

Enantioselective Total Syntheses of FR901464 and Spliceostatin A and Evaluation of Splicing Activity of Key Derivatives

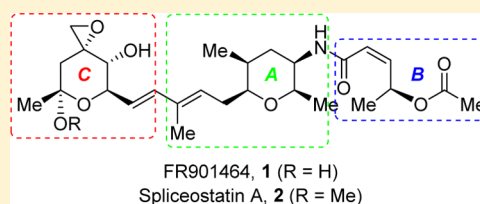
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S Supporting Information

ABSTRACT: FR901464 (**1**) and spliceostatin A (**2**) are potent inhibitors of spliceosomes. These compounds have shown remarkable anticancer activity against multiple human cancer cell lines. Herein, we describe efficient, enantioselective syntheses of FR901464, spliceostatin A, six corresponding diastereomers and an evaluation of their splicing activity. Syntheses of spliceostatin A and FR901464 were carried out in the longest linear sequence of 9 and 10 steps, respectively. To construct the highly functionalized tetrahydropyran A-ring, we utilized CBS reduction, Achmatowicz rearrangement, Michael addition, and reductive amination as key steps. The remarkable diastereoselectivity of the Michael addition was specifically demonstrated with different substrates under various reaction conditions. The side chain B was prepared from an optically active alcohol, followed by acetylation and hydrogenation over Lindlar's catalyst. The other densely functionalized tetrahydropyran C-ring was derived from readily available (*R*)-isopropylidene glyceraldehyde through a route featuring 1,2-addition, cyclic ketalization, and regioselective epoxidation. These fragments were coupled together at a late stage through amidation and cross-metathesis in a convergent manner. Six key diastereomers were then synthesized to probe the importance of specific stereochemical features of FR901464 and spliceostatin A, with respect to their *in vitro* splicing activity.



INTRODUCTION

FR901464 (**1**) was isolated from a fermentation broth of the bacterium *Pseudomonas* sp. No. 2663 by Fujisawa Pharmaceutical Co. in 1996 (Figure 1).¹ It exhibited potent anticancer activity. It showed enhancement of activity of a promoter of the SV40 DNA tumor virus at 10 nM concentration in M-8 cells. It also displayed dominant cytotoxicity against multiple human cancer cell lines with IC₅₀ values ranging from 0.6 to 3.4 nM *in vitro* and exhibited a prominent effect at 0.056–1 mg/kg

dosage against human solid tumors implanted in mice.^{1b} Yoshida and co-workers also reported that spliceostatin A (**2**) displayed remarkable antitumor activity similar to FR901464.² Spliceostatin A is a methoxy derivative of FR901464 at the C1 position and shows better chemical stability than FR901464. Most importantly, both FR901464 and spliceostatin A exhibited a novel mechanism of action by inhibiting *in vitro* splicing and promoting pre-mRNA accumulation by binding to SF3b, a protein in the spliceosome.^{2b} To date, FR901464 and the structurally distinct pladienolide B (**3**),^{3,4} which has entered human clinical trials for cancer,⁵ are the only known molecular scaffolds capable of modulating splicing and generating an antitumor response.

Exceptional biological activity of FR901464 and spliceostatin A has attracted considerable interest from the synthetic community.⁶ In 2000, the first total synthesis of FR901464 was reported by Jacobsen and co-workers using an asymmetric hetero-Diels–Alder reaction as the key transformation.⁷ The synthesis was accomplished in the longest linear sequence of 19 steps (40 total steps). Subsequently, total syntheses of FR901464 and spliceostatin A were presented by Kitahara and co-workers in 2001.⁸ They took full advantage of the chiral pool to build each fragment and completed the syntheses with 22 linear steps (41 total steps). Recently, Koide and co-workers

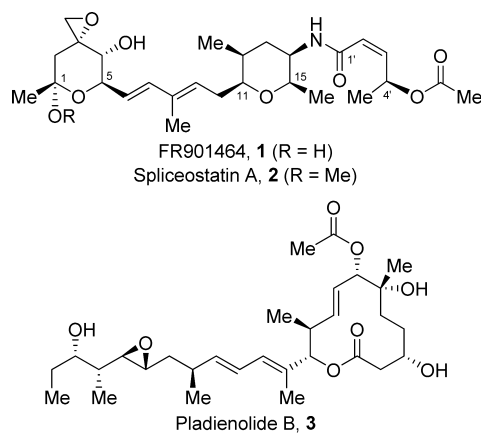


Figure 1. Structures of FR901464, spliceostatin A, and pladienolide B.

Received: April 15, 2014

Published: May 30, 2014

reported their total synthesis of FR901464 and related analogues in the longest linear sequence of 13 steps (29 total steps), featuring a Zr/Ag-promoted alkynylation and [2,3]-sigmatropic rearrangement as the key steps.⁹

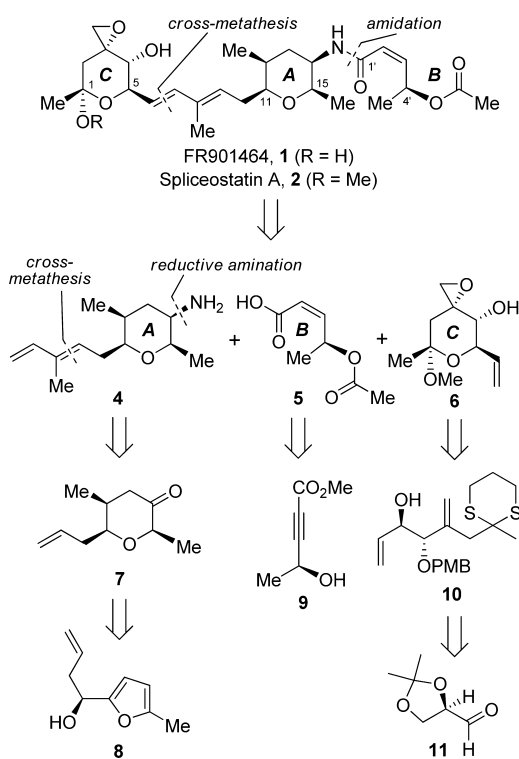
Our interest in FR901464 and spliceostatin A arose from their unique biological profile and novel mechanism of action. Therefore, we sought to develop a more concise and versatile procedure toward the syntheses of FR901464 and spliceostatin A.¹⁰ Herein, we provide a full account of our work which culminated in the total syntheses of spliceostatin A and FR901464 with the longest linear sequence of 9 or 10 steps, respectively. Six additional diastereomers were then synthesized to probe the importance of specific stereochemical features of spliceostatin A and FR901464. These derivatives were evaluated for their *in vitro* splicing activity.

RESULTS AND DISCUSSION

(I). Syntheses of FR901464 (1) and Spliceostatin A (2).

FR901464 and spliceostatin A both feature a relatively complex molecular architecture consisting of two highly functionalized tetrahydropyran A- and C-rings connected through a diene system. They also possess an ester side chain B attached to the central tetrahydropyran A-ring via an α,β -unsaturated amide bond. Furthermore, both agents contain nine stereogenic centers, two of which are quaternary centers. Our initial retrosynthetic analysis of FR901464 (1) and spliceostatin A (2) is depicted in Scheme 1. Disconnection of the diene (C6–C7) and the amide (C1'–N) leads to three fragments (4–6). We anticipated that amine 4 and acid 5 could be coupled under standard amidation conditions, followed by formation of the diene using cross-metathesis¹¹ at a very late stage of the synthesis. Fragment 4 would be derived from ketone 7 by means of cross-metathesis and reductive amination. An

Scheme 1. Retrosynthetic Analysis of FR901464 and Spliceostatin A



Achmatowicz rearrangement¹² of chiral furan 8 might be utilized to build pyranone 7. Acid 5 could be conveniently obtained from the known optically active alcohol 9.¹³ Construction of pyran 6 could be carried out by a sequence of deprotection/cyclic ketalization and regioselective epoxidation of intermediate 10. Compound 10 would be synthesized from commercially available (*R*)-isopropylidene glyceraldehyde 11.¹⁴

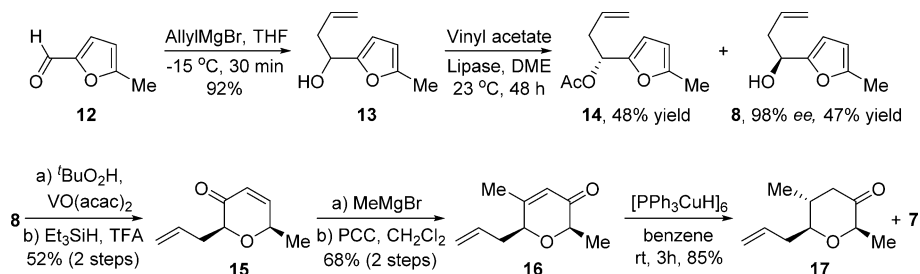
Our initial attempt at constructing pyranone 7, according to the scheme described above, commenced with preparation of the known chiral alcohol 8,¹⁵ as shown in Scheme 2. Treatment of 5-methylfurfural 12 with allylmagnesium bromide, followed by lipase resolution of the resulting racemic, homoallylic alcohol 13, provided optically active 8 in 98% *ee* (determined by HPLC analysis using a chiral column) and 47% yield. Achmatowicz reaction of 8 with *t*-BuO₂H in the presence of a catalytic amount of VO(acac)₂ furnished a rearranged hemiketal, which was directly reduced to enone 15 as a single diastereomer, according to a procedure developed by Kishi and co-workers.¹⁶ 1,2-Addition of enone 15 with methylmagnesium bromide afforded a tertiary alcohol as a mixture of diastereomers. Oxidation of the mixture of tertiary alcohols to enone 16 was achieved using 3 equiv of PCC in 75% yield.¹⁷

Our synthetic plan then required stereoselective 1,4-reduction of enone 16 to give *cis*-pyranone 7 as a major product. However, treatment of 16 with Stryker's reagent¹⁸ in benzene resulted in a mixture of desired 7 and unexpected 17 in a ratio of 1:10, which could not be separated via flash chromatography. Subsequently, a series of reducing reagents including LiAlH(*t*-BuO)₃,¹⁹ Na₂S₂O₄,²⁰ Ph₂SiH₂/ZnCl₂/(Ph₃P)₄Pd,²¹ In/NH₄Cl,²² LiAlH₄/CuI/HMPA,²³ MeLi/CuI/HMPA/Dibal-H,²⁴ Al/NiCl₂,²⁵ NaBH₄/NiCl₂,²⁶ and Li/NH₃ (liquid)²⁷ were carefully examined. Unfortunately, these conditions provided ketone 17 as the major product. Presumably, nucleophilic addition to pyranone ring 16 proceeded from the β -face (path a, Scheme 3) over the α -face (path b) due to developing nonbonding interactions. On the basis of this assumption, an alternative method for constructing pyran 7 was carried out. We speculated that nucleophilic addition of a methyl anion to structurally modified enone 18 should lead to the desired product (Scheme 3).

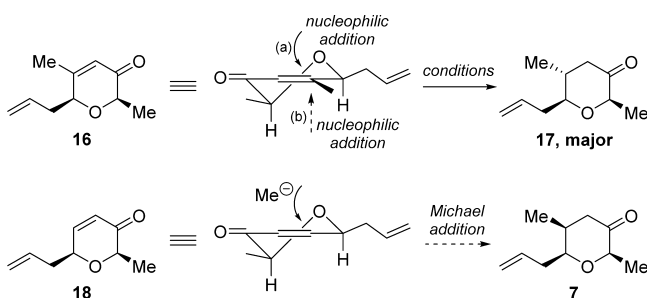
Accordingly, we turned our attention to the preparation of enone 18. As shown in Scheme 4, Corey–Bakshi–Shibata reduction²⁸ of commercially available acetyl furan 19 with (*S*)-2-Me-CBS and BH₃·Me₂S provided chiral alcohol 20 in 94% yield and 93% *ee* (determined by HPLC analysis using a chiral column). Treatment of alcohol 20 with *t*-BuO₂H and catalyst VO(acac)₂ afforded an unstable hemiketal, which was directly reduced using Et₃SiH/TFA to afford enone 18 as a single diastereomer in 63% yield over two steps. Next, the aforementioned Michael addition of enone 18 was investigated. To our delight, reaction of 18 with lithium dimethylcopper generated *in situ* efficiently furnished the expected *cis*-pyranone 7 in 92% yield and excellent diastereoselectivity (25:1).

