions. Deprotection of the *p*-methoxybenzyl group and acetonide prior to elimination of the sulfone avoided most of the side reactions in the elimination of the sulfone to give L-showdomycin.

More generally, what we have demonstrated is a novel approach to the synthesis of *C*-nucleosides. The palladium-catalyzed enantioselective allylic alkylation has been used previously with amine nucleophiles to prepare carbanucleosides and nucleosides, but this is the first example of a carbon nucleophile in the desymmetrization of a heterocyclic substrate. With alternative carbon nucleophiles, other *C*-nucleosides could be synthesized by the same method. The second carbon side chain also is introduced efficiently with complete chemo-, regio-, and diastereoselectivity using a second palladium-catalyzed alkylation. Furthermore, utilization of a methoxycarbonyl group as a precursor to a hydroxymethyl group offers flexibility for structural diversification of this unit as well as have intrinsic interest. The 3,4-double bond in the initial doubly alkylated intermediate represents an opportunity for facile variation of the substitution pattern at these carbons, which has proven of interest for several clinically important nucleoside analogues. Thus, this strategy has considerable flexibility to vary structure and should be a versatile route to the preparation of biologically interesting natural and unnatural *C*-nucleosides.

Experimental Section

General Methods. Unless otherwise noted, reactions were run in flame-dried glassware under a positive pressure of nitrogen gas. The reaction flasks were sealed with rubber

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septa, and the contents were magnetically stirred. Liquids were transferred by oven-dried syringes or cannulas. Solvents were fresly distilled under nitrogen prior to use: benzene, acetonitrile, methylene chloride, and triethylamine from calcium hydride; tetrahydrofuran and diethyl ether from sodium benzophenone ketyl; acetone from calcium sulfate; and methanol from magnesium methoxide. Flash chromatography was performed with Kieselgel 60, 230−400 mesh. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm precoated silica gel plates from Merck, Kieselgel 60, F_{254}. Melting points were determined using open capillaries on a Thomas-Hoover unimelt apparatus and are uncorrected. High-resolution mass spectroscopy was performed by the NIH Mass Spectral Facility at UC San Francisco on a Kratos MS9 instrument. Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter.

Preparation of 3-Phenylsulfonylsuccinimide (10). To maleimide (5.0 g, 51.5 mmol) in water (100 mL) were added monopotassium phosphate buffer (10% aqueous, 84 mL, 61.8 mmol) and sodium benzenesulfinate (9.30 g, 56.7 mmol). The mixture was stirred at room temperature for 1 h, during which time a white solid precipitated. The solid was filtered and evaporated in vacuo to give 9.11 g (74%) of **10**. Mp: 156−158 °C. R_f: 0.27 (50:50-petroleum ether:ethyl acetate). IR (neat): 3264, 1793, 1724, 1346, 1312 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.79 (d, J = 7.9 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 4.49 (m, 1H), 3.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 169.2, 135.9, 134.8, 129.3, 128.9, 64.1, 31.0. HRMS (*m*/*e*): calcd for $C_{10}H_9NO_4S$ 239.0252, found 239.0252.

Preparation of 3-Phenylsulfonyl-*N*-(4-methoxybenzyl)-succinimide (8). To a cooled solution (−78 °C) of **10** (1.78 g, 7.4 mmol), triphenylphosphine (1.95 g, 7.4 mmol), and 4-methoxybenzyl alcohol (925 μL, 7.4 mmol) in THF (37 mL, 0.2 M) was added diisopropyl azodicarboxylate (1.46 ml, 7.4 mmol). The mixture was then transferred to an ice bath. The reaction turned from yellow to orange within 10 min, and TLC (50:50 petroleum ether/ethyl acetate) indicated that the starting material had been consumed. The reaction mixture was poured into ethyl acetate/petroleum ether (200 mL, 50:50 mixture), and the organic products were filtered through a silica plug (200 mL), using ethyl acetate/petroleum ether (800 mL, 50:50 mixture) washes to collect the crude product. After evaporation in vacuo, the yellow oil was dissolved in methanol (50 mL) and cooled for 24 h in the refrigerator. The newly formed white crystals were filtered to give 1.28 g (48%) of **8**. On a smaller scale (556 mg), purification by flash chromatography gave 504 mg (61%) of **8**: Mp: 136−138 °C (methanol). R_f: 0.46 (50:50 petroleum ether/ethyl acetate). IR (neat): 2940, 1712, 1514, 1397, 1326 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.3 Hz, 2H), 7.68 (t, J = 8.6 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 4.53 (s, 2H), 4.30 (dd, J = 9.6, 3.7 Hz, 1H), 3.76 (s, 3H), 3.30 (dd, J = 19.1, 3.8 Hz, 1H), 3.02 (dd, J = 19.1, 9.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 168.2, 159.4, 136.2, 134.8, 130.1, 129.2, 126.9, 113.9, 63.2, 55.2, 42.5, 29.8. HRMS (*m*/*e*): calcd for $C_{18}H_{17}NO_5S$ 359.0827, found 359.0821.

