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Graphical Abstract

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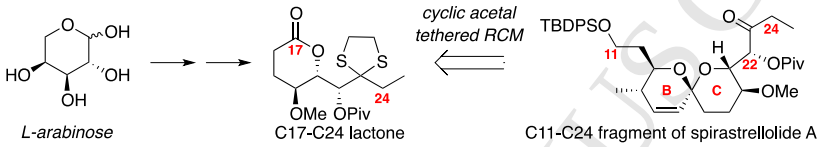

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A Carbohydrate Based Chiron Approach to the Lactone Intermediate Employed in the Synthesis of BC-Ring Fragment of (+)-Spirastrellolide A.†

Chao-Chao Wang,[a] Yu Tang,*[a] Ka Yang,[a] Xiao-Yu Li,[a] Yi-Biao Wu,[a] and Richard P. Hsung*[b]

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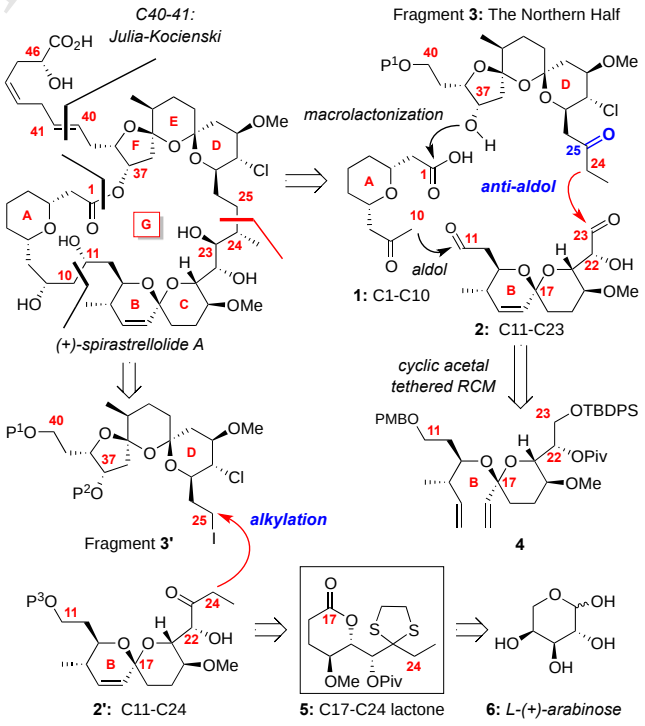
Abstract—A concise and stereoselective synthesis of the key intermediate used for constructing the BC-ring fragment of (+)-spirastrellolide A is described. The synthetic sequence represents a chiron approach that employs readily available and inexpensive L-arabinose and sets up the stereochemical triad at C20-C22 all from the sugar. This lactone can be used to assemble the spiroketal in the Southern Half through a cyclic acetal–tethered ring-closing metathesis strategy, and is poised for connecting with the Northern Half at C24-C25.

Key Word: Spirastrellolide A, spiroketal containing marine natural product, cyclic acetal-tethered RCM, chiron approach, and carbohydrate.

1. Introduction

(+)-Spirastrellolide A, a marine macrolide isolated from the Caribbean sponge *Spirastrella coccinea* off the coast of Dominica displays rather profound antimitotic properties (**Scheme 1**). Its isolation was first documented by Roberge and Andersen *et al.*[1a] Initially, relative stereochemistry was sketchy at multiple stereogenic centers. Subsequently in 2004, all relative stereochemistry of (+)-spirastrellolide A sans C46 and complete structural assignment were reported.[1b] Ultimately in 2007, the isolation of (+)-spirastrellolide B allowed for concise assignment of the absolute configuration of the macrocyclic core through X-ray crystallography.[1c] In the same year, isolations of (+)-spirastrellolide C-G from the same marine sponge *Spirastrellolide coccinea* were also reported.[1d]

The methyl esters of these macrolides exhibit potent inhibitory activity against protein PP2A [IC_{50} ca. 1 nm] with an excellent selectivity for PP2A over PP1, and those do not inhibit PP2C.[2] Its biological activities, therefore, resemble other known Ser/Thr phosphatase inhibitors fostriecin and okadaic acid.[3] Development of protein phosphatase inhibitors has lagged behind the interest in kinase inhibitors because of the perceived notion that kinases are more highly regulated and specific.[4] However, there has been a renewed interest in recent years because reversible protein phosphorylation is critical "as the other half" of checkpoints in cell cycles, and protein phosphatases assume an equally important role in regulating cellular signal transductions and should not be ignored.



Scheme 1. Strategies for A Totasl Synthesis (+)-Spirastrellolide A.

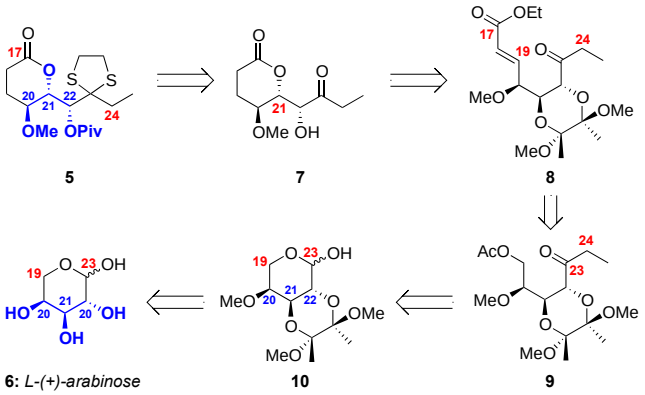
Those remarkable biological activities for the key regulatory enzyme suggest that the spirastrellolides might

represent promising lead compounds for the therapeutic reagents for treatment of cancer. To date, there have been many papers describing elegant synthetic efforts towards these natural products[4] in addition to two completed total syntheses by Paterson[5] and Fürstner.[6] We became interested in this natural product when we developed a new methodology for constructing spiroketals.[7] This strategy features a cyclic acetal–tethered[8a-c] ring-closing metathesis RCM,[8d-g,9] and we were able to complete a synthesis of C11-C23 fragment to showcase our method.[10a-c]