Pyranone 7 was subjected to cross-metathesis coupling with known alkene 21²⁹ in the presence of Grubbs' second-generation catalyst³⁰ in refluxing CH₂Cl₂ for 7 h to form a terminal tosylate (Scheme 5). Base-promoted elimination³¹ of the resulting tosylate afforded diene 22 in 41% yield over two steps. Our subsequent synthesis required stereoselective installation of an amine group at the C14 position, which we envisioned could be accomplished by a substrate-controlled reductive amination reaction. As expected, treatment of ketone

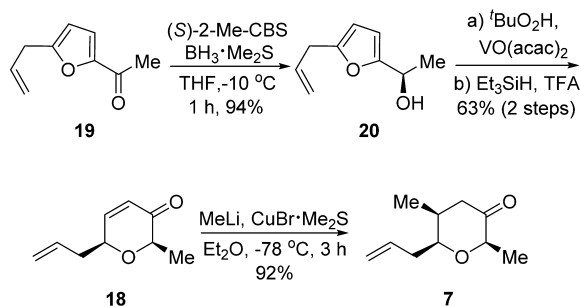
Scheme 2. Preparation and Examination of Stereoselective 1,4-Reduction



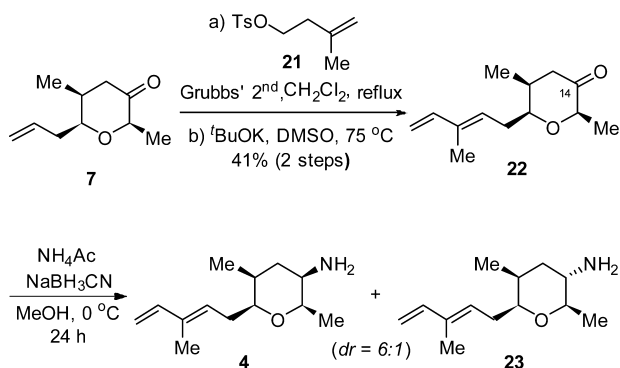
Scheme 3. Proposed Process for the 1,4-Reduction and Michael Addition



Scheme 4. Synthesis of Ketone 7



Scheme 5. Syntheses of Amines 4 and 23



22 with $\text{NH}_4\text{Ac}/\text{NaBH}_3\text{CN}$ in methanol furnished *cis*-amine 4 as a major product along with diastereomer 23 ($\text{dr} = 6:1$). The mixture could not be separated by silica gel chromatography. We therefore planned to carry out our amide formation using the mixture with the corresponding side chain acid prior to separation of isomers.

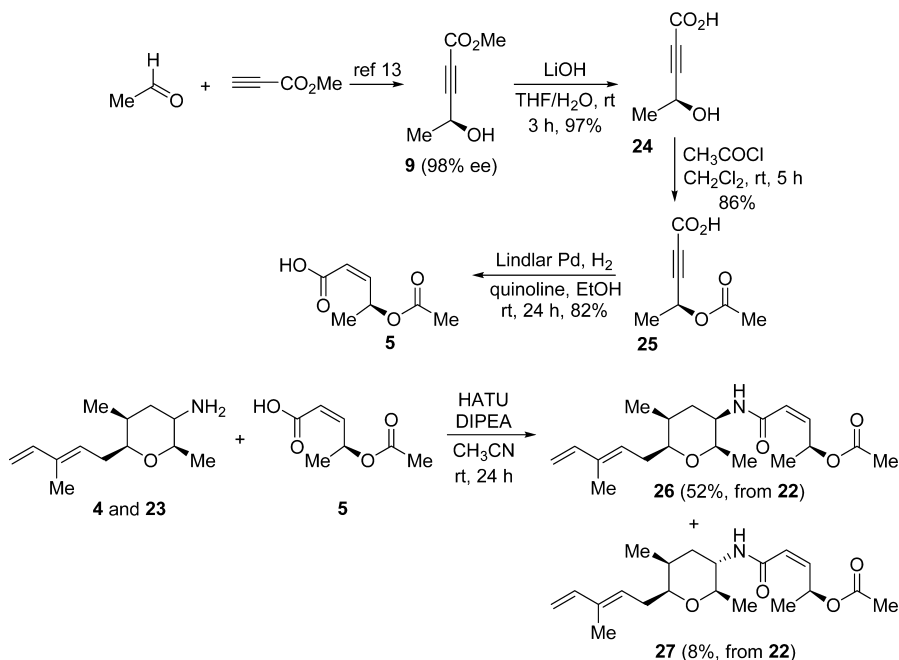
Recently, Trost and Quintard reported an efficient enantioselective protocol for the synthesis of chiral propargylic alcohols, including alcohol 9.¹³ This alcohol could be utilized to construct the *Z*-allylic acetate side chain in FR901464 (1). As

depicted in Scheme 6, hydrolysis of ester 9 with LiOH in aqueous THF for 3 h afforded acid 24 in 97% yield. Acetylation of acid 24 followed by Lindlar hydrogenation³² conveniently provided the desired side chain acid 5 in 82% yield. Subsequently, coupling carboxylic acid 5 to the mixture of amines 4 and 23, under standard amidation conditions, gave the separable diastereomers 26 and 27 in the ratio of 6.5:1.

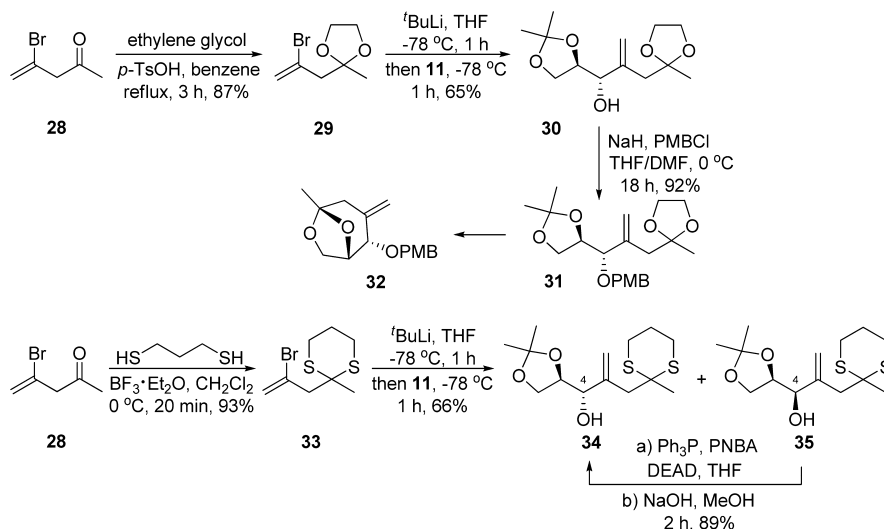
Our next objective was the enantioselective synthesis of the other highly functionalized tetrahydropyran 6 (Scheme 7). Treatment of the commercially available ketone 28 with ethylene glycol furnished dioxolane 29 in 87% yield. 1,2-Addition of the vinyl lithium reagent derived *in situ* from 29 to (*R*)-isopropylidene glyceraldehyde (11) afforded *anti*-product 30 as a major diastereomer ($\text{dr} = 5:1$). The diastereoselectivity of 30 is due to the directing effect of the α -stereogenic center of 11.³³ Treatment of alcohol 30 with NaH/PMBCl provided 31 in excellent yield. However, selective removal of the isopropylidene group in 31 without affecting the dioxolane moiety proved to be difficult after extensive examinations. A stable, bridged ketal 32 was obtained in most cases. Thus, we turned to explore substrate with a more tolerant protecting group, such as 1,3-dithiane, instead of the dioxolane moiety in 31. Reaction of ketone 28 with 1,3-propanedithiol furnished dithiane 33 in 93% yield. However, subsequent 1,2-addition of the lithium reagent generated from 33 to aldehyde 11 gave diastereomers 34 and 35 in an approximate ratio of 1:1 with no stereoselectivity. This outcome was unexpected because of the high diastereoselectivity displayed in the preparation of 30. Further investigation of this 1,2-addition in the presence of Lewis acids such as CeCl_3 ,³⁴ ZnCl_2 ,³⁵ and MgBr_2 ³⁶ in THF or Et_2O showed similar results. To improve the overall yield for the formation of 34, the undesired epimer 35 was subjected to Mitsunobu conditions³⁷ to invert the C4 stereocenter, followed by methanolysis of the resulting ester, to provide 34 in 89% yield.

The hydroxy group in 34 was then protected as its PMB ether, and the isopropylidene group was conveniently removed by treatment with TFA, in a one-pot manner, to afford diol 36 in 93% yield (Scheme 8). Regioselective tosylation of diol 36 was performed in the presence of dibutyltin oxide,³⁸ furnishing monotosylate 37 in nearly quantitative yield. Tosylate 37 was initially treated with NaH in THF to form terminal epoxide 38. However, the instability of epoxide 38 prompted us to seek one-pot conditions for epoxide formation and subsequent opening to give the chiral allylic alcohol 10. In light of this idea, tosylate 37 was subjected to excess Corey–Chaykovsky dimethylsulfonium methylide³⁹ (prepared by adding 5 equiv of *n*- BuLi dropwise to 6 equiv of trimethylsulfonium iodide) in THF for 3 h, providing allylic alcohol 10 in 88% yield. A similar functional group transformation was previously reported by Carreira and co-workers.⁴⁰

Scheme 6. Syntheses of Amides 26 and 27



Scheme 7. Preparation of Alcohol 34

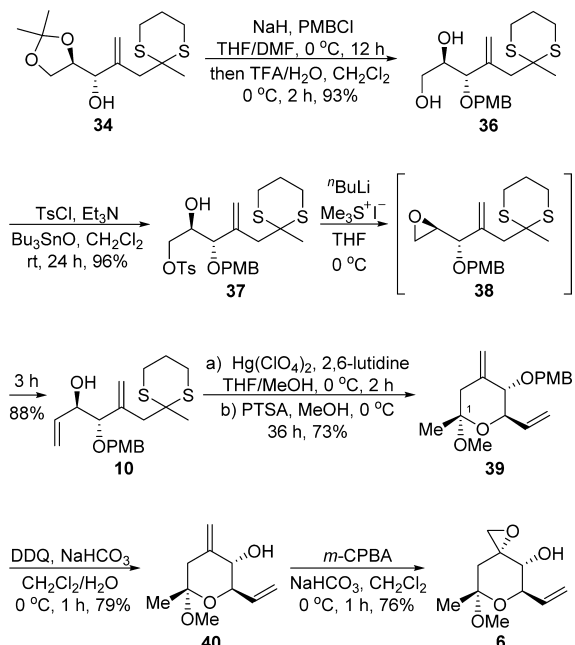


Removal of the dithiane unit in **10** and subsequent cyclic ketalization to form the pyran ring was carried out using 2 equiv of Hg(ClO₄)₂ and 10 equiv of 2,6-lutidine in methanol, thereby affording the corresponding methyl ketals as a mixture of **39** and its C1-anomer.⁴¹ Epimerization of 1-*epi*-**39** by treating the crude mixture of anomers with a catalytic amount of PTSA in methanol at 0 °C provided the single thermodynamic product **39** in 73% yield. Oxidative cleavage of the PMB group with DDQ⁴² under basic conditions gave alcohol **40** in 79% yield. The last step to build the highly functionalized tetrahydropyran **6** was hydroxyl-induced stereoselective epoxidation. The initial attempt with *t*-BuO₂H in the presence of a catalytic amount of VO(acac)₂ only resulted in decomposition of starting material. However, reaction of **40** with *m*-CPBA and NaHCO₃ in CH₂Cl₂ stereoselectively furnished the desired segment **6** as a white solid in 76% yield.