Preparation of (2*S*,5*S*)-2-[3′-Phenylsulfonyl-*N*′-(4-methoxybenzyl)succinimid-3′-yl]-5-benzoyloxy-2,5-dihydrofuran (16). To sodium hydride (68% oil, 3.9 mg, 0.097 mmol) in a cooled sonicator bath (0 °C) was added **8** (46 mg, 0.13 mmol) in THF (300 μL). The mixture was degassed with argon while bubbling ensued for 3−5 min. A prestirred solution of **7** (20 mg, 0.064 mmol), bis(η^3-allyl)di-μ-chlorodipalladium[31] (0.5 mg, 5 mol % Pd), and ligand **14** (3.0 mg, 15%) in THF (300 μL) under argon was cannulated into the solution of nucleophile in the sonicator. Additional THF was added to help wash all the material into the reactive flask (200 μL, 0.08 M overall). The reaction mixture was degassed by bubbling with argon with sonication for 10 min. The mixture was sealed and stirred for 4 h at 0 °C. Direct application to flash chromatography (50:50 petroleum ether/ethyl acetate) gave a crude oil with a ratio of starting material to product of 8:92. The product was purified by flash chromatography (75:25 petroleum ether/ethyl acetate) to give 24 mg (67%) of **16** as a colorless oil. The diastereomeric ratio was 7:3 by proton NMR. The diastereomers were separated by flash chromatography (80:20 petroleum ether/ethyl acetate) for enantiomeric excess determination by chiral HPLC. The enantiomeric excess for both the major and minor diastereomers was 92%. To obtain racemic **16**, the same method was used, but dppp was substituted for the chiral ligand. R_f 0.20 (70:30 petroleum ether/ethyl acetate). IR (neat): 2934, 1714, 1515, 1397, 1325 cm^{-1}. ^{1}H NMR major diastereomer (400 MHz, $CDCl_3$): δ 7.79−7.86 (m, 4H), 7.66 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.05 (s, 1H), 7.00 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 6.1 Hz, 1H), 6.62 (d, J = 8.7 Hz, 2H), 6.26 (d, J = 6.1 Hz, 1H), 5.62 (s, 1H), 4.48 (d, J = 14.4 Hz, 1H), 4.36 (d, J = 14.3 Hz, 1H), 3.71 (s, 3H), 3.27 (d, J = 19.2 Hz, 1H), 3.15 (d, J = 19.1 Hz, 1H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 172.4, 170.1, 164.8, 159.0, 135.2, 133.6, 131.5, 130.3, 129.7, 129.6, 129.4, 129.3, 128.7, 128.5, 126.6, 113.8, 102.0, 84.5, 73.6, 55.1, 42.4, 30.8. Anal. Calcd for $C_{29}H_{25}NO_8S$: C, 63.61; H, 4.60; N, 2.56. Found: C, 63.62; H, 4.84; N, 2.42.

Determination of Enantiomeric Excess for 16. High-pressure liquid chromatography (HPLC) was used to separate and quantify the enantiomeric products. A Chiralcel OD column, cellulose tris(3,5-dimethylphenyl carbamate) on a 10 μm silica gel substrate, was used to separate the enantiomers on a 250 × 4.6 mm column. A flow rate of 1.0 mL/min was established with 80:20 2-propanol/*n*-heptane as the eluting solvent. The substrate had to be heated to dissolve it in the eluting solvent before it was applied to the column by injecting 10 μL of a 0.91 mM solution. As the enantiomers were eluted off the column, they were detected and quantified by UV at 254 nm. The racemic **16** was injected on the column, and four peaks eluted but with considerable overlap. Therefore, in the asymmetric case, the diastereomers were separated by flash chromatography before HPLC analysis. The enantiomers of the major diastereomer eluted at 21 and 39 min resulting in an enantiomeric excess of 92%. The enantiomers of the minor diastereomer eluted at 30 and 38 min also resulting in an enantiomeric excess of 92%. The major enantiomer for both diastereomers has the 2*S*,5*S* stereochemistry.