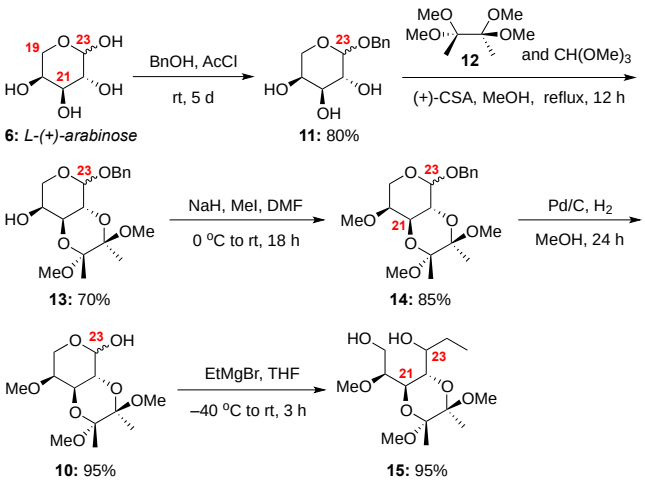
Our synthetic strategy is outlined in **Scheme 1**. The side chain at C40-C41 will be connected by using Julia-Kocienski olefination,[4v] The central macrolide core can be divided into three major fragments: **1** [C1-C10],[10d] **2** [C11-C23],[10-a-c] and **3** [C24-C40], and penultimate macrolactonization[5a,5b] would involve C1-COOH and C37-OH to close the macrolide. A methyl ketone enolate 1,3-*anti*-aldol empolying the Mukaiyama aldol reaction conditions[11] would connect fragments **1** and **2** at C10 and C11, and we have already demonstrated such feasibility previously.[10b-d,12] The original plan was also to pursue an *anti*-aldol linking together fragments **2** and **3** at C24 and C23 and a reductive removal of the C25-oxo group. Our revised approach would involve the connection of two new fragments **2'** and **3'** at C24 and C25 *via* an enolate alkylation. While neither fragment has been reported in our previous synthetic efforts, synthesis of the new BC-ring fragment **2'** will again adopt our cyclic acetal tethered RCM strategy. Consequently, the new lactone intermediate **5** would be required for such effort, and we envision its synthesis commencing from sugar L-(+)-arabinose **6**. We report here details of a carbohydrate-based chiron approach for synthesizing this lactone intermediate that contains the C17-24 subunit of (+)-spirastrellolide A.

2. Results and Discussions.

To access lactone **5**, we designed a carbohydrate based chiron approach that can provide a concise and high-yielding synthetic process in comparison with our previous effort. Our retrosynthetic strategy is shown in **Scheme 2**. We envisioned reaching lactone **5** *via* keto-lactone **7** after protections of C22-OH and C23-ketone. Keto-lactone **7** could be derived from the α,β-unsaturated ester **8** through a sequence of hydrogenation, deprotection and lactonization. Ester **8** could be obtained *via* selected Horner-Emmons-Wadsworth olefination of dicarbonyl compound generated from ketone **9**, which could be synthesized from the tri-protected L-(+)-arabinose **10** through standard transformations including a Grignard addition to introduce C24. It is noteworthy that we are adopting here Ley's protecting strategy to assemble **10**.[13,14]

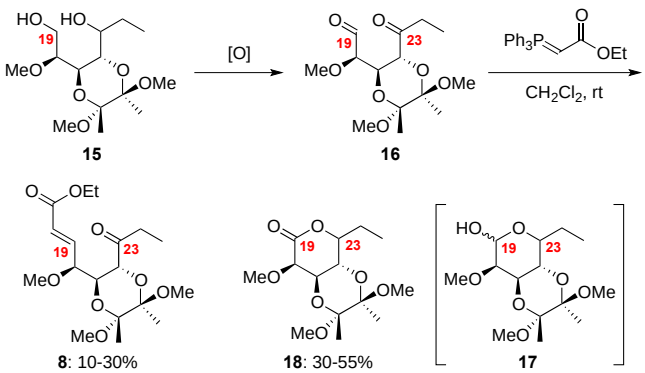


Scheme 2. Retrosynthetic Analysis for Lactone **5**.



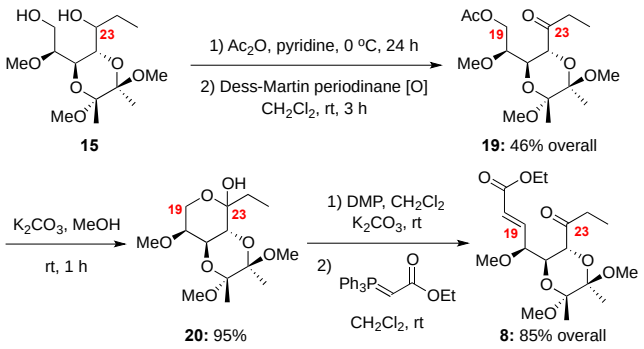
Scheme 3. Synthesis of Diol **15**.

Our synthesis commenced with benzylation of L-(+)-arabinose at C23-OH using BnOH and AcCl (**Scheme 3**). The resulting benzyl ether **11** was protected bis-acetal **13** by treatment with 2,2,3,3-tetramethoxybutane **12**.[15] Bis-acetal **13** was subsequently methylated with MeI to give methyl ether **14** in 85% yield. With methyl ether **14** in hand, hydrogenation with Pd-C gave the tri-protected L-(+)-arabinose **10** in 98% yield. Reaction of **10** with excess of EtMgBr in THF at -40 °C to rt afforded diol **15** as a nearly 1:1 mixture of diastereomers in 95% isolated yield.



Scheme 4. Synthesis of Ester **8** *via* Bis-Oxidation and Wittig Reaction.

For constructing the α,β-unsaturated ester **8**, we initially envisioned an oxidation of the diol to afford the dicarbonyl compound **16**, and then, pursuing a subsequent Wittig olefination of **16** (**Scheme 4**). However, after screening a number of conditions for example Swern oxidation, IBX, Dess-Martin periodinane oxidation [DMP], PCC, Ley oxidation, the desired α,β-unsaturated ester **8** was obtained in poor yields (10-30%). The byproduct was found to be lactone **18**, which is likely formed from oxidation of the hemi-acetal intermediate **17**.