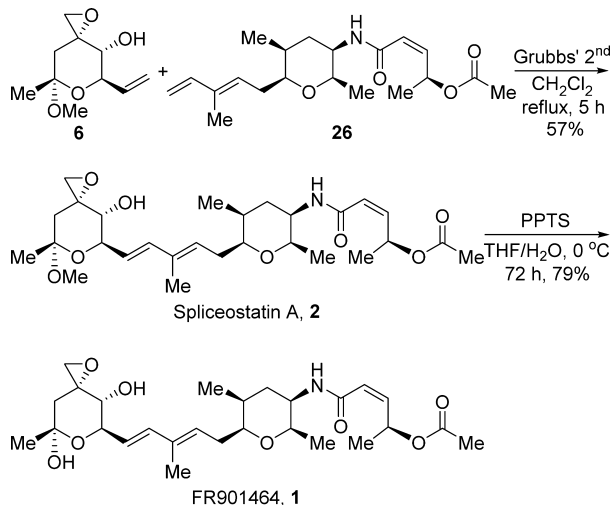
With fully functionalized fragments **6** and **26** in hand, the stage was set to examine the cross diene-ene metathesis (Scheme 9). To our delight, treatment of **6** and **26** with Grubbs' second-generation catalyst in refluxing CH₂Cl₂ gave the metathesis adduct splicingostatin A (**2**) as a white solid in 57% yield based on one recycle of unreacted **6** and **26** to the same conditions. Subsequently, hydrolysis of the ketal moiety in **2** proceeded smoothly using PPTS in wet THF⁴³ at 0 °C to afford FR901464 (**1**) as a white powder in 79% yield. The ¹H and ¹³C NMR of our synthetic FR901464 {[α]_D²³ -13.0 (*c* 0.45, CH₂Cl₂)} are in full agreement with the reported spectra of natural {[α]_D²³ -12.0 (*c* 0.5, CH₂Cl₂)}^{1a} and synthetic FR901464.⁷⁻⁹

(II). Syntheses of FR901464 (1), Splicingostatin A (2) and Their Diastereomers. During the total syntheses of FR901464 (**1**) and splicingostatin A (**2**), epimers **27** and **35** of two advanced intermediates **26** and **34** were obtained at C4 and

Scheme 8. Synthesis of Fragment 6



Scheme 9. Syntheses of Spliceostatin A and FR901464

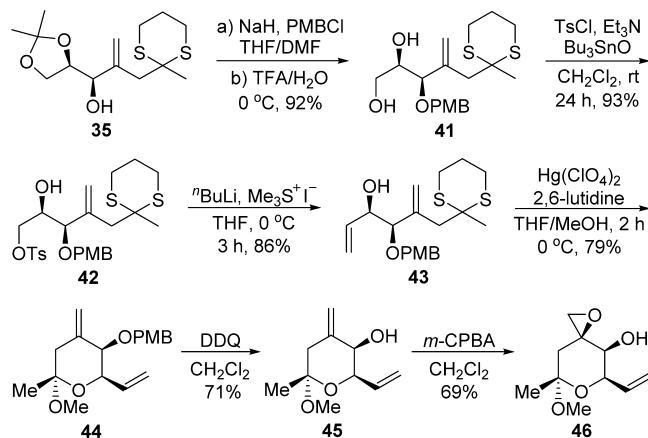


C14 positions, respectively. We envisioned that these epimers could be utilized to synthesize the corresponding diastereomers of FR901464 and spliceostatin A to probe the importance of C4 and C14 stereochemical requirement for biological activity. As shown in Scheme 10, for the preparation of the corresponding ring C, a similar strategy as pyran 6 was employed. The synthesis of epimer 46 from alcohol 35 was completed in 28% overall yield (6 steps). One detail different from the previous synthesis was that cyclic ketalization of compound 43 using $\text{Hg}(\text{ClO}_4)_2$ and 2,6-lutidine directly gave ketal 44 as a single product.

After all segments 46, 26, 6, and 27 had been synthesized, six diastereomers 47–52 of spliceostatin A and FR901464 were synthesized by following the sequence of cross-metathesis coupling and hydrolysis in good yields as solid powders (Scheme 11).

(III). **Biological Activity Studies.** The biological properties of FR901464 (1), spliceostatin A (2), along with their six

Scheme 10. Synthesis of Compound 46



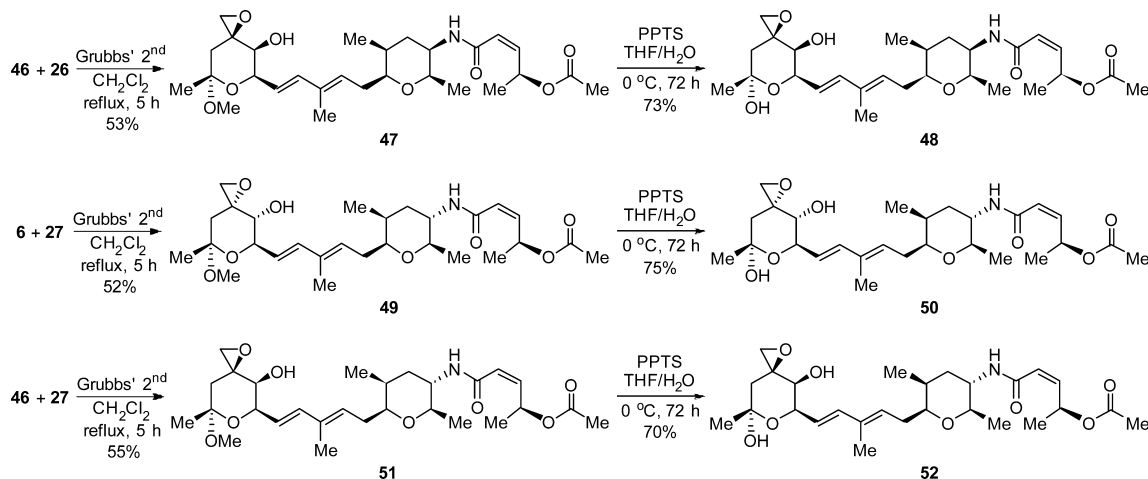
diastereomers (47–52) were evaluated in an *in vitro* splicing system (Figure 2).⁴⁴ We added the compounds to splicing reactions containing a synthetic pre-mRNA substrate, ATP, and nuclear extract from HeLa cells. Splicing chemistry was examined by denaturing PAGE to separate the substrate and product mRNA, while splicing efficiency was quantified as the percent of pre-mRNA converted to mRNA. In this system, DMSO alone has no effect on splicing efficiency, while spliceostatin A (2) and FR901464 (1) both inhibit splicing with an IC_{50} of 0.01 and 0.05 μM , respectively (Figure 2, A, C, and D). Surprisingly, compounds 47, 49, and 50 showed an approximately 100-fold reduction in potency relative to spliceostatin A, with IC_{50} values between 1 and 1.5 μM (Figure 2, A–D). Additionally, compounds 48, 51, and 52 were the least potent splicing inhibitors with IC_{50} between 10 and 35 μM .

We also examined the effect of the compounds on spliceosome assembly. Spliceosome assembles on pre-mRNA substrates via an ordered series of intermediate complexes. A subset of these complexes (H/E, A, B, and C) can be visualized by native gel analysis of the same *in vitro* splicing reactions described above. H/E and A complexes form as early intermediates that convert to B and subsequently to C complexes, at which point the splicing reaction is catalyzed. As with splicing chemistry, DMSO alone has no effect, and spliceosomes assemble over time in the normal progression from H/E \rightarrow A \rightarrow B \rightarrow C complex (Figure 2, A and B). With increasing concentrations of spliceostatin A (2) and FR901464 (1) spliceosome assembly halts at a previously observed A-like complex.¹⁹ The six diastereomers have the same effect on spliceosome assembly, but with decreased potencies that coincide directly with inhibition of splicing chemistry (Figure 2, A and B).

CONCLUSION

We have achieved the enantioselective total syntheses of spliceostatin A (2) and FR901464 (1) in 19 and 20 total steps with the longest linear sequence of 9 and 10 steps, respectively. While constructing the highly functionalized tetrahydropyran A-ring, a series of transformations including CBS reduction, Achmatowicz rearrangement, and Michael addition were successfully carried out. In particular, diastereoselectivity of the Michael addition was investigated under various reaction conditions. Side chain B was rapidly prepared from a known chiral propargylic alcohol. Subsequently, another densely

Scheme 11. Syntheses of Diastereomers of Spliceostatin A and FR901464



functionalized tetrahydropyran C-ring was built from (*R*)-isopropylidene glyceraldehyde by a route featuring cyclic ketalization and regioselective epoxidation. Finally, these three segments were coupled to afford spliceostatin A and FR901464.

Furthermore, six diastereomers of FR901464 and spliceostatin A were synthesized in the same manner. They were utilized to probe the importance of certain stereochemical features of FR901464 and spliceostatin A in terms of biological activity studies. Strikingly, all diastereomers showed over 100-fold reduction in potency relative to spliceostatin A, which indicates that each modification strongly impacts their activity at some level. In particular, the stereochemistry at C4 had the largest influence on splicing inhibitory activity, although there appears to be some synergistic effects with the modifications at C1 and C14.

EXPERIMENTAL SECTION

General Experimental Details. Those reactions which required anhydrous conditions were carried out under an argon atmosphere using oven-dried glassware (120 °C). All chemicals and reagents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were obtained as follows: anhydrous tetrahydrofuran and diethyl ether were distilled from sodium metal under argon; anhydrous dichloromethane was dried via distillation from CaH₂ immediately prior to use under argon; anhydrous methanol and ethanol were distilled from activated magnesium under argon. All other solvents were reagent grade. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 μm thickness, F-254 indicator). Flash chromatography was performed using 230–400 mesh, 60 Å pore diameter silica gel. ¹H NMR spectra were recorded at 400, 500, or 800 MHz. ¹³C NMR spectra were recorded at 100 or 150 MHz. Chemical shifts are reported in parts per million and are referenced to the deuterated residual solvent peak. NMR data are reported as δ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet). IR spectra were recorded on a Varian 2000 infrared spectrophotometer and are reported as cm⁻¹. LRMS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center using both ion trap and quadrupole analyzers. Melting points were measured on a melting point apparatus and were uncorrected.

Alcohol (8). To a solution of 5-methylfurfural **12** (550 mg, 5.1 mmol) in THF (10 mL) at -15 °C was added allyl magnesium bromide (1.0 M in THF, 6.5 mL, 6.5 mmol) dropwise over 10 min. The reaction mixture was stirred for an additional 20 min and then quenched with water (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over

MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (10:1 to 8:1 hexane/ethyl acetate) to afford racemic **13** (700 mg, 92%) as a light yellow oil.

