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Graphical Abstract

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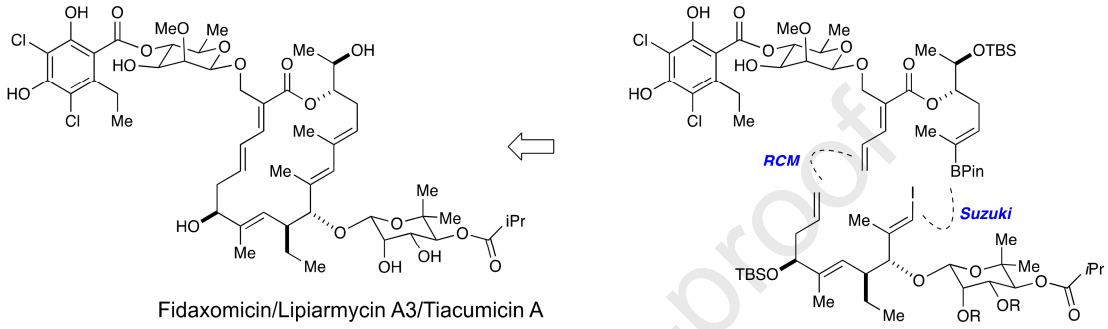

Fidaxomicin/Lipiarmycin A3/Tiacumicin A

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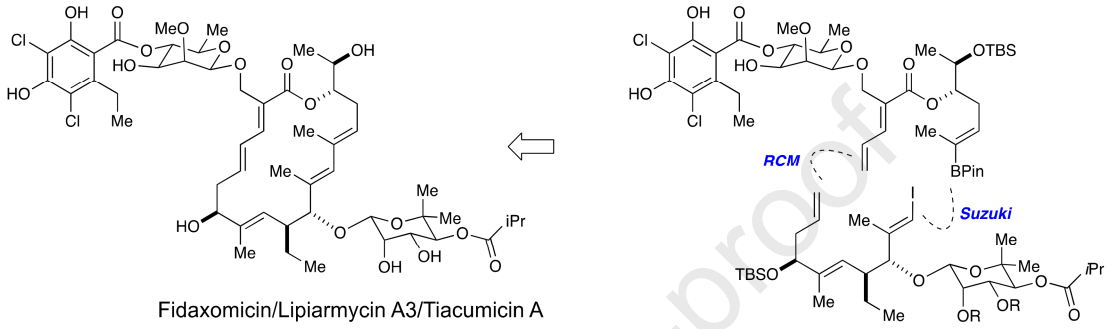

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ABSTRACT

Efficient approaches that enable the synthesis of analogs of natural product antibiotics are needed to keep up with the emergence of multiply-resistant strains of pathogenic organisms. One promising candidate in this area is fidaxomicin, which boasts impressive in vitro anti-tubercular activity but has poor systemic bioavailability. We designed a flexible synthetic route to this target to enable the exploration of new chemical space and the future development of analogs with superior pharmacokinetics. We developed a robust approach to each of the key macrocyclic and sugar fragments, their union via stereoselective glycosylation, and a convergent late-stage macrolide formation with fully glycosylated fragments. Although we were able to demonstrate that the final Suzuki cross-coupling and ring-closing metathesis steps enabled macrocycle formation in the presence of the northern resorcylic rhamnoside and southern novioside sugars, these final steps were hampered by poor yields and the formation of the unwanted *Z*-macrocycle as the major stereoisomer.