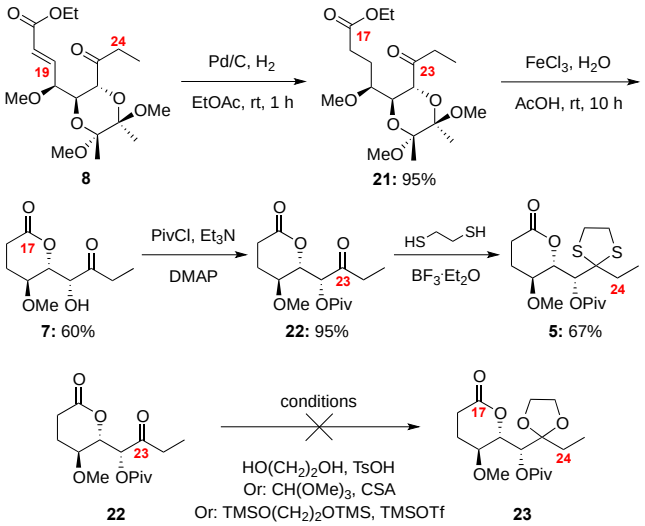


Scheme 5. A Successful Homologation.

Recognizing that we might have asked too much in an attempt to shorten the synthesis, we elected an alternative route. The primary alcohol at C19 was first protected with Ac_2O in anhydrous pyridine at 0 °C, and subsequently, a DMP oxidation of the secondary alcohol at C23 afforded ester ketone **19** (**Scheme 5**). Methanolysis of **19** occurred smoothly using K_2CO_3 in MeOH at room temperature to give hemi-acetal **20** in 95% yield. Oxidation of the hemi-acetal **20** using Dess-Martin periodinane protocol occurred without incident, and the crude aldehyde reacted with ethyl (triphenylphosphoranylidene) acetate to give the desired α,β-unsaturated ester **8** in 85% yield over two steps.

Hydrogenation of sester **8** with Pd/C gave ester **21** in almost quantitative yield (**Scheme 6**). A variety of acids were screened to deketalization, upon which it was found that most acid conditions [for example TFA, H_2SO_4] could not afford the desired products. Ley's deprotecting protocol using $FeCl_3$[16] was identified as the most superior for deketalization, and the ensuing facile lactonization gave keto-lactone **7** in 60% yield. The free alcohol in keto-lactone **7** was protected as pivalate **22** in 97% yield.

We recognized that there were two carbonyl groups in pivalate **22**, one being a ketone at C23, and the other at C17. Thus, they may pose problems for our cyclic acetal-tethered RCM given that they may possess similar reactivity toward nucleophile including simple reduction using $NaBH_4$.[17] We then decided to investigate the protection of C23-ketone (**Scheme 6**). Initially, we had hoped to selectively protect the C23 ketone as a ketal. However, after a number of acids were screened to effect this transformation, it was found that neither Lewis acids nor Brønsted acids could produce the desired ketal **23**. The crude NMR spectra revealed that the moiety of lactone was unstable to acidic conditions. Ultimately, treatment of pivalate **22** with 1,2-ethanedithiol was catalyzed by $BF_3{\cdot}Et_2O$ to afford the lactone intermediate **5** with the dithiane protecting unit in 67% yield.[18]



Scheme 6. Completing the Synthesis of Lactone **5**.

It is noteworthy that this new synthetic route to the orthogonally protected lactone **5** is comparable in efficiency to our earlier approach, as it took an overall 14 steps from L-(+)-arabinose. Our earlier synthesis of a related lactone that contains the C17-C23 subunit started from tartrate.[10a-c] Although it only took 12 steps, the resulting lactone is two-carbon less than that of **5**. More importantly, the current lactone **5** containing the C17-24 subunit should prove to be much more versatile for synthesizing the C11-C24 BC-ring fragment **2'** through the cyclic acetal-tethered RCM strategy developed by our group,[10a-c,] and ultimately for assembling the entire Southern Half as well as connecting with the Northern Half of (+)-spirastrellolide A now through the new strategy of C24–C25 bond formation. Consequently, success in achieving route well worthy of effort because this should provide an overall more efficient approach to (+)-spirastrellolide A.

3. Conclusion.

In summary, we have developed here a concise and stereoselective synthesis of the key lactone intermediate used for constructing the BC-ring fragment of (+)-spirastrellolide A. This chiron approach employs readily available and inexpensive L-(+)-arabinose, and sets up the stereochemical triad at C20-C22 all from the sugar, leading the orthogonally protected lactone intermediate in 14 steps. This lactone fragment can be utilized for assembling the

Southern Half through the cyclic acetal tethered RCM approach, as well as for connecting with the Northern Half of (+)-spirastrellolide A through the C24–C25 bond formation. These efforts are currently underway.

4. Experimental Section.

All reactions were carried out without precaution of air and stirred magnetically. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz BRUKER AVANCE and 600 MHz BRUKER AVANCE spectrometer at 25 ^{o}C. Chemical shifts values are given in ppm and referred as the internal standard to TMS: 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets and dq, doublet of quartets; The coupling constants *J*, are reported in Hertz (Hz). Optical rotations were measured on an Anton Paar MLP 200 modular circular digital polarimeter by using a 2-mL cell with a path length of 1 dm. IR was recorded on a Bio Rad FTS-185 Fourier Transform Infrared Spectrometer. Mass spectrum was obtained on Agilent 6310 Ion Trap mass spectrometer. High-resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro (BRUKER) spectrometer. Melting points were determined with a national Micro Melting point apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 40 °C in vacuum. TLC plates were visualized by exposure to ultraviolet light.

Tetrahydrofuran (THF) was freshly distilled under N_2 from sodium-benzophenone immediately prior to use. Dichloro-methane (CH_2Cl_2) and triethylamine (Et_3N) were distilled under N_2 from calcium hydride (CaH_2). Methanol (MeOH) was dried over magnesium (Mg) under N_2 prior to use. All reactions were performed in standard glassware, heated at 70 ^{o}C for 3 h before use. Flash column chromatography was performed over silica gel 100-200 m and the eluent was a mixture of ethyl acetate (EtOAc) and petroleum ether either in gradient or isocratic manner.