To a solution of racemic **13** (700 mg, 4.6 mmol) in dimethoxyethane (11 mL) at 23 °C under argon was added vinyl acetate (2.77 g, 32.2 mmol) and Amano lipase (1.86 g, 10 wt % on Celite). The resulting mixture was stirred for 12 h at 23 °C, and then it was filtered and concentrated. The residue was purified via silica gel chromatography (15:1 to 8:1 hexane/ethyl acetate) to afford (*R*)-ester **14** (429 mg, 48% yield) and (*S*)-alcohol **8** (329 mg, 47% yield, 98% *ee*) as colorless oil. Optical purity (98% *ee*) was determined by HPLC analysis using a Daicel Chiralcel OD-H column (98.5:1.5 hexane:isopropanol, flow rate 0.5 mL/min, UV = 210 nm, retention time: *t*_{minor} = 22.7 min, *t*_{major} = 24.1 min). (*S*)-Alcohol **8**: [α]_D²⁰ -34.3 (c 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.10 (d, *J* = 2.4 Hz, 1H), 5.89 (s, 1H), 5.80 (ddd, *J* = 20.0, 10.0, 7.2 Hz, 1H), 5.18 (s, 1H), 5.12 (d, *J* = 11.2 Hz, 1H), 4.65 (t, *J* = 2.4 Hz, 1H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.27 (s, 3H), 2.24 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.1, 151.6, 133.9, 118.2, 106.9, 105.9, 66.8, 39.9, 13.4; IR (neat) 3399, 1694, 1565, 1221, 1022 cm⁻¹; LRMS (ESI), *m/z* 175.1 (M + Na)⁺.

Enone (15). To a solution of **8** (791 mg, 5.2 mmol) in dichloromethane (12 mL) at 0 °C was added VO(acac)₂ (138 mg, 0.5 mmol) and ^tBuOOH (5.5 M, 1.23 mL, 6.8 mmol). After stirring for 2 h, the mixture was treated with water (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated to give the crude hemiketal as a yellow oil.

The crude hemiketal was dissolved in anhydrous dichloromethane (10 mL) at -45 °C under argon. Et₃SiH (4.15 mL, 25.9 mmol) and TFA (5.79 mL, 77.9 mmol) were then added subsequently. After stirring at -45 °C for 1 h, the mixture was treated with 30% NaHCO₃ to adjust the pH to a range of ~8–9. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (15:1 to 10:1 hexane/ethyl acetate) to afford **15** (412 mg, 52%, 2 steps) as a light yellow oil: [α]_D²⁰ -21.3 (c 1.05, ethyl acetate); ¹H NMR (400 MHz, CDCl₃) δ 6.89 (dd, *J* = 10.0, 1.2 Hz, 1H), 6.07 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.94–5.80 (m, 1H), 5.13 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.50–4.41 (m, 1H), 4.00 (ddd, *J* = 8.0, 4.0, 2.0 Hz, 1H), 2.77–2.68 (m, 1H), 2.40 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H), 1.38 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.4, 152.7, 134.0, 126.3, 117.2, 80.0, 70.3, 33.9, 20.5; IR (neat) 1784, 1694, 1309, 1172, 918 cm⁻¹; LRMS (ESI), *m/z* 175.1 (M + Na)⁺.

Enone (16). To a solution of enone **15** (592 mg, 3.9 mmol) in THF (8 mL) at 0 °C was added methyl magnesium bromide (3.0 M in Et₂O, 1.69 mL, 5.1 mmol) dropwise over 5 min. The reaction mixture was stirred for an additional 1 h and then quenched with water (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL).

Alcohol (20). To a solution of (*S*)-2-Me-CBS catalyst (4.357 g, 15.7 mmol) in anhydrous THF (80 mL) at 0 °C under argon was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (3.3 mL, 34.6 mmol). After stirring for 30 min, the mixture was cooled to -10 °C, and a solution of **19** (4.716 g, 31.4 mmol) in THF (20 mL) was added. The resulting mixture was stirred for 30 min and then quenched with MeOH (10 mL) and water (20 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (10:1 to 6:1 hexane/ethyl acetate) to afford **20** (4.49 g, 94% yield, 93% ee) as a colorless oil. Optical purity (93% ee) was determined by HPLC analysis using a Daicel Chiralcel OD-H column (98:2 hexane:isopropanol, flow rate 0.5 mL/min, UV = 210 nm, retention time: $t_{\text{minor}} = 25.3$ min, $t_{\text{major}} = 28.4$ min). $[\alpha]_{\text{D}}^{20} +20.6$ (c 1.10, ethyl acetate); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.12 (d, $J = 2.8$ Hz, 1H), 6.00–5.86 (m, 2H), 5.21–5.05 (m, 2H), 4.83 (q, $J = 6.0$ Hz, 1H), 3.37 (d, $J = 6.4$ Hz, 2H), 2.02 (s, 1H), 1.51 (d, $J = 6.4$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.3, 153.4, 133.8, 116.9, 106.0, 105.8, 63.6, 32.6, 21.1; IR (neat) 3366, 2361, 1643, 1558, 1371, 1181, 1077, 919 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_9\text{H}_{12}\text{O}_2\text{Na}$ 175.0735, found 175.0736.

Enone (18). To a solution of **20** (2.37 g, 15.6 mmol) in dichloromethane (60 mL) at 0 °C was added $\text{VO}(\text{acac})_2$ (414 mg, 1.6 mmol) and $^t\text{BuOOH}$ (5.5 M, 3.7 mL, 20.4 mmol). After stirring for 3 h, the mixture was treated with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated to give the crude hemiketal as a yellow oil.

The crude hemiketal was dissolved in anhydrous dichloromethane (60 mL) at -45 °C under argon. Et_3SiH (12.47 mL, 78.1 mmol) and TFA (17.40 mL, 234.3 mmol) were then added subsequently. After stirring at -45 °C for 2 h, the mixture was treated with 30% NaHCO_3 to adjust the pH to a range of ~8–9. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (40:1 to 20:1 hexane/ethyl acetate) to afford **18** (1.497 g, 63%, 2 steps) as a light yellow oil: $[\alpha]_{\text{D}}^{20} +34.4$ (c 1.03, ethyl acetate); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.94 (d, $J = 10.0$ Hz, 1H), 6.09 (dd, $J = 10.0, 2.4$ Hz, 1H), 5.92–5.77 (m, 1H), 5.25–5.09 (m, 2H), 4.40 (t, $J = 5.6$ Hz, 1H), 4.07 (dt, $J = 6.4, 5.2$ Hz, 1H), 2.55–2.33 (m, 2H), 1.38 (d, $J = 6.4$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 197.0, 150.6, 133.0, 126.7, 118.4, 77.0, 73.5, 39.0, 15.4; IR (neat) 1732, 1694, 1446, 1374, 1237, 1097, 924, 741 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_9\text{H}_{12}\text{O}_2\text{Na}$ 175.0735, found 175.0737.

Ketone (7). To a suspension of $\text{CuBr} \cdot \text{Me}_2\text{S}$ (1.30 g, 6.3 mmol) in anhydrous Et_2O (10 mL) at -78 °C under argon was added MeLi (3 M, 3.9 mL, 11.7 mmol). After stirring for 1 h, a solution of **18** (594 mg, 3.9 mmol) in Et_2O (5 mL) was added. The resulting mixture was stirred for an additional 2 h and then quenched with water (5 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (50:1 to 30:1 hexane/ethyl acetate) to afford **7** (604 mg, 92%) as a colorless oil: $[\alpha]_{\text{D}}^{20} -75.1$ (c 1.01, ethyl acetate); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.87–5.73 (m, 1H), 5.15–4.99 (m, 2H), 3.95–3.83 (m, 2H), 2.61 (dd, $J = 11.2, 6.0$ Hz, 1H), 2.43–2.23 (m, 3H), 2.15 (dt, $J = 14.4, 7.2$ Hz, 1H), 1.23 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 208.6, 134.5, 117.0, 79.3, 78.5, 46.6, 36.8, 34.8, 14.9, 12.9; IR (neat) 1732, 1715, 1417, 1379, 1244, 1078, 984, 921 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$)⁺ Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2\text{Na}$ 191.1048, found 191.1050.

Diene (22). A solution of **7** (240 mg, 1.4 mmol) was prepared in anhydrous dichloromethane (4 mL) at room temperature under argon. To a stirred solution of **21** (3.428 g, 14.3 mmol) in anhydrous dichloromethane (10 mL) was added an aliquot of solution **7** (1 mL) followed by Grubbs' second-generation catalyst (121 mg, 0.14 mmol) under argon. The resulting mixture was heated at reflux for 1.5 h, after which an additional aliquot of solution **7** (1 mL) was added. This

additional process was repeated after 3 and 5 h. Following 7 h of reaction time, the mixture was concentrated under reduced pressure. The residue was purified via silica gel chromatography (10:1 to 5:1 hexane/ethyl acetate) to afford the crude terminal tosylate as a yellow oil.

The crude terminal tosylate was then dissolved in DMSO (4 mL) followed by addition of $^t\text{BuOK}$ (320 mg, 2.9 mmol). The resulting mixture was heated to 75 °C for 12 h, cooled to room temperature, and diluted with CH_2Cl_2 (10 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (50:1 to 40:1 hexane/acetone) to afford **22** (122 mg, 41%, 2 steps) as a colorless oil: $[\alpha]_{\text{D}}^{20} -33.4$ (c 1.07, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.39 (dd, $J = 17.2, 10.4$ Hz, 1H), 5.50 (t, $J = 7.2$ Hz, 1H), 5.13 (d, $J = 14.8$ Hz, 1H), 4.98 (d, $J = 10.8$ Hz, 1H), 4.00–3.85 (m, 2H), 2.64 (dd, $J = 15.2, 6.0$ Hz, 1H), 2.53–2.41 (m, 1H), 2.38–2.25 (m, 3H), 1.78 (s, 3H), 1.28 (d, $J = 6.4$ Hz, 3H), 0.98 (d, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 208.7, 141.2, 135.9, 127.9, 111.4, 79.5, 78.8, 46.7, 34.9, 31.4, 15.0, 13.1, 11.9; IR (neat) 1724, 1643, 1607, 1444, 1385, 1260, 1228, 1111, 894 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2\text{Na}$ 231.1361, found 231.1355.

Acid (24). To a solution of **9** (539 mg, 4.2 mmol) in THF (5 mL) and water (1 mL) at room temperature was added LiOH (303 mg, 12.7 mmol). After stirring for 3 h, hydrochloric acid (37%, 1.2 mL) was added at 0 °C to adjust the pH to a range of ~1–2. The resulting mixture was concentrated, and the residue was purified via silica gel chromatography (10:1 to 5:1 dichloromethane/methanol) to afford **24** (466 mg, 97%) as a colorless oil: $[\alpha]_{\text{D}}^{20} -48.5$ (c 1.08, ethyl acetate); $^1\text{H NMR}$ (400 MHz, CD_3OH) δ 5.06 (brs, 2H), 4.58 (q, $J = 6.8$ Hz, 1H), 1.44 (d, $J = 6.4$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CD_3OH) δ 156.2, 90.0, 76.4, 58.2, 23.7; IR (KBr) 3379, 2990, 2237, 1699, 1376, 1269, 1057 cm^{-1} ; LRMS (ESI), m/z 137.0 ($\text{M} + \text{Na}$)⁺.

Ester (25). To a solution of **24** (477 mg, 4.2 mmol) in anhydrous dichloromethane (10 mL) at room temperature under argon was added an excess of acetyl chloride (5 mL). After stirring for 5 h, the resulting mixture was concentrated, and the residue was purified via silica gel chromatography (1:1 to 1:2 hexane/ethyl acetate) to afford **25** (561 mg, 86%) as a colorless oil: $[\alpha]_{\text{D}}^{20} -114.4$ (c 1.06, ethyl acetate); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.64 (brs, 1H), 5.51 (q, $J = 6.8$ Hz, 1H), 2.09 (s, 3H), 1.54 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.1, 156.4, 86.9, 75.7, 59.5, 20.8, 20.1; IR (neat) 3501, 2996, 2249, 1732, 1374, 1233, 1050 cm^{-1} ; LRMS (ESI), m/z 179.0 ($\text{M} + \text{Na}$)⁺.