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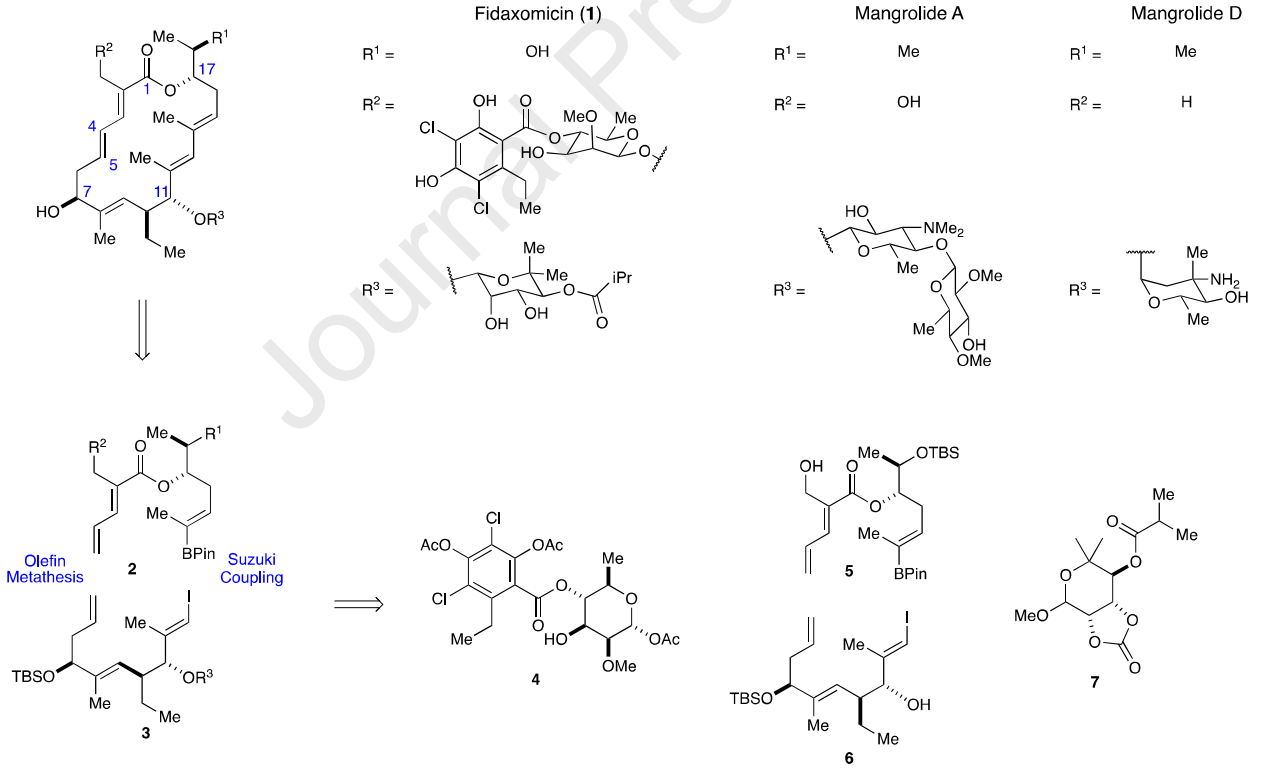
1. Introduction

Fidaxomicin (**1**) is an FDA approved macrolide antibiotic[1] with modest *in vitro* efficacy against Gram-positive bacteria and notably potent activity against *Clostridium difficile* (MIC_{50} = 31 μg/mL)[2] and *Mycobacterium tuberculosis* (MIC_{50} = 15 μg/mL) including drug resistant strains (MIC_{50} = 8–45 μg/mL).[3] A recently obtained cryo-EM structure of fidaxomicin bound to RNA-polymerase[4] has provided insight on the binding mode and biochemically important structural features of fidaxomicin.

Despite its promising anti-tubercular activity, approved clinical use of fidaxomicin is limited to treatment of *C. difficile* associated colitis.[5] Unfortunately, fidaxomicin has poor oral bioavailablity and is rapidly cleared following alternative dosing modes.[6] These limitations preclude its use for the systemic treatment of tuberculosis infections. Thus, a fidaxomicin analog with improved bioavailability could represent a new class of antibiotics for the treatment of systemic bacterial infections, including tuberculosis and multidrug-resistant tuberculosis. Semisynthetic approaches have been severely hampered by the instability of the macrolide, which is readily available by fermentation,[7] to standard acid mediated glycolysis methods.[8] Several groups have reported the structure and bioactivity of biosynthetically prepared analogs.[9] However, a robust medicinal chemistry program would enable access to a wider variety of structural modifications than is generally possible using bioengineering approaches. In this context, fidaxomicin has gained significant attention as a synthetic target in recent two syntheses of the natural product have been reported since 2015.[12,13] Additionally, we and others have completed syntheses of the structurally related mangrolides A and D, which share the macrolactone core of fidaxomicin (see scheme 1).[14] Here we report our approach to the synthesis of fully glycosylated northern and southern fragments of fidaxomicin, and explore their union via Suzuki cross-coupling and ring-closing metathesis.