4.1. Benzyl Ether 11. Acetyl chloride (6.30 mL, 88.0 mmol) was added dropwise to BnOH (108.0 mL, 1.00 mol), which was cooled to 0 ^{o}C in an ice-water bath with stirring. To this solution at 0 ^{o}C was added L-(+)-arabinose (20.0 g, 133.3 mmol), and after the addition, the resulting reaction mixture was warmed to rt. The resulting mixture was vigorously stirred at rt for 5 d. Petroleum Ether (400 mL) was then added to precipitate the product, and the mixture was filtered and the crude white solid was washed with Petroleum Ether (200 mL). Recrystallization of the crude solid from EtOH (1 L) gave benzyl ether **11** (25.6 g, 80%) as white crystals.

11: R_f = 0.66 [16% $CHCl_3$ in MeOH]; mp 177-178 ^{o}C; $[\alpha]_D^{20}$ = +201.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.46 (dd, 1 H, *J* = 2.4, 11.4 Hz), 3.64-3.73 (m, 4H), 4.45 (d, 1H, *J* = 12.4 Hz), 4.58 (s, 2H), 4.66 (d, 1H, *J* = 12.4 Hz), 4.75 (s, 1H), 7.26-7.39 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 63.8, 68.8, 68.9, 69.1, 69.5, 99.4, 127.8, 127.9, 128.6, 138.7; IR (KBr) cm^{-1} 3254brs, 2936m, 2856w, 1449m, 1337m, 1259m, 1135s, 1090s, 1070s, 1050s; mass spectrum (ESI): m/e (% relative intensity) 279.0 (100) $[M + K]^+$; m/e calcd for $C_{12}H_{16}O_5Na^+$ $(M + Na)^+$ 263.0890, found 263.0913.

4.2 Bis-Acetal 13. To a suspension of benzyl ether **11** (24.0 g, 100.0 mmol) in CH_3OH (500 mL) were added 2,2,3,3-tetramethoxybutane[13c] (21.4 g, 120.0 mmol), trimethyl orthoformate (43.8 mL) and camphorsulfonic acid (CSA) (230.0 mg). The resulting mixture was heated under reflux for 12 h before it was cooled to rt and treated with powdered $NaHCO_3$ (ca. 20.0 g). The resulting mixture was filtered through Celite™, and the filtrate was concentrated under reduced pressure. The crude residue was purified through silica gel flash column chromatograph (Isocratic eluent: 30% EtOAc in Petroleum Ether) to afford bis-acetal **13** as a white solid (24.8 g, 70%). Recrystallization from Petroleum Ether/EtOAc gave **13** as white prisms.

13: R_f = 0.45 [50% EtOAc in Petroleum Ether]; mp 140-141^{o}C; $[\alpha]_D^{20}$ = +18.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.33 (s, 3H), 2.21 (brs, 1H), 3.22 (s, 3H), 3.27 (s, 3H), 3.70 (dd, 1H, *J* = 1.8, 12.6 Hz), 3.81 (dd, 1H, *J* = 1.2, 12.6 Hz), 3.92 (s, 1H), 4.14 (dd, 1H, *J* = 3.0, 10.8 Hz), 4.18 (dd, 1H, *J* = 3.0, 10.8 Hz), 4.70 (q, 2H, *J* = 12.6 Hz), 4.95 (d, 1H, *J* = 3.0 Hz), 7.42-7.28 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.8, 47.8, 47.9, 63.0, 65.2, 65.8, 68.1, 69.3, 96.9, 100.1, 100.2, 127.5, 127.9, 128.2, 137.7; IR (KBr) cm^{-1} 3462brs, 2994m, 2932s, 2838w, 1459w, 1357w, 1126m, 1045s, 1001s; mass spectrum (ESI): m/e (% relative intensity) 393.3 (100) $[M + K]^+$; m/e calcd for $C_{18}H_{26}O_7Na^+$ $(M + Na)^+$ 377.1571, found 377.1571.

4.3. 2*R*,3*R*,4a*R*,8*S*,8a*S*-5-(Benzyloxy)-2,3,8-trimethoxy-2,3-dimethyl-hexahydro-2*H*-pyrano[3,4-*b*][1,4]dioxine (14). To a solution of bis-acetal **13** (3.00 g, 8.50 mmol) in freshly distilled THF (120 mL) was added NaH (0.80 g, 21.2 mmol) in portion-wise under N_2 atmosphere and at 0 ^{o}C with stirring. After addition, the mixture was stirred for an additional 15 min at 0 ^{o}C. Subsequently, MeI (1.10 mL, 16.9 mmol) was introduced and the resulting mixture was stirred for 8 h before being warmed up to rt. The reaction mixture was then quenched using sat aq NH_4Cl and extracted with EtOAc (100 mL × 2). Combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified through silica gel flash column chromatograph (Isocratic eluent: 20% EtOAc in Petroleum Ether) to afford methyl ether **14** (2.65 g, 85%) as a white solid.

14: R_f = 0.60 [50% EtOAc in Petroleum Ether]; mp 96-97 °C; $[\alpha]_D^{20}$ = +22.0 (*c* 0.50, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (s, 6H), 3.23 (s, 3H), 3.27 (s, 3H), 3.46 (s, 3H), 3.49 (s, 1H), 3.67 (d, 1H, *J* = 12.6 Hz), 3.75 (d, 1H, *J* = 12.6 Hz), 4.15-4.20 (m, 2H), 4.71 (q, 2H, *J* = 12.6 Hz), 4.95 (d, 1H, *J* = 2.4 Hz), 7.42-7.26 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.8, 17.9, 47.8, 47.9, 57.7, 60.3, 65.5, 66.2, 69.3, 76.9, 96.9, 99.7, 99.9, 127.4, 127.9, 128.2, 137.9; IR (KBr) cm^{-1} 2995m, 2934s, 2839m, 1459w, 1357w, 1131m, 1125m, 1044s, 1003s; mass spectrum (ESI): m/e (% relative intensity) 407.9 (100) $[M + K]^+$; m/e calcd for $C_{19}H_{28}O_7Na^+$ $(M + Na)^+$ 391.1727, found 391.1721.