Preparation of (2*S*,5*S*)- and (2*R*,5*R*)-5-(Dibenzyloxycarbonylbenzyloxycarbonyloxy)-2-benzyloxy-2,5-dihydrofuran (*ent*-17 and 17). Method A (Optimized for Yield, *ent*-17). Into a prestirred solution of **7** (500 mg, 1.6 mmol), bis(η^3-allyl)di-μ-chloro-dipalladium (15 mg, 5.0 mol % Pd), and ligand **14** (83 mg, 15 mol %) in acetonitrile (12 mL) under argon in a cooled (0 °C) sonicator was cannulated a solution of **9** (840 mg, 1.9 mmol) and DBU (265 μL, 1.7 mmol) in acetonitrile (8 mL). The reaction mixture was degassed by bubbling with argon with sonication for 10 min. The reaction was sealed and stirred under an argon balloon for 3 h at 0 °C. Direct application to flash chromatography (50:50 petroleum ether/ethyl acetate) gave a crude oil. The product was further purified by flash chromatography (70:30 petroleum ether/ethyl acetate) to give 930 mg (93%) of ***ent*-17** as a colorless oil. The enantiomeric excess, determined by chiral HPLC, was 78%. To obtain racemic **17**, the same method was used but dppp was substituted for the chiral ligand. R_f 0.21 (80:20 petroleum ether/ethyl acetate). IR (neat): 3065, 3034, 2959, 1755, 1455, 1382 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.16−7.37 (m, 17H), 7.06 (s, 1H), 6.32 (d, J = 6.0 Hz, 1H), 6.00 (d, J = 6.0 Hz, 1H), 5.63 (s, 1H), 5.11−5.28 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 164.2, 163.8, 153.7, 134.6, 134.5, 133.0, 130.8, 130.0, 129.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 101.8, 87.4, 84.2, 70.4, 68.2, 68.1. Anal. Calcd for $C_{36}H_{30}O_{10}$: C, 69.45; H, 4.86. Found: C, 69.55; H, 4.91.

Method B (Optimized for Enantiomeric Excess, 17). Into a prestirred solution of **7** (25 mg, 0.082 mmol), bis(η^3-allyl)di-μ-chlorodipalladium (1.5 mg, 10 mol % Pd), and ligand **18** (10 mg, 15 mol %) in methylene chloride (320 μL) under

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argon in a cooled (0 °C) sonicator was cannulated a solution of **9** (43 mg, 0.098 mmol) and DBU (13.5 μL, 0.090 mmol) in methylene chloride (500 μL). The reaction mixture was degassed by bubbling with argon with sonication for 10 min. The reaction was sealed and stirred under an argon balloon for 3 h at 0 °C and then 2 h at room temperature. Direct application to flash chromatography gave a crude oil with both product and unreacted starting material. The product was further purified by flash chromatography (70:30 petroleum ether/ethyl acetate) to give 28 mg (54%) of **17** as a colorless oil. The starting material was separated from excess **9** by hydrogenation and silica filtration to give 7.0 mg of **7**, making the overall yield 74% based on recovered starting material. The enantiomeric excess, determined by chiral HPLC, was 90%. This material was identical spectroscopically to the material above.

Determination of Enantiomeric Excess for 17. HPLC was used to separate and quantify the enantiomeric products. A Chiralpak AD column, amylose tris(3,5-dimethylphenyl carbamate) on a 10 μm silica gel substrate, was used to separate the enantiomers on a 250 × 4.6 mm column. A flow rate of 1.0 mL/min was established with 85:15 2-propanol/*n*-heptane as the eluting solvent. The substrate had to be heated to dissolve it in the eluting solvent before it was applied to the column by injecting 10 μL of a 0.80 mM solution. As the enantiomers were eluted off the column, they were detected and quantified by UV at 254 nm. The enantiomers eluted at 24 min (2*S*,5*S*) and 35 min (2*R*,5*R*). The enantiomeric excess was determined to be 90%.