2. Results and Discussion

Our synthesis was designed to be as convergent and modular as possible to expedite subsequent syntheses of natural product analogs. As outlined in Scheme 1, we envisioned unification of northern and southern fragments **2** and **3** by a sequential Suzuki cross coupling and ring closing metathesis (RCM) sequence. This strategy was adapted from our longstanding work on the mangrolide family.[15] The Gademann group also utilized these disconnections in their synthesis of both fidaxomicin and the mangrolides.[12c,14c,14d] However, where they appended the rhamnoside unit post macrolactone formation, we endeavored to pursue the unification of fully glycosylated northern and southern fragments. This would, in principle, allow us to reduce the number of linear manipulations at the end of the sequence. To that end we needed to develop a β-selective rhamnosylation of northern macrolide fragment **5** with a fully functionalized resorcyl rhamnoside **4**. Southern fragment **3** on the other hand, would be



Scheme 1: Structures of fidaxomicin, mangrolide A, and mangrolide D and retrosynthetic strategy towards Fidaxomicin

accessible via the previously described Koenigs-Knorr glycosylation of southern macrolide fragment **6** with novioside **7**.[13a] Our initial objective was to develop robust, scalable routes towards fragments **4**-**7** and explore their unification via stereoselective glycosylation.

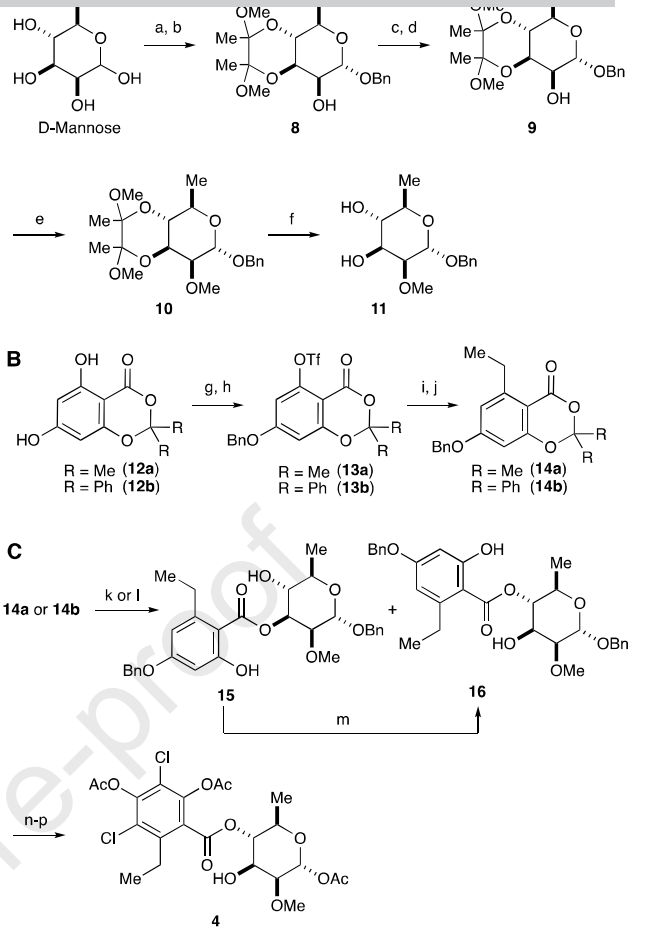
Our forward synthesis began with the preparation of resorcylated D-rhamnoside donor **4** (Scheme 2A). In an adaption of the procedure reported by Gademann and coworkers for the corresponding anomeric methyl ether, the anomeric position of D-mannose was derivatized as a benzyl ether, followed by masking the 3- and 4-hydroxyl groups as the butanediacetal **8** in 55% yield for the two steps.[16] A Garegg-Samuelsson iodination/hydrogenolysis sequence removed the 6-hydroxyl group to provide rhamnoside **9** in good yield. Methylation of the remaining alcohol proceeded with excellent yield to give **10** and was followed by final cleavage of the butanediacetal under mild hydrolytic conditions to provide up to nine grams of key rhamnoside **11** in a single batch.