4.4. 2*R*,3*R*,4a*R*,8*S*,8a*S*-2,3,8-Trimethoxy-2,3-dimethyl-hexahydro-2*H*-pyrano[3,4-*b*][1,4]dioxin-5-ol (10). To a solution of methyl ether **14** (1.80 g, 4.90 mmol) in MeOH (60 mL) was added 5% Pd/C (300.0 mg, 5% mol) and the mixture was stirred at 25 °C under an atmosphere of H_2. After being stirred at rt under H_2 for 12 h, the mixture was filtered through Celite™ and the filtrate was concentrated under reduced pressure to give the tri-protected L-(+)-arabinose **10** (1.30 g, 95%) as a white solid.

10 [*A mixture of two diastereomers*]: R_f = 0.20 [50% EtOAc in Petroleum Ether]; ^{1}H NMR (600 MHz, $CDCl_3$) *diastereomer-I*: δ 1.31 (s, 3H), 1.33 (s, 3H), 3.26 (s, 3H), 3.27 (s, 3H), 3.48 (s, 3H), 3.53 (s, 1H), 3.86 (d, 1H, *J* = 12.0 Hz), 3.96 (d, 1H, *J* = 12.0 Hz), 4.12-4.14 (m, 1H), 4.19 (dd, 1H, *J* = 3.0, 10.6 Hz), 5.27 (d, 1H, *J* = 3.0 Hz); *diastereomer-II*: δ 1.32 (s, 3H), 1.35 (s, 3H), 3.27 (s, 3H), 3.30 (s, 3H), 3.47 (s, 3H), 3.48 (s, 1H), 3.77 (dd, 1H, *J* = 3.0, 10.6 Hz), 3.84-3.87 (m, 2H), 4.12-4.14 (m, 1H), 4.67 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) *diastereomer-I*: δ 14.1, 17.7, 47.8, 47.9, 60.3, 65.6, 65.7, 76.8 (overlapped by $CDCl_3$), 91.9, 99.92, 100.0, 171.1; *diastereomer-II*: δ 17.8, 21.0, 57.5, 57.6, 64.1, 68.8, 69.9, 76.1, 95.8, 99.6, 99.96, 171.1 (overlap); IR (KBr) cm^{-1} 3475brs, 2950s, 2904s, 2844m, 1459m, 1382m, 1329m, 1129s, 1071s, 1037s; mass spectrum (ESI): m/e (% relative intensity) 301.1 $[M + Na]^+$; m/e calcd for $C_{12}H_{22}O_7Na^+$ $(M + Na)^+$ 301.1258, found 301.1259.

4.5.1-((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-2-Hydroxy-1-methoxyethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-propan-1-ol (15). To a solution of **10** (2.00 g, 7.20 mmol) in THF at -40 °C was added EtMgBr (32.3 mL, 32.3 mmol, 1 *M* in THF) dropwise via a syringe. The solution was then allowed to warm up to rt over 2 h. The reaction was diluted with sat aq NH_4Cl and extracted with EtOAc (100 mL × 2). The combined organic solutions were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was purified through silica gel flash column chromatography (Isocratic eluent: 40% EtOAc in Petroleum Ether) to afford diol **15** (2.20 g, 95%) as colorless oil.

15 [*A mixture of two diastereomers*]: R_f = 0.30 [60% EtOAc in Petroleum Ether]; ^{1}H NMR (600 MHz, $CDCl_3$) *diastereomer-I*: δ 0.99 (t, 3H, *J* = 11.0 Hz), 1.27 (s, 6H), 1.50-1.61 (m, 1H), 1.68-1.79 (m, 1H), 2.37 (brs, 2H), 3.24 (s, 3H), 3.27 (s, 3H), 3.31-3.33 (m, 1H), 3.43 (s, 3H), 3.55-3.58 (m, 1H), 3.73-3.90 (m, 3H), 4.41-4.48 (m, 1H); *diastereomer-II*: δ 1.01 (t, 3H, *J* = 10.3 Hz), 1.28 (s, 6H), 1.50-1.61 (m, 1H), 1.68-1.79 (m, 1H), 2.37 (brs, 2H), 3.25 (s, 3H), 3.28 (s, 3H), 3.31-3.33 (m, 1H), 3.41 (s, 3H), 3.55-3.58 (m, 1H), 3.73-3.90 (m, 3H), 4.09-4.15 (m, 1H, overlapped by EtOAc); ^{13}C NMR (150 MHz, $CDCl_3$) *diastereomer-I*: δ 10.6, 17.4, 26.3, 47.9, 57.3, 60.4, 67.8, 71.4, 71.6, 80.7, 98.5, 98.7; *diastereomer-II*: δ 10.2, 17.5, 24.9, 48.1, 56.9, 59.7, 69.1, 72.7, 73.4, 80.7 (overlap), 98.5, 98.6; IR (KBr) cm^{-1} 3508brs, 2951s, 2833s, 1458m, 1376m, 1237s, 1201m, 1132s, 1042s; mass spectrum (ESI): m/e (% relative intensity) 331.1 $[M + Na]^+$; m/e calcd for $C_{14}H_{28}O_7Na^+$ $(M + Na)^+$ 331.1727, found 331.1745.

4.6. 2*R*,3*R*,4a*S*,8*R*,8a*R*-5-ethyl-2,3,8-trimethoxy-2,3-dimethyl-tetrahydro-2*H*-pyrano[3,4-b][1,4]dioxin-7(3H)-one (18). To a solution of diol **15** (100.0 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (285.0 mg, 0.67 mmol) portion-wise. The solution was stirred at rt for 4 h when the TLC plate showed complete consumption of the starting material **15**. Ethyl (triphenylphosphoranylidene)acetate (133.8 mg, 0.38 mmol) was then added to the solution, and the resulting mixture was stirred for an additional 4 h. The mixture was filtered with Celite™ and the filtrate was concentrated under reduced pressure. The crude residue was purified through silica gel flash column chromatography (Gradient eluent: 5% to 10% EtOAc in Petroleum Ether) to afford the desired α,β-unsaturated ester **8** (35.9 mg, 30%) as colorless oil (see information for **8**), along with the undesired lactone **18** (53.5 mg, 55%) as a white solid.