Preparation of (2*S*,5*R*)-5-(Dibenzyloxycarbonylbenzyloxycarbonyloxy)-2-[3′-phenylsulfonyl-*N*′-(4-methoxybenzyl)-succinimid-3′-yl]-2,5-dihydrofuran (6). Method A: From substrate 17. To a suspension of sodium hydride (68% oil, 45 mg, 2.6 mmol) in THF (7 mL) placed in a cooled sonicator bath (0 °C) was added **8** (616 mg, 3.4 mmol) in THF (7 mL). The mixture was degassed with argon while bubbling ensued for 3−5 min. A prestirred solution of **17** (534 mg, 1.7 mmol), bis(η^3-allyl)di-μ-chlorodipalladium (7.8 mg, 5 mol % Pd), and dppp (27 mg, 15 mol %) in THF (7 mL) under argon was cannulated into the solution of the nucleophile in the sonicator. Additional THF was added (27 mL). The reaction mixture was degassed by bubbling with argon with sonication at 0 °C for 10 min. The mixture was sealed and stirred for 3 h at 0 °C. Direct application to flash chromatography (50:50 petroleum ether/ethyl acetate) and evaporation in vacuo gave a crude oil. The product was further purified by flash chromatography (70:30 petroleum ether/ethyl acetate) to give 617 mg (84%) of **6** as a foamy colorless glass. R_f 0.77 (50:50 petroleum ether/ethyl acetate). IR (neat): 3035, 2956, 1757, 1718, 1515, 1397, 1279 cm^{-1}. ^{1}H NMR major diastereomer (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.31−7.46 (m, 4H), 7.15−7.30 (m, 5H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 6.4 Hz, 1H), 6.08 (d, *J* = 6.1 Hz, 1H), 5.62 (s, 1H), 5.37 (s, 1H), 5.14−5.26 (m, 4H), 4.99 (s, 2H), 4.39 (d, *J* = 14.3 Hz, 1H), 4.20 (d, *J* = 14.3 Hz, 1H), 3.73 (s, 3H), 3.63 (d, *J* = 19.3 Hz, 1H), 3.09 (d, *J* = 19.3 Hz, 1H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 172.1, 169.9, 163.8, 162.9, 158.9, 152.9, 134.8, 134.5, 134.4, 134.2, 134.1, 130.2, 129.9, 129.8, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.5, 126.9, 113.6, 86.9, 84.2, 83.5, 73.9, 70.5, 68.2, 67.9, 54.9, 41.9, 30.0. Anal. Calcd for $C_{47}H_{41}NO_{13}S$: C, 65.65; H, 4.81; N, 1.63. Found: C, 65.47; H, 4.91; N, 1.81.

Method B: From Substrate 16. Into a prestirred solution of **16** (31 mg, 0.057 mmol), bis(η^3-allyl)di-μ-chlorodipalladium (0.5 mg, 2.5 mol % Pd), and dppp (1.7 mg, 7.5 mol %) in acetonitrile/THF (1:1, 1 mL) under argon was cannulated a solution of **9** (30 mg, 0.068 mmol) and cesium carbonate (22 mg, 0.068 mmol) in acetonitrile/THF (1:1, 1 mL). The reaction mixture was degassed by bubbling with argon with sonication for 10 min. The reaction was sealed and stirred under an argon balloon for 27 h. Direct application to flash chromatography (50:50 petroleum ether/ethyl acetate) gave a crude oil. The product was further purified by flash chromatography (80:20 petroleum ether/ethyl acetate) to give 31 mg (66%) of **6** as an oil. This material was identical spectroscopically to the material above.

Preparation of (2*S*,3*S*,4*R*,5*R*)-5-(Dibenzyloxycarbonylbenzyloxycarbonyloxy)-2-[3′-phenylsulfonyl-*N*′-(4-methoxybenzyl)succinimid-3′-yl]-3,4-dihydroxytetrahydrofuran (19). To a solution of **6** (617 mg, 0.72 mmol) in methylene chloride (0.5 M, 1.43 mL) were added monopotassium phosphate buffer (10% aqueous, 2.91 mL), osmium tetraoxide (0.19 M solution, 755 μL), and NMO (500 mg, 4.27 mmol). After the two-phase mixture was stirred vigorously for 24 h at room temperature, a solution of sodium metabisulfite (10% aqueous, 10 mL) was added, and the mixture was stirred for 1 h. The organic products were extracted with methylene chloride (3 × 10 mL). The combined organic products were dried over magnesium sulfate, filtered, and evaporated in vacuo. The product was purified by flash chromatography (50:50 petroleum ether/ethyl acetate) to give 570 mg (89%) of **19** as a foamy colorless glass. R_f 0.35 (50:50 petroleum ether/ethyl acetate). IR (neat): 3494, 2956, 1756, 1715, 1515, 1397 cm^{-1}. ^{1}H NMR major diastereomer (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.07−7.45 (m, 19H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.10−5.19 (m, 4H), 4.77 (d, *J* = 13.1 Hz, 1H), 4.68−4.71 (m, 2H), 4.58 (d, *J* = 5.7 Hz, 1H), 4.47 (d, *J* = 1.7 Hz, 1H), 4.37 (d, *J* = 14.0 Hz, 1H), 4.31−4.35 (m, 1H), 4.20 (d, *J* = 14.3 Hz, 1H), 3.72 (d, *J* = 3.7 Hz, 1H), 3.66 (s, 3H), 3.37 (d, *J* = 18.8 Hz, 1H), 3.23 (d, *J* = 18.8 Hz, 1H), 2.90 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 172.1, 169.9, 163.6, 163.3, 159.2, 152.8, 135.2, 134.4, 134.2, 133.7, 130.5, 130.1, 129.1, 128.7, 128.5, 128.2, 128.0, 127.9, 126.8, 113.8, 84.9, 84.1, 79.2, 73.7, 72.0, 71.2, 70.8, 68.6, 68.1, 55.1, 42.3, 30.5. Anal. Calcd for $C_{47}H_{43}NO_{15}S$: C, 63.15; H, 4.85; N, 1.57. Found: C, 63.05; H, 4.90; N, 1.73.