photochemical methods for the preparation of hindered salicylate and resorcylate esters and amides using dioxinones similar to **14a** and **14b**.[17] In order to explore these approaches for the introduction of the homoorsellinate residue we prepared both **14a** and **14b** starting with trihydroxybenzoic acid derivatives **12a** and **12b** (Scheme 2B). Selectively etherification of the *para*-phenol under Mitsunobu conditions, followed by triflation of the remaining *ortho*-phenol under standard conditions efficiently provided **13a** and **13b.**[17c,18] Subsequent Stille cross-coupling with tributyl(vinyl)tin proceeded in excellent yields, and the resultant styrenes could be selectively reduced in the presence of the benzyl ether using a $NiCl_2$/sodium borohydride system[19] to provide **14a** or **14b** on multigram scale.

Sodium hydride promoted acylation of **11** with **14a** proceeded with moderate thermodynamic selectivity for the desired 4-acyl isomer **16** (31% yield of **15**, 52% yield of **16**, Scheme 2C).[17a,20] Resubmission of **15** to the sodium hydride acylation conditions provided additional **16**. By contrast, photochemical acylation of **11** with **14b** proceeded in lower yield, and afforded a kinetic mixture of acylated products **15** and **16** in which the undesired regioisomer **15** dominated (37% and 20% isolated yield respectively).[17b,c] Using the superior sodium hydride mediated acylation of rhamnoside **11** with **14a**, we prepared up to a gram of **16** in one batch. In preparation for glycosylation of the northern fragment (vide infra), intermediate **16** was sequentially debenzylated via hydrogenolysis, chlorinated using sulfuryl chloride, and carefully tris-acetylated to afford the fully functionalized rhamnoside **4** in good overall yield.

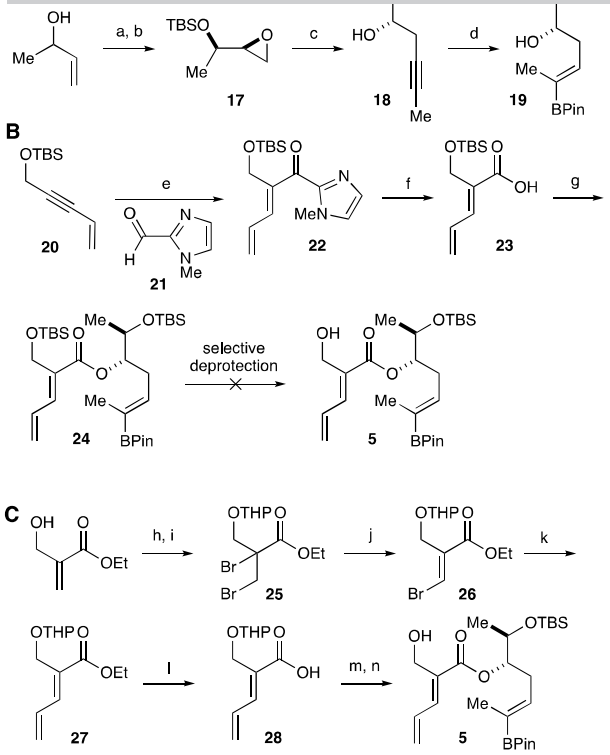
Our synthesis of northern macrolide fragment **5** initiates with a stereoselective synthesis of borylated homopropargyl alcohol **19** and tracks with that of previous reports.[12a,13a] As shown in Scheme 3A, Sharpless epoxidation and silylation of 1-butene-3-ol yielded enantiomerically enriched **17** (38% yield for 2 steps).[21] Epoxide opening with propynyl lithium occurred as expected to afford the desired alkyne **18** in high yield.[12a] We found that regio- and stereoselective borylation of the alkyne was most efficient using conditions developed by the Carretero group,[22] providing the needed secondary alcohol **19** with high yield and excellent selectivity on gram scale.