18: R_f = 0.30 [20% EtOAc in Petroleum Ether]; mp 54-56 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J* = 7.4 Hz), 1.26 (s, 3H), 1.27 (s, 3H), 1.54-1.60 (m, 1H), 1.67-1.74 (m, 1H), 3.22 (s, 3H), 3.26 (s, 3H), 3.48 (s, 3H), 3.63-3.65 (m, 1H), 3.85 (dd, 1H, *J* = 1.2, 9.8 Hz), 3.93 (d, 1H, *J* = 2.8 Hz), 4.31 (dd, 1H, *J* = 2.8, 9.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.3, 17.43, 17.45, 26.3, 47.9, 58.8, 69.1, 69.7, 71.5, 80.7, 98.9, 99.2, 171.5; IR (KBr) cm^{-1} 3453s, 2959s, 1733s, 1462w, 1380m, 1303m, 1129s, 1037s; mass spectrum (ESI): m/e (% relative intensity) 327.1 $[M + Na]^+$; m/e calcd for $C_{14}H_{24}O_7Na^+$ $(M + Na)^+$ 327.1414, found 327.1413.

4.7. *S*-2-(2*S*,3*R*,5*R*,6*R*-5,6-Dimethoxy-5,6-dimethyl-3-propiony-l-1,4-dioxan-2-yl)-2-methoxy-ethyl acetate (19). To a solution of diol **15** (200.0 mg, 0.65 mmol) in pyridine (7.0 mL) was added Ac_2O (0.067 mL, 0.71 mmol). The solution was stirred at rt for 10 h until the TLC plate showed complete consumption of the starting material. The

solution was concentrated under reduced pressure and the residue was purified through silica gel flash column chromatography (Gradient eluent: 5% to 30% EtOAc in Petroleum Ether) to afford the desired acetate (0.15 g, 65%) as yellow oil.

The Acetate Intermediate [*A mixture of two diastereomers*]: R_f = 0.45 [40% EtOAc in Petroleum Ether]; ^{1}H NMR (600 MHz, $CDCl_3$) *diastereomer-I*: δ 0.99 (t, 3H, *J* = 7.2 Hz), 1.25 (s, 3H), 1.28 (s, 3H), 1.53-1.60 (m, 1H), 1.69-1.77 (m, 1H), 2.06 (s, 3H), 2.32 (brs, 1H), 3.23 (s, 3H), 3.25(s, 3H), 3.42 (s, 3H), 3.43-3.45 (m, 1H), 3.57-3.59 (m, 1H), 3.62-3.64 (m, 1H), 4.12 (dd, 1H, *J* = 5.4, 9.6 Hz), 4.17-4.21 (m, 1H), 4.55 (dd, 1H, *J* = 3.0 , 12.0 Hz); *diastereomer-II*: δ 1.00 (t, 3H, *J* = 7.2 Hz), 1.26 (s, 3H), 1.27 (s, 3H),1.44-1.50 (m, 1H), 1.69-1.77 (m, 1H), 2.06 (s, 3H), 2.32 (brs, 1H), 3.27 (s, 3H), 3.28 (s, 3H), 3.40 (s, 3H), 3.53-3.55 (m, 1H), 3.53-3.59 (m, 1H), 3.72 (dd, 1H, *J* = 4.8, 9.6 Hz), 3.83 (dd, 1H, *J* = 7.2, 9.6 Hz), 4.17-4.21 (m, 1H), 4.60 (dd, 1H, *J* = 2.4, 12.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) *diastereomer-I*: δ 10.6, 17.40, 20.9, 26.2, 47.9, 57.6, 62.1, 66.9, 71.8, 72.6, 79.4, 98.48, 98.57, 170.9; *diastereomer-II*: δ 10.2, 17.45, 17.47, 20.9 (overlap), 24.9, 47.8, 57.3, 61.3, 68.2, 71.6, 73.7, 79.4 (overlap), 98.63, 98.8, 170.9 (overlap); IR (KBr) cm^{-1} 3510brs, 2950s, 2834s, 1740s, 1457m, 1376m, 1238s, 1132s, 1043s; mass spectrum (ESI): m/e (% relative intensity) 373.0 (100) $[M + Na]^+$; m/e calcd for $C_{16}H_{30}O_8Na^+$ $(M + Na)^+$ 373.1833, found 373.1832.

To a solution of the above acetate (0.63 g, 1.80 mmol) in CH_2Cl_2 (15 mL) was added Dess-Martin periodinane (1.14 g, 2.70 mmol) portion-wise. The solution was stirred rt for 4 h and TLC showed complete consumption of the starting material. The mixture was filtered through Celite™ and the filtrate was concentrated under reduced pressure. The residue was purified through silica gel flash column chromatography (Isocratic eluent: 30% EtOAc in Petroleum Ether) to afford ester ketone **19** (0.44 g, 70%) as colorless oil.

19: R_f = 0.60 [30% EtOAc in Petroleum Ether]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* = 7.2 Hz), 1.27 (s, 3H), 1.30 (s, 3H), 2.06 (s, 3H), 2.56-2.68 (m, 2H), 3.24 (s, 3H), 3.25 (s, 3H), 3.28 (s, 3H), 3.40-3.41 (m, 1H), 4.00-4.11 (m, 3H), 4.54 (d, 1H, *J* = 12.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 6.9, 17.3, 17.4, 20.8, 31.9, 47.9, 48.0, 57.4, 61.4, 67.2, 77.0, 78.6, 98.7, 98.9, 170.7, 206.1; IR (KBr) cm^{-1} 2946s, 1739s, 1457m, 1375m, 1238s, 1131s, 1042s; mass spectrum (ESI): m/e (% relative intensity) 371.2 (100) $[M + Na]^+$; m/e calcd for $C_{16}H_{28}O_8Na^+$ $(M + Na)^+$ 371.1676, found 371.1675.