Acid (5). To a solution of **25** (500 mg, 3.2 mmol) in anhydrous ethanol (10 mL) was added Lindlar catalyst (58 mg) and quinoline (38 μL , 0.3 mmol). The mixture was exposed to an atmosphere of H_2 at room temperature. After 24 h, the resulting mixture was filtered and concentrated. The residue was purified via silica gel chromatography (10:1 to 8:1 hexane/ethyl acetate) to afford **5** (415 mg, 82%) as a colorless oil: $[\alpha]_{\text{D}}^{20} +20.6$ (c 1.18, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.30–6.19 (m, 2H), 5.86–5.78 (m, 1H), 2.05 (s, 3H), 1.38 (d, $J = 5.6$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.5, 170.2, 150.4, 119.3, 68.7, 21.1, 19.5; IR (neat) 2986, 1732, 1652, 1434, 1372, 1244, 1121, 1049, 826 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_7\text{H}_{10}\text{O}_4\text{Na}$ 181.0477, found 181.0479.

Amides 26 and 27. To a solution of **22** (65 mg, 0.3 mmol) in anhydrous methanol (3 mL) at 0 °C under argon was added ammonium acetate (482 mg, 6.3 mmol) and NaBH_3CN (99 mg, 1.6 mmol). The reaction mixture was then gradually warmed to room temperature. After stirring for 24 h, the reaction mixture was added to aqueous NaOH (4 M, 1.2 mL) to adjust the pH to a range of ~8–9 and then diluted with ethyl acetate (10 mL). The resulting mixture was directly dried over MgSO_4 , filtered, and concentrated to give crude amines (**4** and **23**) as a light yellow oil.

To a stirred solution of acid **5** (59 mg, 0.4 mmol) in anhydrous acetonitrile (2 mL) at room temperature under argon was added HATU (143 mg, 0.4 mmol) and DIPEA (273 μL , 1.6 mmol). The resulting mixture was then transferred via cannula to a stirred solution of crude amines (**4** and **23**) in acetonitrile (2 mL) at room

temperature and rinsed with additional acetonitrile (1 mL). After stirring for 24 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (3 mL) and then diluted with ethyl acetate (15 mL). The aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (5:1 to 3:1 hexane/ethyl acetate) to afford amide **26** (57 mg, 52%, 2 steps) and amide **27** (9 mg, 8%, 2 steps) as colorless oil. Amide **26**: $[\alpha]_{\text{D}}^{20} -58.6$ (*c* 1.05, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.36 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.26 (dt, *J* = 13.6, 6.8 Hz, 1H), 6.00 (d, *J* = 8.8 Hz, 1H), 5.89 (dd, *J* = 11.6, 8.0 Hz, 1H), 5.70 (d, *J* = 11.6 Hz, 1H), 5.46 (t, *J* = 6.8 Hz, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 3.94 (t, *J* = 3.2 Hz, 1H), 3.67 (dd, *J* = 6.4, 2.0 Hz, 1H), 3.54 (dt, *J* = 7.6, 2.8 Hz, 1H), 2.45–2.32 (m, 1H), 2.30–2.17 (m, 1H), 2.04 (s, 3H), 2.00–1.86 (m, 2H), 1.84–1.75 (m, 1H), 1.75 (s, 3H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.4, 164.8, 143.6, 141.3, 135.7, 128.1, 122.5, 111.1, 80.8, 76.0, 68.9, 47.1, 35.8, 31.9, 28.9, 21.2, 20.0, 17.8, 15.0, 11.9; IR (neat) 3358, 2977, 2934, 1739, 1668, 1634, 1520, 1369, 1243, 1049, 1011 cm^{-1} ; HRMS (ESI), *m/z* (*M* + *Na*)⁺ calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_4\text{Na}$ 372.2151, found 372.2152. Amide **27**: $[\alpha]_{\text{D}}^{20} -6.9$ (*c* 1.01, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.80 (d, *J* = 8.8 Hz, 1H), 6.35 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.82–5.75 (m, 2H), 5.66 (t, *J* = 10.0 Hz, 1H), 5.44 (t, *J* = 7.2 Hz, 1H), 5.09 (d, *J* = 17.6 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 3.98–3.82 (m, 1H), 3.46 (t, *J* = 6.0 Hz, 1H), 3.24 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.40–2.30 (m, 1H), 2.24 (q, *J* = 7.6 Hz, 1H), 2.05 (s, 3H), 1.94–1.79 (m, 2H), 1.74 (s, 3H), 1.57 (dt, *J* = 12.4, 4.4 Hz, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 171.5, 165.0, 141.3, 138.0, 135.4, 128.5, 125.4, 110.9, 79.5, 78.1, 69.1, 46.9, 38.2, 31.7, 31.3, 21.2, 20.2, 19.1, 12.0, 11.9; IR (neat) 3300, 2973, 2933, 1738, 1668, 1634, 1538, 1371, 1242, 1048, 1014 cm^{-1} ; HRMS (ESI), *m/z* (*M* + *Na*)⁺ calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_4\text{Na}$ 372.2151, found 372.2153.

1,3-Dioxolane (29). A solution of ketone **28** (4.09 g, 25.1 mmol), ethylene glycol (2.8 mL, 50.2 mmol), and *p*-TsOH (474 mg, 2.5 mmol) in benzene (60 mL) under argon was refluxed for 2 h in a Dean–Stark apparatus. The reaction mixture was then cooled and poured into saturated aqueous NaHCO_3 solution (10 mL), and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (50:1 to 20:1 hexane/ethyl acetate) to afford 1,3-dioxolane **29** (4.52 g, 87%) as a light yellow oil: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.72 (s, 1H), 5.60 (d, *J* = 0.8 Hz, 1H), 3.99 (brs, 4H), 2.80 (s, 2H), 1.43 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 127.0, 121.1, 108.7, 64.6, 49.6, 23.9; IR (neat) 1627, 1380, 1157, 1046 cm^{-1} ; LRMS (ESI), *m/z* 229.0 (*M* + *Na*)⁺.

Alcohol (30). To a solution of **29** (1.03 g, 4.9 mmol) in anhydrous THF (20 mL) at -78 °C under argon was added *tert*-butyllithium (1.7 M, 7.33 mL, 12.5 mmol). After stirring at -78 °C for 1 h, a solution of aldehyde **11** (971 mg, 7.5 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 1 h and then quenched with water (10 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (8:1 to 4:1 hexane/ethyl acetate) to afford alcohol **30** (835 mg, 65%) as a colorless oil: $[\alpha]_{\text{D}}^{20} +25.9$ (*c* 1.09, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.28 (s, 1H), 5.18 (s, 1H), 4.13–3.98 (m, 4H), 3.97 (s, 3H), 3.82 (d, *J* = 3.2 Hz, 1H), 2.58 (d, *J* = 14.0 Hz, 1H), 2.48 (d, *J* = 14.0 Hz, 1H), 1.43 (s, 3H), 1.36 (d, *J* = 4.4 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 142.2, 118.9, 109.7, 109.4, 75.6, 66.5, 64.8, 41.6, 26.7, 25.3, 24.1; IR (neat) 3450, 1380, 1215, 1049 cm^{-1} ; LRMS (ESI), *m/z* 281.1 (*M* + *Na*)⁺.

Ether (31). To a solution of **30** (318 mg, 1.2 mmol) in anhydrous THF (3 mL) and DMF (1.5 mL) at 0 °C under argon was added NaH (60%, 150 mg, 3.7 mmol). After stirring at 0 °C for 1 h, PMBCl (335 μL , 2.5 mmol) was added dropwise. The resulting mixture was stirred for 11 h at this temperature and then concentrated. The residue was purified via silica gel chromatography (6:1 to 4:1 hexane/ethyl acetate) to afford ether **31** (429 mg, 92%) as a light yellow oil: $[\alpha]_{\text{D}}^{20} +15.3$ (*c*

1.07, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.34 (s, 1H), 5.31 (s, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.10–3.86 (m, 8H), 3.80 (s, 3H), 2.47 (s, 2H), 1.41 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.1, 142.6, 130.6, 129.4, 116.7, 113.7, 109.9, 109.3, 82.1, 77.7, 70.5, 67.1, 64.7, 64.3, 55.3, 41.3, 26.6, 25.4, 23.9; IR (neat) 1613, 1514, 1249, 1049 cm^{-1} ; HRMS (ESI), *m/z* (*M* + *Na*)⁺ calcd for $\text{C}_{21}\text{H}_{30}\text{O}_6\text{Na}$ 401.1940, found 401.1943.

Ketal (32). To a solution of **31** (48 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (3 mL) and MeOH (1 mL) at 0 °C under argon was added *p*-TsOH (5 mg, 0.03 mmol). After stirring at 0 °C for 5 h, the mixture was concentrated. The residue was purified via silica gel chromatography (8:1 to 4:1 hexane/ethyl acetate) to afford ketal **32** (26 mg, 73%) as a light yellow oil: $[\alpha]_{\text{D}}^{20} -58.1$ (*c* 0.97, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.27 (d, *J* = 10.0 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.18 (s, 1H), 5.03 (s, 1H), 4.65 (s, 1H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H), 3.78 (d, *J* = 6.8 Hz, 1H), 3.61 (d, *J* = 7.2 Hz, 1H), 3.56 (s, 1H), 2.63 (d, *J* = 14.0 Hz, 1H), 2.32 (d, *J* = 14.0 Hz, 1H), 1.51 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 159.2, 138.7, 130.1, 129.5, 118.5, 113.8, 107.7, 77.4, 77.1, 68.9, 66.7, 55.3, 42.4, 23.5; IR (neat) 1613, 1514, 1249, 1023 cm^{-1} ; LRMS (ESI), *m/z* 299.1 (*M* + *Na*)⁺.

1,3-Dithiane (33). To a solution of **11** (3.43 g, 21.1 mmol) and 1,3-propanedithiol (2.54 mL, 25.3 mmol) in anhydrous dichloromethane (55 mL) at 0 °C under argon was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.6 mL, 21.1 mmol) dropwise over 5 min. The reaction mixture was stirred for an additional 15 min and then quenched with 5% NaOH (120 mL). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (30:1 to 15:1 hexane/ethyl acetate) to afford **33** (4.939 g, 93%) as a light yellow oil: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.72 (s, 1H), 5.68 (d, *J* = 1.2 Hz, 1H), 3.12 (s, 2H), 2.97–2.75 (m, 4H), 2.08–1.85 (m, 2H), 1.71 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 126.5, 122.5, 51.3, 47.8, 27.7, 26.8, 24.7; IR (neat) 1622, 1423, 1372, 1276, 1139, 1071, 906, 816 cm^{-1} ; LRMS (ESI), *m/z* 275.0 (*M* + *Na*)⁺.