Preparation of (2*S*,3*S*,4*R*,5*R*)-5-(Dibenzyloxycarbonylbenzyloxycarbonyloxy)-2-[3′-phenylsulfonyl-*N*′-(4-methoxybenzyl)succinimid-3′-yl]-3,4-dihydroxyacetonide-tetrahydrofuran (5). To a solution of **19** (570 mg, 0.64 mmol) in methylene chloride (6.3 mL, 0.1 M) were added 2,2-dimethoxypropane (313 μL, 2.56 mmol) and PPTS (16 mg, 0.064 mmol). The mixture was warmed to 35 °C and stirred for 24 h, sealed with a nitrogen balloon. The solvent was evaporated in vacuo, and the residue was applied to flash chromatography for purification (70:30 petroleum ether/ethyl acetate). The product was collected, and the solvents were evaporated in vacuo to give 549 mg (92%) of **5** as a foamy colorless glass. R_f 0.43 (70:30 petroleum ether/ethyl acetate). IR (neat): 2936, 1759, 1715, 1515, 1398, 1250, 1151, 1083 cm^{-1}. ^{1}H NMR major diastereomer (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.2 Hz, 2H), 7.10−7.40 (m, 17H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.05−5.18 (m, 6H), 4.83−4.90 (m, 2H), 4.71 (d, *J* = 12.3 Hz, 1H), 4.49 (d, *J* = 2.5 Hz, 1H), 4.37−4.45 (m, 2H), 3.65 (s, 3H), 3.38 (d, *J* = 18.8 Hz, 1H), 3.28 (d, *J* = 18.8 Hz, 1H), 1.60 (s, 3H), 1.33 (s, 3H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 172.4, 170.5, 163.5, 163.1, 152.8, 135.0, 134.9, 134.4, 134.3, 134.2, 134.1, 131.5, 130.6, 129.7, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 126.8, 114.9, 113.9, 84.2, 82.5, 80.9, 80.4, 73.1, 70.9, 68.6, 68.2, 55.0, 42.4, 30.3, 29.7, 27.2, 25.3. Anal. Calcd for $C_{50}H_{47}NO_{15}S$: C, 64.30; H, 5.07; N, 1.50. Found: C, 64.34; H, 5.23; N, 1.49.

Preparation of (2*S*,3*S*,4*R*,5*R*)-2-[*N*′-(4-Methoxybenzyl)-maleimid-3′-yl]-5-(dibenzyloxycarbonylbenzyloxycarbonyloxy)-3,4-dihydroxyacetonidetetrahydrofuran (20). To a solution of **5** (49 mg, 0.052 mmol) in chloroform (5 mL, 0.01 M) was added DBU (8.7 μL, 0.057 mmol). The mixture was stirred at room temperature for 10 min. The reaction mixture was directly applied to flash chromatography for purification (70:30 petroleum ether/ethyl acetate). The product was collected, and the solvents were evaporated in vacuo to give 23 mg (55%) of **20** as a colorless oil. R_f 0.15 (80:20 petroleum ether: ethyl acetate). IR (neat): 2938, 1756, 1710, 1514, 1402 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.37 (m, 17H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.47 (s, 1H), 5.12−5.28 (m, 6H), 5.01−5.04 (m, 1H), 4.86−4.88 (m, 1H), 4.75 (d, *J* = 2.8 Hz, 1H), 4.62−4.65 (m, 1H), 4.51 (s, 2H), 3.76 (s, 3H), 1.51 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 164.0, 163.8, 159.1, 151.0, 145.7, 134.5, 134.3, 130.0, 128.7, 128.6, 128.5, 128.4, 128.2, 114.4, 113.9, 86.7, 84.2, 84.1, 81.3, 80.8, 70.7, 70.6,

68.6, 55.2, 40.8, 27.2, 25.2. Anal. Calcd for $C_{44}H_{41}NO_{13}$: C, 66.74; H, 5.22; N, 1.77. Found: C, 66.57; H, 5.33; N, 1.72.