4.8. 1-(2*R*,3*S*,5*R*,6*R*)-3-(*S*)-2-Hydroxy-1-methoxy-ethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-propan-1-one (20). To a solution of ester ketone **19** (0.42 g, 1.20 mmol) in MeOH (2 mL) was added K_2CO_3 (165.5 mg, 0.12 mmol). The solution was stirred at room temperature for 1 h. The mixture was filtered through Celite™ and the filtrate was concentrated under reduced pressure to get hemi-acetal **20** (0.35 g, 95%) as a white solid.

20: R_f = 0.30 [50% EtOAc in Petroleum Ether]; mp 104-108 °C; $[\alpha]_D^{20}$ = -82.8 (*c* 0.70, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J* = 7.8 Hz), 1.29 (s, 3H), 1.32 (s, 3H), 1.69-1.75 (m, 1H), 1.79-1.86 (m, 1H), 2.43 (brs, 1H), 3.25 (s, 3H), 3,26 (s, 3H), 3.46 (s, 3H), 3.48-3,49 (m, 1H), 3.87 (m, 2H), 4.00 (d, 1H, *J* = 10.3 Hz), 4.08-4.11 (dd, 1H, *J* = 3.0, 10.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 6.4, 17.8, 17.9, 30.6, 47.8, 57.6, 61.1, 67.2, 67.5, 76.8, 97.7, 99.8, 100.1; IR (KBr) cm^{-1} 3477brs, 2983s, 2943s, 1460m, 1370m, 1189s, 1117s, 1076s, 1038s; mass spectrum (ESI): m/e (% relative intensity) 329.0 (100) $[M + Na]^+$; m/e calcd for $C_{14}H_{26}O_7Na^+$ $(M + Na)^+$ 329.1571, found 329.1575.

4.9. (*E*)-ethyl 4-(2*S*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-propionyl-1,4-dioxan-2-yl)-4-methoxy-but-2-enoate (8). To a solution of hemi-acetal **20** (0.31 g, 1.01 mmol) in CH_2Cl_2 was added Dess-Martin periodinane (0.64 g, 1.50 mmol) portion-wise, followed by addition of K_2CO_3 (14.0 mg, 0.10 mmol). The solution was stirred at rt for 4 h when TLC showed complete consumption of the starting material **20**. Ethyl (triphenylphosphoranylidene) acetate (0.52 g, 1.50 mmol) was added to this solution, and stirred for another 4 h. The mixture was filtered through Celite™ and the filtrate was concentrated under reduced pressure. The residue was purified through silica gel flash column chromatography (Gradient eluent: 2% to 10% EtOAc in Petroleum Ether) to afford α,β-unsaturated ester **8** (0.32 g, 85%) as colorless oil.

8: R_f = 0.55 [20% EtOAc in Petroleum Ether]; $[\alpha]_D^{20}$ = -85.0 (*c* 1.00, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (t, 3 H, *J* = 10.6 Hz), 1.27-1.31 (m, 9H), 2.58-2.66 (m, 2H), 3.18 (s, 3H), 3.20 (s, 3H), 3.25 (s, 3H), 3.80-3.90 (m, 2H), 4.04 (d, 1H, *J* = 14.0 Hz), 4.20 (q, 2H, *J* = 10.6 Hz), 6.05 (d, 1H, *J* = 24.0 Hz), 6.93 (dd, 1H, *J* = 9.0, 24.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.0, 14.2, 17.3, 17.4, 32.2, 48.0, 48.1, 57.1, 60.4, 70.5, 76.8, 79.7, 98.8, 98.9, 123.6, 144.1, 165.9, 206.5; IR (KBr) cm^{-1} 2984m, 2942m, 2835m, 1722s, 1699w, 1458m, 1372m, 1270m, 1269s, 1129s, 1040s; mass spectrum (ESI): m/e (% relative intensity) 397.5 (100) $[M + Na]^+$; m/e calcd for $C_{18}H_{30}O_8Na^+$ $(M + Na)^+$ 397.1833, found 397.1837.

4.10. *S*-Ehyl 4-((2*S*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-propionyl-1,4-dioxan-2-yl)-4-methoxy-butanoate (21). To a solution of α,β-unsaturated ester **8** (1.40 g, 3.74 mmol) in EtOAc (40 mL) was added 5% Pd/C (400.0 mg, 5% mol) and the mixture was stirred at 25 °C under an atmosphere of H_2. After stirring at rt under H_2 for 2 h, the mixture was filtered through Celite™ and the

filtrate was concentrated under reduced pressure to give ester **21** (1.40 g, 95%) as colorless oil.

21: R_f = 0.45 [20% EtOAc in Petroleum Ether]; $[\alpha]_D^{20}$ = -102.9 (*c* 1.40, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* = 7.2 Hz), 1.25 (t, 3H, *J* = 7.2 Hz), 1.28 (s, 3H), 1.30 (s, 3H), 1.91-1.96 (m, 1H), 1.97-2.02 (m, 1H), 2.39-2.42 (m, 2H), 2.60-2.64 (m, 2H), 3.21 (s, 3H), 3.26 (s, 3H), 3.29 (s, 3H), 3.30-3.32 (m, 1H), 3.95 (dd, 1H, *J* = 6.4, 10.0 Hz), 4.02 (d, 1H, *J* = 10.0 Hz), 4.20 (q, 2H, *J* = 10.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.0, 14.2, 17.4, 17.5, 24.6, 29.6, 32.3, 48.1, 48.2, 57.3, 60.3, 68.3, 76.1, 79.3, 98.72, 98.75, 173.6, 206.5; IR (KBr) cm^{-1} 2983s, 2943s, 2834s, 1731s, 1456m, 1376s, 1256m, 1139m, 1131s, 1041s; mass spectrum (ESI): m/e (% relative intensity) 399.0 (100) $[M + Na]^+$; m/e calcd for $C_{18}H_{32}O_8Na^+$ $(M + Na)^+$ 399.1989, found 399.2038.