Alcohols 34 and 35. To a solution of **33** (2.27 g, 9.1 mmol) in anhydrous THF (45 mL) at -78 °C under argon was added *tert*-butyllithium (1.7 M, 13.3 mL, 22.6 mmol). After stirring at -78 °C for 1 h, a solution of aldehyde **11** (1.75 g, 13.5 mmol) in THF (15 mL) was added. The resulting mixture was stirred for 1 h and then quenched with water (20 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (60 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (20:1 to 15:1 hexane/ethyl acetate) to afford **34** (932 mg, 34%) and **35** (877 mg, 32%) as a colorless oil. Compound **34**: $[\alpha]_{\text{D}}^{20} -5.6$ (*c* 1.07, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.43 (s, 1H), 5.16 (s, 1H), 4.41 (d, *J* = 5.2 Hz, 1H), 4.20 (q, *J* = 6.0 Hz, 1H), 4.00–3.90 (m, 2H), 2.97–2.69 (m, 6H), 2.52 (brs, 1H), 2.05–1.78 (m, 2H), 1.63 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 143.6, 117.8, 109.4, 77.7, 73.3, 65.3, 48.3, 45.1, 28.0, 26.9, 26.8, 26.6, 25.1, 24.9; IR (neat) 3460, 2907, 1643, 1424, 1372, 1213, 1157, 1066, 909 cm^{-1} ; HRMS (ESI), *m/z* (*M* + *Na*)⁺ calcd for $\text{C}_{14}\text{H}_{24}\text{O}_3\text{S}_2\text{Na}$ 327.1065, found 327.1067. Compound **35**: $[\alpha]_{\text{D}}^{20} +8.8$ (*c* 1.03, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.36 (s, 1H), 5.21 (s, 1H), 4.30–4.23 (m, 2H), 4.01 (t, *J* = 8.0 Hz, 1H), 3.80 (t, *J* = 7.2 Hz, 1H), 3.02–2.78 (m, 5H), 2.75–2.62 (m, 2H), 2.08–1.89 (m, 2H), 1.65 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 143.9, 118.5, 109.7, 77.8, 74.5, 66.3, 48.3, 44.8, 27.9, 26.8, 26.6, 25.3, 24.9; IR (neat) 3467, 2922, 1643, 1455, 1372, 1212, 1157, 1067, 909 cm^{-1} ; HRMS (ESI), *m/z* (*M* + *Na*)⁺ calcd for $\text{C}_{14}\text{H}_{24}\text{O}_3\text{S}_2\text{Na}$ 327.1065, found 327.1068.

Conversion of Alcohol 35 into Alcohol 34. To a solution of **35** (230 mg, 0.8 mmol) in anhydrous THF (4 mL) at room temperature under argon was added triphenylphosphine (397 mg, 1.5 mmol) and *p*-nitrobenzoic acid (253 mg, 1.5 mmol), which was stirred for a period of 10 min. DEAD (239 μL , 1.5 mmol) was then added dropwise. After stirring at room temperature for an additional 12 h, the reaction

mixture was diluted with CH_2Cl_2 (10 mL) and quenched with 10% NaHCO_3 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated to give crude product as a yellow oil.

The aforementioned crude product was dissolved in anhydrous MeOH (5 mL) at room temperature under argon, and NaOH (91 mg, 2.3 mmol) was then added. After stirring at room temperature for 2 h, the reaction mixture was concentrated to give a yellow oil which was then purified via silica gel chromatography (10:1 to 5:1 hexane/ethyl acetate) to afford **34** (205 mg, 89%) as a colorless oil.

Diol (36). To a solution of **34** (1.206 g, 3.9 mmol) in anhydrous THF (12 mL) and DMF (6 mL) at 0°C under argon was added NaH (60%, 476 mg, 11.9 mmol). After stirring at 0°C for 1 h, PMBCl (1.08 mL, 7.9 mmol) was added dropwise. The resulting mixture was stirred for 11 h at this temperature and then concentrated. The residue was then dissolved in anhydrous CH_2Cl_2 (40 mL) at 0°C , to which TFA (3 mL) and H_2O (3 mL) were added. After stirring at 0°C for 2 h, the reaction mixture was concentrated to give a yellow oil which was purified via silica gel chromatography (4:1 to 1:2 hexane/ethyl acetate) to afford **36** (1.417 g, 93%) as a light yellow oil: $[\alpha]_{\text{D}}^{20} +32.1$ (c 1.07, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.25 (d, $J = 8.0$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.50 (s, 1H), 5.41 (s, 1H), 4.62 (d, $J = 11.2$ Hz, 1H), 4.37–4.25 (m, 2H), 3.80 (s, 3H), 3.82–3.67 (m, 2H), 3.64 (d, $J = 7.6$ Hz, 1H), 3.00–2.75 (m, 5H), 2.64 (d, $J = 14.8$ Hz, 1H), 2.29 (brs, 1H), 2.05–1.89 (m, 2H), 1.72 (s, 3H), 1.62 (brs, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 152.3, 140.9, 130.1, 129.4, 118.5, 113.8, 84.3, 71.4, 71.3, 62.7, 55.2, 48.4, 43.5, 28.4, 26.9, 26.8, 24.9; IR (neat) 3418, 2909, 1613, 1514, 1423, 1248, 1034, 909 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4\text{S}_2\text{Na}$ 407.1327, found 407.1322.

Tosylate (37). To a solution of **36** (2.43 g, 6.3 mmol) in anhydrous dichloromethane (50 mL) at room temperature under argon was added Et_3N (1.33 mL, 9.5 mmol), Bu_3SnO (95 mg, 0.4 mmol), and TsCl (1.443 g, 7.6 mmol) subsequently. The reaction mixture was stirred for 24 h and then concentrated. The residue was purified via silica gel chromatography (4:1 to 3:1 hexane/ethyl acetate) to afford **37** (3.270 g, 96%) as a light yellow oil: $[\alpha]_{\text{D}}^{20} +22.0$ (c 1.10, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 5.43 (s, 1H), 5.40 (s, 1H), 4.53 (d, $J = 11.2$ Hz, 1H), 4.30–4.19 (m, 2H), 4.19–4.05 (m, 2H), 3.87 (s, 1H), 3.80 (s, 3H), 2.95–2.75 (m, 5H), 2.62 (d, $J = 15.2$ Hz, 1H), 2.44 (s, 3H), 2.05–1.86 (m, 2H), 1.68 (s, 3H), 1.66 (brs, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.1, 144.7, 140.7, 132.7, 129.9, 129.7, 129.3, 127.8, 119.2, 113.6, 81.4, 71.2, 70.8, 55.1, 48.2, 43.3, 28.1, 26.7, 24.8, 21.5; IR (neat) 3516, 2908, 1613, 1514, 1360, 1249, 1176, 1096, 984 cm^{-1} ; LRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$.

Allyl alcohol (10). To a suspension of trimethylsulfonium iodide (5.18 g, 25.4 mmol) in anhydrous THF (50 mL) at 0°C under argon was added $^n\text{BuLi}$ (1.6 M, 13.2 mL, 21.2 mmol) dropwise. After stirring at 0°C for 1 h, a solution of **37** (2.276 g, 4.2 mmol) in THF (20 mL) was added. The resulting mixture was stirred for an additional 2 h and then quenched with water (10 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (60 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified via silica gel chromatography (5:1 to 3:1 hexane/ethyl acetate) to afford **10** (1.415 g, 88%) as a colorless oil: $[\alpha]_{\text{D}}^{20} +42.4$ (c 1.09, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.27 (d, $J = 8.0$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.92 (ddd, $J = 16.8, 10.8, 5.2$ Hz, 1H), 5.44 (s, 1H), 5.37 (s, 1H), 5.28 (d, $J = 17.2$ Hz, 1H), 5.18 (d, $J = 10.4$ Hz, 1H), 4.64 (d, $J = 11.2$ Hz, 1H), 4.34 (d, $J = 11.6$ Hz, 1H), 4.22 (s, 2H), 3.80 (s, 3H), 3.00–2.72 (m, 5H), 2.63 (d, $J = 14.8$ Hz, 1H), 2.32 (d, $J = 4.8$ Hz, 1H), 2.05–1.90 (m, 2H), 1.71 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.1, 140.4, 136.5, 130.4, 129.3, 118.6, 116.2, 113.7, 84.2, 73.3, 70.8, 55.2, 48.5, 43.9, 28.2, 26.8, 24.9; IR (neat) 3468, 2907, 1613, 1514, 1423, 1248, 1034, 920 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$ calcd for $\text{C}_{20}\text{H}_{28}\text{O}_3\text{S}_2\text{Na}$ 403.1378, found 403.1381.

Pyran (39). To a solution of **10** (460 mg, 1.2 mmol) in anhydrous THF (4 mL) and MeOH (4 mL) at 0°C under argon was added 2,6-

lutidine (564 μL , 4.8 mmol) and $\text{Hg}(\text{ClO}_4)_2$ (969 mg, 2.4 mmol). After stirring at 0°C for 2 h, the mixture was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic phase was washed with 10% CuSO_4 (20 mL), and the combined aqueous phases were extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was then dissolved in anhydrous MeOH (4 mL) at 0°C under argon, and PTSA (12 mg, 0.06 mmol) was added. The resulting mixture was stirred at 0°C for 36 h and then concentrated. The residue was purified via silica gel chromatography (15:1 to 10:1 hexane/ethyl acetate) to afford **39** (269 mg, 73%) as a light yellow oil: $[\alpha]_{\text{D}}^{20} +163.0$ (c 1.07, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.27 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 5.94 (ddd, $J = 17.2, 10.4, 6.8$ Hz, 1H), 5.41 (d, $J = 17.2$ Hz, 1H), 5.25 (d, $J = 10.4$ Hz, 1H), 5.19 (s, 1H), 4.92 (s, 1H), 4.61 (d, $J = 11.2$ Hz, 1H), 4.48 (d, $J = 10.8$ Hz, 1H), 3.90 (t, $J = 8.0$ Hz, 1H), 3.80 (s, 3H), 3.60 (d, $J = 9.2$ Hz, 1H), 3.19 (s, 3H), 2.55 (d, $J = 9.6$ Hz, 1H), 2.36 (d, $J = 14.0$ Hz, 1H), 1.36 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.3, 141.4, 136.2, 130.2, 129.5, 117.5, 113.7, 108.6, 99.0, 79.7, 75.1, 72.7, 55.3, 48.2, 45.0, 22.8; IR (neat) 1698, 1600, 1513, 1463, 1260, 1160, 1033, 833 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$ calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}$ 327.1572, found 327.1576.

Alcohol (40). To a solution of **39** (113 mg, 0.4 mmol) in dichloromethane (3 mL) at 0°C was added NaHCO_3 (64 mg, 0.8 mmol), water (30 μL), and DDQ (85 mg, 0.4 mmol). After stirring at 0°C for 30 min, NaHCO_3 (64 mg, 0.8 mmol), water (30 μL), and DDQ (85 mg, 0.4 mmol) were added again. After an additional 30 min, the mixture was quenched with saturated NaHCO_3 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was then purified via silica gel chromatography (8:1 to 5:1 hexane/ethyl acetate) to afford **40** (54 mg, 79%) as a colorless oil: $[\alpha]_{\text{D}}^{20} +190.6$ (c 1.02, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.96 (ddd, $J = 17.6, 10.4, 7.2$ Hz, 1H), 5.43 (d, $J = 17.2$ Hz, 1H), 5.35 (d, $J = 10.4$ Hz, 1H), 5.16 (s, 1H), 4.93 (s, 1H), 3.88–3.70 (m, 2H), 3.21 (s, 3H), 2.56 (d, $J = 14.0$ Hz, 1H), 2.41 (d, $J = 13.6$ Hz, 1H), 1.75 (d, $J = 4.8$ Hz, 1H), 1.38 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 142.9, 136.0, 119.3, 107.7, 99.0, 77.1, 71.7, 48.3, 44.8, 22.8; IR (neat) 3435, 2992, 1379, 1230, 1184, 1060, 890, 668 cm^{-1} ; LRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$.

Epoxide (6). To a solution of **40** (55 mg, 0.3 mmol) in anhydrous dichloromethane (3 mL) at 0°C under argon was added NaHCO_3 (101 mg, 1.2 mmol) and *m*-CPBA (62 mg, 0.4 mmol). After stirring at 0°C for 30 min, *m*-CPBA (62 mg, 0.4 mmol) was again added. After an additional 30 min, the mixture was quenched with 5% NaOH (5 mL). The aqueous phase was extracted with CH_2Cl_2 (5×5 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was then purified via silica gel chromatography (2:1 to 1:1 hexane/ethyl acetate) to afford **6** (46 mg, 76%) as a white powder: mp 53–57 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} +187.2$ (c 1.05, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.00 (ddd, $J = 17.2, 10.4, 6.4$ Hz, 1H), 5.43 (d, $J = 17.2$ Hz, 1H), 5.29 (d, $J = 10.4$ Hz, 1H), 3.98 (dd, $J = 9.6, 6.4$ Hz, 1H), 3.57 (t, $J = 10.4$ Hz, 1H), 3.26 (s, 3H), 2.99 (d, $J = 4.4$ Hz, 1H), 2.49 (d, $J = 4.4$ Hz, 1H), 2.29 (d, $J = 14.8$ Hz, 1H), 1.75 (d, $J = 3.2$ Hz, 1H), 1.72 (d, $J = 6.4$ Hz, 1H), 1.38 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 135.6, 117.8, 98.5, 73.1, 67.3, 56.4, 48.3, 47.1, 41.9, 23.0; IR (KBr) 3418, 2910, 1646, 1378, 1236, 1160, 1012, 919 cm^{-1} ; HRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4\text{Na}$ 223.0946, found 223.0948.