Preparation of (2*S*,3*S*,4*R*,5*R*)-5-Hydroxymethyl-2-[3′-phenylsulfonyl-*N*′-(4-methoxybenzyl)succinimid-3′-yl]-3,4-dihydroxyacetonidetetrahydrofuran (24). To a solution of **5** (344 mg, 0.37 mmol) in ethyl acetate (0.7 mL, 0.5 M) was added 10% Pd/C (39 mg). The air in the reaction vessel was evacuated, and a balloon of hydrogen gas was attached. The reaction was vigorously stirred over 16 h. The mixture was filtered through Celite, and the organic products were evaporated in vacuo to give 220 mg (97%) of **22** as a foamy colorless glass. IR (neat): 3212, 1745, 1712, 1515, 1401, 1314 cm^{-1}. ^1H NMR major diastereomer (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.3 Hz, 2H), 7.64 (t, J = 6.7 Hz, 1H), 7.45 (t, J = 7.0 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.81 (d, J = 8.2 Hz, 2H), 4.75−4.86 (m, 3H), 4.40−4.60 (m, 3H), 3.74 (s, 3H), 3.55 (d, J = 18.3 Hz, 1H), 3.40 (d, J = 18.6 Hz, 1H), 1.54 (s, 3H), 1.36 (s, 3H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 175.1, 170.9, 169.5, 169.4, 159.0, 135.2, 134.0, 131.5, 129.4, 128.7, 126.7, 114.8, 114.0, 84.3, 82.9, 81.5, 80.7, 79.5, 73.2, 55.3, 42.4, 30.6, 27.3, 25.3.

To cooled (0 °C) lead tetraacetate (99.9%, 106 mg, 0.24 mmol) was added a cooled solution (0 °C) of **22** (74 mg, 0.12 mmol) in dry acetone (2.4 mL, 0.05 M) and water (2.7 μL, 0.15 mmol). The mixture was allowed to warm to room temperature over 1.5 h with stirring. Sodium bisulfate (10% aqueous, five drops), water (10 mL), and brine (10 mL) were added, and the organic products were extracted with diethyl ether (3 × 10 mL). The combined organic products were dried over magnesium sulfate, filtered, and evaporated in vacuo to give a crude **23a**, which was used directly in the next step. IR (neat): 3475, 2929, 1710, 1514, 1401 cm^{-1}. ^1H NMR major diastereomer (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.9 Hz, 2H), 7.68 (m, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.25 (br s, 1H), 4.82 (s, 2H), 4.64 (d, J = 14.4 Hz, 1H), 4.55 (s, 1H), 4.54 (d, J = 14.0 Hz, 1H), 4.45 (d, J = 1.8 Hz, 1H), 3.77 (s, 3H), 3.49 (d, J = 1.9 Hz, 1H), 3.09 (d, J = 1.9 Hz, 1H), 1.39 (s, 3H), 1.25 (s, 3H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 172.8, 171.8, 170.8, 159.2, 135.2, 134.2, 131.3, 129.7, 128.7, 126.6, 115.7, 113.8, 84.1, 83.8, 81.3, 80.5, 72.8, 55.2, 42.7, 31.5, 27.2, 25.3. HRMS (*m*/*e*): calcd for $C_{26}H_{27}NO_{10}S$ 545.1356, found 545.1361.

To crude **23a** (approximately 0.12 mmol) was added 1,3-dicyclohexylcarbodiimide (49 mg, 0.24 mmol), 1-hydroxybenzotriazole (42 mg, 0.31 mmol), and THF (6 mL, 0.02 M). The mixture was stirred at room temperature for 5 h, during which time a white solid formed. The reaction was cooled to −10 °C with a brine-ice bath, and lithium borohydride (2 M in THF, 90 μL, 0.18 mmol) was added. The reaction mixture was then warmed to room temperature over 1 h. Triethylamine hydrochloride (30% aqueous, five drops), water (10 mL), and sodium bisulfate (10% aqueous, 10 drops) were added, and the organic products were extracted with diethyl ether (3 × 10 mL). The combined organic products were dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was applied to flash chromatography for purification twice (diethyl ether), to separate the product from the dicyclohexylurea. The product was collected, and the solvents were evaporated in vacuo to give 40 mg (63% over two steps) of **24** as a colorless foamy glass. R_f 0.36 (50:50 petroleum ether/ethyl acetate). IR (neat): 3532, 2936, 1712, 1515, 1399, 1316 cm^{-1}. ^1H NMR major diastereomer (400 MHz, $CDCl_3$): δ 7.84 (d, J = 7.3 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.9 Hz, 2H), 7.25 (d, J = 9.1 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.64−4.69 (m, 3H), 4.53 (d, J = 14.3 Hz, 1H), 4.37 (d, J = 4.7 Hz, 1H), 3.92 (d, J = 3.0 Hz, 1H), 3.77 (s, 3H), 3.46−3.52 (m, 3H), 3.06 (d, J = 18.6 Hz, 1H), 1.79 (t, J = 5.3 Hz, 1H), 1.54 (s, 3H), 1.36 (s, 3H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 172.9, 171.0, 159.6, 134.9, 134.8, 131.5, 129.9, 128.4, 127.0, 115.1, 113.8, 83.9, 82.9, 81.2, 81.1, 73.2, 62.1, 55.3, 42.6, 31.6, 27.3, 25.3. Anal. Calcd for $C_{26}H_{29}NO_9S$: C, 58.75; H, 5.50; N, 2.63. Found: C, 58.56; H, 5.65; N, 2.67.