4.11. (5*S*,6*R*)-6-(*R*-1-Hydroxy-2-oxobutyl)-5-methoxy-tetrahydro-2*H*-pyran-2-one (7). To a solution of **21** (0.67 g, 1.78 mmol) and anhyd $FeCl_3$ (14.4 mg, 0.089 mmol) in glacial acetic acid (7.5 mL) was added a solution of H_2O in AcOH (5% v/v, 0.37 mL) at rt. The reaction mixture was stirred at rt for ~ 12 h when TLC analysis indicated complete consumption of the starting material. The volatiles were removed under reduced pressure. The residue was purified through silica gel flash column chromatography (Gradient eluent: 10% to 50% EtOAc in Petroleum Ether) to give keto-lactone **7** (0.23 g, 60%) as colorless oil.

7: R_f = 0.30 [40% EtOAc in Petroleum Ether]; $[\alpha]_D^{20}$ = +37.0 (*c* 1.00, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16 (t, 3H, *J* = 7.0 Hz), 1.86-1.92 (m, 1H), 2.24-2.29 (m, 1H), 2.46-2.58 (m, 2H), 2.60-2.69 (m, 2H), 3.45 (s, 3H), 3.80 (td, 1H, *J* = 4.6, 7.0 Hz), 4.36 (s, 1H), 4.58 (dd, 1H, *J* = 1.6, 7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.4, 23.2, 27.0, 31.1, 56.9, 72.8, 75.6, 81.4, 169.7, 208.1; IR (KBr) cm^{-1} 2985s, 2970m, 1741s, 1468w, 1365m, 1289s, 1244s, 1107m, 1041m; mass spectrum (ESI): m/e (% relative intensity) 239.0 (100) $[M + Na]^+$; m/e calcd for $C_{10}H_{17}O_5^+$ $(M + H)^+$ 217.1071, found 217.1075.

4.12. *R*-1-2*S*,3*S*-3-Methoxy-6-oxo-tetrahydro-2*H*-pyran-2-yl)-2-oxobutyl pivalate (22). To a solution of the unprotected keto-lactone **7** (100.0 mg, 0.46 mmol) and Et_3N (0.60 mL, 4.60 mmol) in CH_2Cl_2 (5 mL) were added PivCl (0.20 mL, 1.39 mmol) and DMAP (11.3 mg, 0.10 mmol). The solution was stirred at rt overnight (~12 h) and quenched with H_2O. The organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (30 mL× 3). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified through silica gel flash column chromatography (Isocratic eluent: 20% EtOAc in Petroleum Ether) to afford pivalate **22** (134.7 mg, 95%) as a white solid.

22: R_f = 0.50 [40% EtOAc in Petroleum Ether]; mp 51-53°C; $[\alpha]_D^{20}$ = +50.0 (*c* 0.20, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06 (t, 3H, *J* = 7.2 Hz), 1.31 (s, 9H), 1.88-1.94 (m, 1H), 2.11-2.16 (m, 1H), 2.39 (dq, 1H, *J* = 7.0, 18.8 Hz), 2.47 (ddd, 1H, *J* = 6.0, 7.6, 14.0 Hz), 2.61 (dq, 1H, *J* = 7.0, 18.8 Hz), 2.71 (ddd, 1H, *J* = 6.0, 7.6, 14.0 Hz), 3.34 (s, 3H), 3.42 (td, 1H, *J* = 5.2, 7.6 Hz), 4.71 (dd, 1H, *J* = 2.2, 7.6 Hz), 5.34 (d, 1H, *J* = 2.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 6.8, 23.3, 27.0, 27.2, 32.6, 39.1, 56.9, 72.4, 76.3, 80.4, 169.6, 177.5, 206.4; IR (KBr) cm^{-1} 2975s, 2890m, 1744s, 1466w, 1361m, 1294m, 1202s, 1140s, 1109s, 1044m; mass spectrum (ESI): m/e (% relative intensity) 301.0 (100) $[M + H]^+$; m/e calcd for $C_{15}H_{25}O_6^+$ $(M + H)^+$ 301.1646, found 301.1648.

4.13. *R*-2-Ethyl-1,3-dithiolan-2-yl-(2*S*,3*S*)-3-methoxy-6-oxotetra-hydro-2*H*-pyran-2-yl)-methyl pivalate (5). To a solution of ketone **22** (140.0 mg, 0.47 mmol) in CH_2Cl_2 (3 mL) were added 1,2-ethanedithiol (66.3 mg, 0.70 mmol) of) and BF_3-OEt_2 (0.10 mL) in this order. The resulting mixture was stirred at rt overnight (~12 h) and 5% NaOH (1 mL) was added. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified through silica gel flash column chromatography (Gradient eluent: 5% to 20% EtOAc in Petroleum Ether) to afford lactone **5** (176.7 mg, 67%) as a white solid.

5: R_f = 0.30 [30% EtOAc in Petroleum Ether]; mp 73-74 °C; $[\alpha]_D^{20}$ = +40.0 (*c* 1.00, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, 3H, *J* = 7.2 Hz), 1.25 (s, 9H), 1.87-1.93 (m, 1H), 1.95-2.01 (m, 1H), 2.08-2.14 (m, 1H), 2.17-2.23 (m, 1H), 2.35 (dt, 1H, *J* = 6.2, 17.6 Hz), 2.67 (ddd, 1H, *J* = 6.4, 9.0, 15.4 Hz), 3.23-3.26 (m, 2H), 3.31-3.36 (m, 3H), 3.43 (s, 3H), 4.82 (d, 1H, *J* = 6.3 Hz), 5.31 (d, 1H, *J* = 1.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.6, 22.5, 26.6, 27.2, 29.5, 39.3, 39.3, 40.2, 56.8, 74.3, 75.6, 75.9, 79.5, 169.9, 177.9; IR (KBr) cm^{-1} 2973s, 2932m, 1735s, 1453w, 1383m, 1207s, 1166s, 1136s, 1038m; mass spectrum (ESI): m/e (% relative intensity) 399.0 (100) $[M + Na]^+$; m/e calcd for $C_{17}H_{28}O_5S_2Na^+$ $(M + Na)^+$ 399.1270, found 399.1278.

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