Spliceostatin A (2). To a solution of **26** (45 mg, 0.13 mmol) in anhydrous dichloromethane (1 mL) at room temperature under argon was added a solution of **6** (31 mg, 0.16 mmol) in anhydrous dichloromethane (500 μL) and Grubbs' second-generation catalyst (11 mg, 0.01 mmol). The resulting mixture was heated to reflux for 5 h and then concentrated. The residue was purified via silica gel chromatography (2:1 to 1:2 hexane/ethyl acetate) to afford spliceostatin A (**2**) (29 mg) as a white powder, in addition to recovery of **6** and **26**.

The recovered of **6** and **26** was combined and dissolved in anhydrous dichloromethane (1 mL) at room temperature under argon, to which Grubbs' second-generation catalyst (5 mg) was added. The resulting mixture was heated to reflux for 5 h and then concentrated. The residue was purified via silica gel chromatography (2:1 to 1:2 hexane/ethyl acetate) to afford spliceostatin A (**2**) (9 mg) as a white powder. The combined yield of spliceostatin A (**2**) after one cycle is 38 mg (57%). Spliceostatin A (**2**): mp 64–68 °C; $[\alpha]_{\text{D}}^{20} +25.3$ (c 1.07, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.40 (d, *J* = 15.6 Hz, 1H), 6.26 (dt, *J* = 13.6, 6.8 Hz, 1H), 6.01 (d, *J* = 9.2 Hz, 1H), 5.89 (dd, *J* = 11.2, 8.0 Hz, 1H), 5.75–5.65 (m, 2H), 5.51 (t, *J* = 6.8 Hz, 1H), 4.05 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.94 (d, *J* = 7.6 Hz, 1H), 3.66 (dd, *J* = 14.2, 6.0 Hz, 1H), 3.60 (t, *J* = 10.2 Hz, 1H), 3.52 (dt, *J* = 6.8, 2.0 Hz, 1H), 3.28 (s, 3H), 2.99 (d, *J* = 4.8 Hz, 1H), 2.50 (d, *J* = 4.4 Hz, 1H), 2.42–2.19 (m, 3H), 2.04 (s, 3H), 1.99–1.85 (m, 2H), 1.79 (s, 3H), 1.78–1.68 (m, 3H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.38 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.3, 164.8, 143.6, 138.1, 134.7, 128.9, 124.1, 122.5, 98.6, 80.8, 75.9, 73.2, 68.9, 67.6, 56.5, 48.4, 47.1, 42.0, 35.8, 32.0, 28.9, 23.0, 21.2, 19.9, 17.8, 15.0, 12.6; IR (KBr) 3450, 2977, 1739, 1669, 1635, 1522, 1368, 1245, 1049, 1010 cm⁻¹; HRMS (ESI), *m/z* (M + Na)⁺ calcd for C₂₈H₄₃NO₈Na: 544.2887, found 544.2886.

FR901464 (1). To a solution of spliceostatin A (**2**) (6.2 mg, 0.01 mmol) in THF/H₂O (3 mL/0.75 mL) at 0 °C under argon was added PPTS (17.9 mg, 0.07 mmol). The resulting solution was stirred for 72 h and was then diluted with ethyl acetate (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (1:1 to 1:4 hexane/ethyl acetate) to afford FR901464 (**1**) (4.8 mg, 79%) as a white powder: mp 64–67 °C; $[\alpha]_{\text{D}}^{23} -13.0$ (c 0.45, CH₂Cl₂); ¹H NMR (500 MHz, CD₂Cl₂) δ 6.38 (d, *J* = 15.5 Hz, 1H), 6.26 (m, 1H), 5.98 (d, *J* = 9.0 Hz, 1H), 5.90 (dd, *J* = 11.5, 8.0 Hz, 1H), 5.71 (dd, *J* = 11.5, 1.0 Hz, 1H), 5.65 (dd, *J* = 15.7, 7.0 Hz, 1H), 5.54 (t, *J* = 7.0 Hz, 1H), 4.24 (dd, *J* = 9.3, 7.0 Hz, 1H), 3.93–3.87 (m, 1H), 3.66 (qd, *J* = 6.5, 2.1 Hz, 1H), 3.57 (t, *J* = 10.0 Hz, 1H), 3.57–3.50 (m, 1H), 3.34 (s, 1H), 3.06 (d, *J* = 4.5 Hz, 1H), 2.55 (d, *J* = 4.5 Hz, 1H), 2.40–2.31 (m, 1H), 2.34 (d, *J* = 14.3 Hz, 1H), 2.28–2.20 (m, 1H), 2.01 (s, 3H), 1.95–1.91 (m, 2H), 1.78 (s, 3H), 1.78–1.76 (m, 1H), 1.64 (d, *J* = 14.5 Hz, 1H), 1.62 (d, *J* = 10.3 Hz, 1H), 1.43 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (150 MHz, CD₂Cl₂) δ 170.6, 164.9, 143.9, 138.3, 134.8, 129.9, 124.6, 122.8, 96.7, 81.1, 76.2, 73.8, 68.9, 68.1, 58.1, 48.1, 47.3, 41.8, 36.2, 32.3, 29.5, 29.1, 21.4, 20.1, 17.9, 15.2, 12.7; IR (KBr) 3449, 2976, 1738, 1667, 1636, 1524, 1369, 1244, 1049, 1010 cm⁻¹; HRMS (ESI), *m/z* (M + Na)⁺ calcd for C₂₇H₄₁NO₈Na 530.2730, found 530.2729.

Diol (41). **41** was prepared by the same procedure as diol **35** to give a light yellow oil: $[\alpha]_{\text{D}}^{20} -52.0$ (c 1.08, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 5.51 (s, 1H), 5.41 (s, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.21 (d, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 3.75–3.57 (m, 3H), 2.99–2.75 (m, 5H), 2.64 (d, *J* = 14.8 Hz, 1H), 2.05–1.91 (m, 2H), 1.70 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 140.8, 130.2, 129.6, 118.7, 113.8, 81.5, 73.4, 70.8, 63.5, 55.2, 48.3, 43.5, 28.1, 26.8, 26.7, 25.0; IR (neat) 3434, 2908, 1612, 1514, 1422, 1248, 1035, 909 cm⁻¹; LRMS (ESI), *m/z* 407.1 (M + Na)⁺.

Tosylate (42). **42** was prepared by the same procedure as tosylate **37** to give a light yellow oil: $[\alpha]_{\text{D}}^{20} -21.0$ (c 0.99, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 5.46 (s, 1H), 5.33 (s, 1H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.33–4.18 (m, 2H), 4.02 (d, *J* = 5.6 Hz, 2H), 3.79 (brs, 4H), 3.01–2.73 (m, 5H), 2.59 (d, *J* = 14.8 Hz, 1H), 2.42 (s, 3H), 2.05–1.85 (m, 2H), 1.65 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 144.9, 140.2, 132.6, 129.8, 129.6, 129.3, 127.9, 118.5, 113.7, 78.9, 71.0, 70.0, 69.8, 55.2, 48.0, 43.2, 28.0, 26.7, 24.8, 21.5; IR (neat) 3533, 2909, 1613, 1514, 1360, 1249, 1177, 1097, 981 cm⁻¹; LRMS (ESI), *m/z* 561.1 (M + Na)⁺.

Allyl alcohol (43). **43** was prepared by the same procedure as allyl alcohol **10** to give a light yellow oil: $[\alpha]_{\text{D}}^{20} -34.0$ (c 1.01, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J* = 8.8 Hz, 2H),

6.87 (d, *J* = 8.4 Hz, 2H), 5.85 (ddd, *J* = 17.2, 10.8, 5.2 Hz, 1H), 5.51 (s, 1H), 5.41 (s, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 3.99 (brs, 2H), 3.80 (s, 3H), 2.93–2.70 (m, 6H), 2.63 (d, *J* = 15.2 Hz, 1H), 2.02–1.94 (m, 2H), 1.71 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 140.8, 136.7, 130.3, 129.5, 118.7, 116.8, 113.8, 84.9, 75.2, 70.9, 55.3, 48.5, 44.4, 28.0, 26.9, 25.0; IR (neat) 3481, 2906, 1613, 1514, 1423, 1248, 1035, 923 cm⁻¹; HRMS (ESI), *m/z* (M + Na)⁺ calcd for C₂₀H₂₈O₃S₂Na 403.1378, found 403.1380.

Pyran (44). **44** was prepared by the same procedure as pyran **39** to give a light yellow oil: $[\alpha]_{\text{D}}^{20} +122.8$ (c 1.10, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.02 (ddd, *J* = 17.2, 10.8, 6.4 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.07 (s, 1H), 4.97 (s, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.21 (d, *J* = 12.4 Hz, 1H), 4.08 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.58 (s, 1H), 3.19 (s, 3H), 2.61 (d, *J* = 14.0 Hz, 1H), 2.28 (d, *J* = 13.6 Hz, 1H), 1.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.0, 140.4, 135.6, 130.2, 129.5, 116.5, 114.5, 113.6, 99.1, 74.3, 68.5, 55.2, 48.4, 40.3, 23.1; IR (neat) 1656, 1613, 1514, 1465, 1248, 1181, 1045, 823 cm⁻¹; LRMS (ESI), *m/z* 327.2 (M + Na)⁺.

Alcohol (45). **45** was prepared by the same procedure as alcohol **40** to give a light yellow oil: $[\alpha]_{\text{D}}^{20} +243.2$ (c 1.05, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 5.94 (ddd, *J* = 17.2, 8.4, 5.2 Hz, 1H), 5.48 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 5.09 (s, 1H), 4.94 (s, 1H), 4.21 (d, *J* = 3.2 Hz, 1H), 3.98 (s, 1H), 3.20 (s, 3H), 2.65 (d, *J* = 14.0 Hz, 1H), 2.30 (d, *J* = 14.0 Hz, 1H), 1.89 (d, *J* = 3.6 Hz, 1H), 1.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 142.7, 134.6, 117.3, 113.1, 99.1, 73.6, 71.7, 48.4, 39.7, 23.0; IR (neat) 3452, 2989, 1378, 1229, 1182, 1060, 962 cm⁻¹; LRMS (ESI), *m/z* 207.1 (M + Na)⁺.

Epoxide (46). **46** was prepared by the same procedure as epoxide **6** to give a light yellow oil: $[\alpha]_{\text{D}}^{20} +165.9$ (c 0.67, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 5.96 (ddd, *J* = 21.2, 16.4, 5.6 Hz, 1H), 5.46 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 4.28 (d, *J* = 4.8 Hz, 1H), 3.23 (d, *J* = 3.6 Hz, 1H), 3.20 (s, 3H), 2.84 (ddd, *J* = 9.6, 4.8, 4.8 Hz, 2H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.03 (d, *J* = 3.6 Hz, 1H), 1.44 (s, 3H), 1.38 (d, *J* = 13.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 134.1, 117.5, 100.0, 72.6, 72.2, 58.1, 54.2, 48.2, 37.6, 23.1; IR (KBr) 3458, 2943, 1649, 1379, 1216, 1033, 814 cm⁻¹; HRMS (ESI), *m/z* (M + Na)⁺ calcd for C₁₀H₁₆O₄Na 223.0946, found 223.0947.