Preparation of (2*S*,3*S*,4*R*,5*R*)-5-Hydroxymethyl-2-[*N*′-(4-methoxybenzyl)maleimid-3′-yl]-3,4-dihydroxyacetonidetetrahydrofuran (25). To a cooled solution (0 °C) of **24** (32 mg, 0.064 mmol) in chloroform (5 mL) was added DBU (9.0 μL, 0.064 mmol) in chloroform (1 mL). After the reaction mixture was stirred for exactly 1 min, monopotassium phosphate buffer (10% aqueous, 5 mL) was added. The organic products were extracted with chloroform (3 × 10 mL), dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was applied to flash chromatography for purification (20:80 petroleum ether/ethyl acetate). The product was collected, and the solvents were evaporated in vacuo to give 20 mg (86%) of **25** as a colorless oil. R_f 0.66 (diethyl ether). IR (neat): 3464, 2937, 1707, 1515, 1403 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.57 (s, 1H), 4.85 (dd, J = 2.5, 5.9 Hz, 1H), 4.71−4.77 (m, 2H), 4.59 (s, 2H), 4.30 (d, J = 2.4 Hz, 1H), 3.84 (d, J = 12.3 Hz, 1H), 3.78 (s, 3H), 3.70 (t, J = 10.0 Hz, 1H), 3.17 (d, J = 9.8 Hz, 1H), 1.58 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 169.1, 159.3, 145.2, 130.1, 129.5, 128.1, 114.6, 114.0, 85.1, 83.9, 82.4, 80.6, 62.9, 55.2, 41.1, 27.6, 25.3. HRMS (*m*/*e*): calcd for $C_{20}H_{23}NO_7$ 389.1475, found 389.1494.

Preparation of (2*S*,3*S*,4*R*,5*R*)-5-Hydroxymethyl-2-(3′-phenylsulfonylsuccinimid-3′-yl)-3,4-dihydroxyacetonidetetrahydrofuran (26). To a cooled solution (0 °C) of **24** (64 mg, 0.20 mmol) in acetonitrile (1.2 mL, 0.1 M) was added dropwise a cooled solution (0 °C) of CAN (229 mg, 0.42 mmol) in water (1.2 mL). The reaction mixture was allowed to warm to room temperature with stirring over 1 h. Ethyl acetate (10 mL) and brine (10 mL) were added, and the organic products were extracted with ethyl acetate (3 × 10 mL). The combined organic products were dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was applied to flash chromatography for purification twice (20:80 petroleum ether/diethyl ether). The product was collected, and the solvents were evaporated in vacuo to give 35 mg (72%) of **26** as a foamy glass. R_f 0.21 (50:50 petroleum ether/ethyl acetate). IR (neat): 3507, 3261, 2989, 2937, 1727, 1316 cm^{-1}. ^1H NMR major diastereomer (400 MHz, $CDCl_3$): δ 8.54 (br s, 1H), 8.03 (d, J = 7.5 Hz, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 4.75 (d, J = 2.1 Hz, 2H), 4.34 (d, J = 2.0 Hz, 1H), 3.99 (d, J = 2.1 Hz, 1H), 3.67 (m, 2H), 3.49 (d, J = 18.6 Hz, 1H), 3.23 (d, J = 18.8 Hz, 1H), 2.34 (br s, 1H), 1.56 (s, 3H), 1.41 (s, 3H). ^{13}C NMR major diastereomer (100 MHz, $CDCl_3$): δ 173.7, 171.2, 135.2, 134.4, 131.6, 128.6, 115.1, 83.9, 82.3, 81.3, 81.1, 74.5, 62.0, 32.1, 27.2, 25.3. HRMS (*m*/*e*): calcd for $C_{17}H_{18}NO_8S$ ($M^+ - CH_3$) 396.0753, found 396.0770.