Diastereomers (47–52). **47–52** were prepared by the same procedure as spliceostatin A (**2**) and FR901464 (**1**) to give white powders:

Diastereomer (47). Mp 60–63 °C; $[\alpha]_{\text{D}}^{20} +2.2$ (c 1.02, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.39 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 13.6, 6.8 Hz, 1H), 5.99 (d, *J* = 8.8 Hz, 1H), 5.89 (dd, *J* = 11.6, 6.6 Hz, 1H), 5.80–5.68 (m, 2H), 5.51 (t, *J* = 7.2 Hz, 1H), 4.31 (d, *J* = 6.0 Hz, 1H), 3.93 (d, *J* = 6.8 Hz, 1H), 3.67–3.64 (m, 1H), 3.54–3.49 (m, 1H), 3.21 (brs, 4H), 2.87–2.80 (m, 2H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.43–2.36 (m, 1H), 2.29–2.21 (m, 1H), 2.04 (brs, 4H), 1.97–1.89 (m, 2H), 1.79 (brs, 4H), 1.44 (s, 3H), 1.40–1.35 (m, 4H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.4, 164.8, 143.6, 137.5, 134.7, 129.1, 122.5, 100.0, 80.8, 75.9, 72.9, 72.7, 68.9, 58.2, 54.3, 48.2, 47.1, 37.5, 35.8, 31.9, 28.8, 23.2, 21.2, 19.9, 17.8, 15.0, 12.6; IR (KBr) 3366, 2937, 1738, 1668, 1640, 1520, 1372, 1244, 1053, 971 cm⁻¹; LRMS (ESI), *m/z* 544.3 (M + Na)⁺.

Diastereomer (48). Mp 58–61 °C; $[\alpha]_{\text{D}}^{20} -12.5$ (c 0.49, CH₂Cl₂); ¹H NMR (800 MHz, CDCl₃) δ 6.37 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, *J* = 7.2, 1.6 Hz, 1H), 5.96 (d, *J* = 8.8 Hz, 1H), 5.90 (dd, *J* = 12.8, 8.8 Hz, 1H), 5.71 (dd, *J* = 12.0, 1.6 Hz, 1H), 5.67 (d, *J* = 6.4 Hz, 1H), 5.54 (t, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 6.4 Hz, 1H), 3.90 (d, *J* = 2.4 Hz, 1H), 3.65 (dd, *J* = 6.4, 1.6 Hz, 1H), 3.53 (d, *J* = 1.6 Hz, 1H), 3.17 (d, *J* = 4.0 Hz, 1H), 2.86–2.80 (m, 2H), 2.40–2.34 (m, 2H), 2.24–2.18 (m, 1H), 2.01 (brs, 4H), 1.97–1.90 (m, 2H), 1.78 (s, 3H), 1.76 (s, 1H), 1.53 (s, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 165.0, 143.9, 137.5, 134.8, 129.9, 123.1, 122.8, 97.7, 81.2, 76.3, 73.3, 73.1, 68.9, 58.2, 47.4, 40.0, 36.2, 32.4, 30.3, 29.6, 21.4, 20.2, 18.0, 15.2, 12.7; IR (KBr) 3369, 2938, 1740, 1665, 1635, 1522, 1371, 1249, 1052, 989 cm⁻¹; LRMS (ESI), *m/z* 530.3 (M + Na)⁺.

Diastereomer (49). Mp 65–69 °C; $[\alpha]_{\text{D}}^{20}$ +27.3 (c 1.05, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.75 (d, J = 9.2 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 5.86–5.74 (m, 2H), 5.73–5.61 (m, 2H), 5.50 (t, J = 6.8 Hz, 1H), 4.04 (dd, J = 9.2, 7.2 Hz, 1H), 3.99–3.83 (m, 1H), 3.60 (t, J = 10.0 Hz, 1H), 3.45 (dd, J = 7.2, 5.2 Hz, 1H), 3.34–3.15 (m, 4H), 2.99 (d, J = 4.4 Hz, 1H), 2.49 (d, J = 4.4 Hz, 1H), 2.43–2.17 (m, 3H), 2.06 (s, 3H), 1.96–1.83 (m, 2H), 1.79 (s, 3H), 1.75–1.68 (m, 2H), 1.61–1.51 (m, 1H), 1.38 (s, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.25 (d, J = 6.0 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 165.0, 138.3, 138.0, 134.5, 129.5, 125.4, 123.9, 98.6, 79.5, 78.1, 73.3, 69.1, 67.6, 56.5, 48.4, 47.1, 47.0, 42.0, 38.3, 31.8, 31.3, 23.0, 21.2, 20.2, 19.1, 12.6, 12.1; IR (KBr) 3317, 2931, 1738, 1668, 1634, 1538, 1372, 1241, 1049, 923 cm⁻¹; HRMS (ESI), *m/z* (M + Na)⁺ calcd for C₂₈H₄₃NO₈Na 544.2887, found 544.2885.

Diastereomer (50). Mp 63–67 °C; $[\alpha]_{\text{D}}^{20}$ -19.2 (c 0.52, CH₂Cl₂); ¹H NMR (800 MHz, CDCl₃) δ 6.43–6.34 (m, 1H), 6.33–6.24 (m, 1H), 5.96–5.87 (m, 1H), 5.79–5.69 (m, 2H), 5.68–5.61 (m, 1H), 5.57–5.51 (m, 1H), 3.93–3.87 (m, 1H), 3.86–3.81 (m, 1H), 3.62–3.52 (m, 1H), 3.49–3.42 (m, 1H), 3.23–3.17 (m, 1H), 3.01–2.94 (m, 1H), 2.54–2.45 (m, 1H), 2.39–2.31 (m, 2H), 2.27–2.18 (m, 1H), 2.02 (s, 3H), 1.91–1.84 (m, 2H), 1.79 (s, 3H), 1.78–1.65 (m, 3H), 1.50–1.46 (m, 3H), 1.33 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 5.6 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.4, 165.0, 140.2, 138.5, 134.7, 130.0, 124.7, 124.0, 106.7, 79.8, 78.5, 74.4, 69.1, 67.8, 56.5, 48.1, 47.1, 40.3, 38.6, 32.2, 32.0, 24.2, 21.4, 20.3, 19.2, 12.7, 12.3; IR (KBr) 3318, 2937, 1739, 1669, 1634, 1535, 1379, 1245, 1047, 989 cm⁻¹; LRMS (ESI), *m/z* 530.3 (M + Na)⁺.

Diastereomer (51). Mp 61–64 °C; $[\alpha]_{\text{D}}^{20}$ +33.8 (c 0.97, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.75 (d, J = 8.8 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 5.82–5.63 (m, 4H), 5.51 (t, J = 7.2 Hz, 1H), 4.31 (d, J = 6.4 Hz, 1H), 3.97–3.86 (m, 1H), 3.45 (dd, J = 7.2, 5.2 Hz, 1H), 3.30–3.13 (m, 5H), 2.91–2.77 (m, 2H), 2.47 (d, J = 12.8 Hz, 1H), 2.43–2.33 (m, 1H), 2.30–2.18 (m, 1H), 2.06 (s, 3H), 2.05–2.01 (m, 1H), 1.97–1.82 (m, 2H), 1.79 (s, 3H), 1.55–1.51 (m, 1H), 1.44 (s, 3H), 1.41–1.32 (m, 4H), 1.25 (d, J = 6.0 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 165.0, 138.0, 137.6, 134.5, 129.6, 125.4, 122.3, 100.0, 79.5, 78.1, 72.9, 72.7, 69.1, 58.2, 54.2, 48.2, 47.0, 38.3, 37.5, 31.8, 31.3, 23.2, 21.2, 20.2, 19.1, 12.6, 12.1; IR (KBr) 3430, 2935, 1738, 1668, 1634, 1538, 1373, 1243, 1048, 982 cm⁻¹; LRMS (ESI), *m/z* 544.3 (M + Na)⁺.

Diastereomer (52). Mp 59–63 °C; $[\alpha]_{\text{D}}^{20}$ -22.3 (c 0.52, CH₂Cl₂); ¹H NMR (800 MHz, CDCl₃) δ 6.37 (d, J = 16.0 Hz, 1H), 6.30 (d, J = 8.8 Hz, 1H), 5.95–5.89 (m, 1H), 5.78–5.69 (m, 2H), 5.65 (dd, J = 16.0, 5.6 Hz, 1H), 5.56–5.50 (m, 1H), 4.69 (d, J = 5.6 Hz, 1H), 3.87–3.81 (m, 1H), 3.45 (dt, J = 7.2, 1.6 Hz, 1H), 3.24–3.15 (m, 2H), 2.93–2.79 (m, 2H), 2.46–2.32 (m, 2H), 2.24–2.19 (m, 1H), 2.06–1.99 (m, 4H), 1.92–1.85 (m, 2H), 1.78 (s, 3H), 1.53 (s, 3H), 1.33 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 5.6 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 165.0, 140.2, 137.6, 134.7, 130.2, 124.8, 123.0, 97.7, 79.8, 78.6, 73.3, 73.1, 69.2, 58.2, 47.2, 38.7, 37.0, 32.2, 32.0, 30.3, 21.4, 20.3, 19.2, 12.7, 12.3; IR (KBr) 3459, 2940, 1739, 1668, 1631, 1540, 1371, 1244, 1047, 913 cm⁻¹; HRMS (ESI), *m/z* (M + Na)⁺ Calcd for C₂₇H₄₁NO₈Na 530.2730, found 530.2728.

In Vitro Splicing Reactions. Pre-mRNA substrate was derived from the adenovirus major late transcript. A ³²P-UTP body-labeled G(5′)ppp(5′)G-capped substrate was generated by T7 runoff transcription followed by gel purification. Nuclear extract was prepared from HeLa cells grown in DMEM/F12 1:1 and 5% (v/v) newborn calf serum. For splicing reactions, 10 nM pre-mRNA substrate was incubated with 60 mM potassium glutamate, 2 mM magnesium acetate, 2 mM ATP, 5 mM creatine phosphate, 0.05 mg mL⁻¹ tRNA, and 50% (v/v) HeLa nuclear extract at 30 °C.

Denaturing Gel Analysis. RNA was extracted from *in vitro* splicing reaction and separated on a 15% (v/v) denaturing polyacrylamide gel. ³²P-labeled RNA species were visualized by phosphorimaging and quantified with ImageQuant software (Molecular Dynamics). Splicing efficiency is the amount of mRNA relative to total RNA and normalized to a DMSO control reaction. IC₅₀ values for inhibitors are the concentration of inhibitor that causes 50% decrease

of splicing efficiency, which were derived from averaged plots of splicing efficiency vs compound concentration.

Native Gel Analysis. Splicing reactions were set up as described above and incubated at 30 °C for 4–30 min. Time point samples were kept on ice until all samples were ready for analysis. Amounts of 10 μL of splicing reactions were mixed with 10 μL of native gel loading buffer (20 mM Trizma base, 20 mM glycine, 25% (v/v) glycerol, 0.1% (w/v) cyan blue, 0.1% (w/v) bromophenol blue, 1 mg mL⁻¹ of heparin sulfate) and incubated at room temperature for 5 min before loading onto a 2.1% (w/v) low-melting temperature agarose gel. Gels were run at 72 V for 3.5 h, dried onto Whatman paper, and exposed to phosphorimaging screens, which were digitized with a Typhoon Scanner (Molecular Dynamics).

■ ASSOCIATED CONTENT

📄 Supporting Information

Full spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the National Institutes of Health and Purdue University is gratefully acknowledged.

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