Preparation of (2*S*,3*S*,4*R*,5*R*)-5-Hydroxymethyl-2-(3′-phenylsulfonylsuccinimid-3′-yl)-3,4-dihydroxytetrahydrofuran (27). To **26** (46 mg, 0.11 mmol) in an ice bath was added dropwise a cooled solution (0 °C) of trifluoroacetic acid in water (80:20, 0.5 mL). After 20 min of stirring at 0 °C, the mixture was dried by a silica gel filtration (ethyl acetate then acetone). All the organic products were collected and evaporated to remove the trifluoroacetic acid. The residue was applied to flash chromatography for purification (ethyl acetate). The product was collected, and the solvents were evaporated in vacuo to give 35 mg (84%) of **27** as a foamy glass. R_f 0.24 (ethyl acetate). IR (neat): 3460, 3072, 2935, 1724, 1313 cm^{-1}. ^1H NMR major diastereomer (300 MHz, acetone-d_6): δ 10.46 (br s, 1H), 8.04 (d, J = 7.3 Hz, 2H), 7.84 (t, J = 7.4 Hz, 1H), 7.67 (t, J = 7.8 Hz, 2H), 4.34−4.46 (m, 4H), 4.14 (dd, J = 11.7, 5.7 Hz, 1H), 3.95 (t, J = 5.2 Hz, 1H), 3.57−3.73 (m, 3H), 3.33 (d, J = 18.6 Hz, 1H), 3.21 (d, J = 18.6 Hz, 1H). ^{13}C NMR major diastereomer (100 MHz, acetone-d_6): δ 174.4, 172.4, 136.4, 135.8, 132.1, 129.7, 84.1, 82.8, 75.8, 72.0, 71.9, 61.6, 32.7. HRMS (*m*/*e*): calcd for $C_9H_{12}NO_6$ ($M^+ - PhSO_2$) 230.0664, found 230.0670.

Preparation of (2*S*,3*S*,4*R*,5*R*)-5-Hydroxymethyl-2-(2′,5′-dioxo-2′,5′-dihydropyrrol-3′-yl)-3,4-dihydroxytetrahydrofuran (L-Showdomycin). To a solution of **27** (18 mg, 0.047 mmol) in DMSO (11.2 mL, 4.2 mM) was added DBU (7.1 μL, 0.047 mmol). The reaction mixture was not stirred, but was manually shaken once every 30 min for 2 h. Trifluoroacetic acid (20 μL) was then added to quench the base, and the solvents were removed by a Kuglerohr vacuum distillation (100 °C, 0.3 mmHg). The residue was applied to flash chromatography for purification twice (ethyl acetate). The crude product

(5.5 mg) consisted of showdomycin and trace amounts (<10%) of unreacted starting material and the isomerized showdomycin, inseparable by chromatography. The reaction and workup had been optimized following the reaction by NMR in DMSO-d_6, and showdomycin was shown to be the only major product, but the collected material only accounted for 51% of the starting material. Showdomycin was recrystallized from acetone/benzene to give 3.5 mg (32%) of showdomycin as a white solid, verified to be pure showdomycin by spectroscopic methods. The material had been prepared from **17** that was only 70% ee. The sulfone elimination reaction was run a second time (35 mg, 0.093 mmol), and the crude product (11.2 mg) was recrystallized from acetone/benzene to give 3.5 mg (16%) of enantiopure material. Mp: 144−145 °C (D isomer lit.[27] mp 153−154 °C, lit.[18a,b] mp 150−151 °C), $[\alpha]^{26}_D$ −47.8° (c = 0.35, H_2O, lit.[27] $[\alpha]^{26}_D$ +49.9°). IR (KBr): 3462, 3405, 3232, 1769, 1703, 1640 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6/AcOD): δ 6.72 (d, J = 1.8 Hz, 1H), 4.53 (dd, J = 1.7, 3.5 Hz, 1H), 3.94 (t, J = 4.0 Hz, 1H), 3.84 (dt, J = 2.7, 6.5 Hz, 1H), 3.73 (m, 1H), 3.59 (dd, J = 2.8, 12.0 Hz, 1H), 3.43 (dd, J = 4.0, 12.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 171.7, 148.9, 128.6, 83.2, 77.4, 74.7, 70.4, 60.8;.

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Supporting Information Available: Copies of IR and ^1H and ^{13}C NMR spectra of **8**, **10**, **26**, **27**, and ***ent*-4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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