To prepare the dienoic acid **23**, we adapted the hydrogen mediated C-C coupling method developed by the Krische group (Scheme 3B).[23] Known enyne **20**,[24] available in two steps from propargyl alcohol, was coupled with aldehyde **21** to provide the allylic alcohol with excellent regio- and stereoselectivity for the desired *E*-diene. The resulting crude alcohol was then oxidized to dienone **22** in 70% yield for the two step sequence. Activation of the *N*-methyl imidazole with methyl triflate was followed by potassium trimethylsilanolate mediated hydrolysis to generate the dienoic acid **23** in good yield (82%, 2 steps).[25] It is worth noting that this alternative synthesis of dienoic acid **23** (6 steps, *E*/*Z* >20:1, 49% overall yield) compares favorably to those previously reported for this or related dienoates.[12a-c] Acid **23** was esterified with alcohol **19** using previously described Yamaguchi conditions to generate known bis-silyl ester **24**.[13a,14b] Conditions to selectively cleave the primary TBS group in the context of an intact macrocycle have been reported.[8b,13a] Unfortunately, we were unable to identify conditions to effect a selective deprotection of the primary silyl ether on the borylated ester **24**, and therefore pursued the synthesis of dienoic acid **28** according to a protocol adapted from Zhu and coworkers (Scheme 3C).[12b]



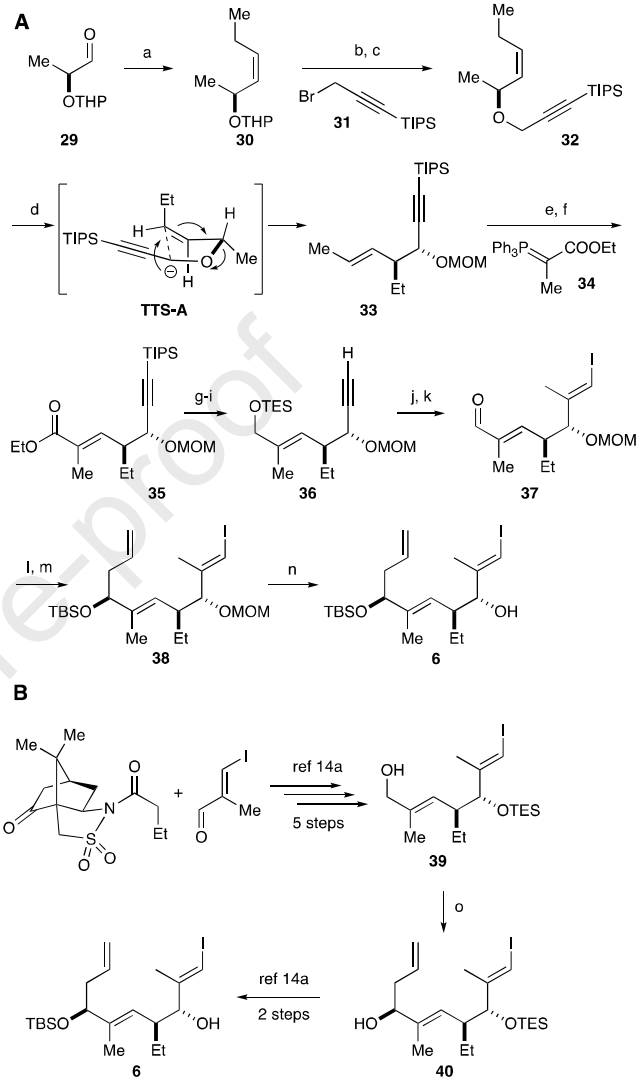
Scheme 2. Synthesis of orsellinic rhamnoside **4**. Reagents and conditions: (a) BnOH, HCl; (b) $(MeO)_3CH$, CSA, butanedione, MeOH; then Et_3N (55%, 2 steps); (c) I_2, PPh_3, imidazole, THF (84%); (d) H_2, Pd/C, MeOH, Et_3N (90%); (e) NaH, MeI, THF (>95%); (f) TFA, DCM, H_2O; Et_3N (69%); (g) BnOH, PPh_3, DIAD, THF; (h) pyridine, Tf_2O (**13a**: 61%, 2 steps; **13b**: 65%, 2 steps); (i) $Pd(PPh_3)_4$, LiCl, dioxane, Et_3N, tributyl(vinyl)tin; (j) $NiCl_2$, $NaBH_4$, MeOH (**14a**: 66%, 2 steps; **14b**: 58%, 2 steps); (k) **14b**, **11**, 300 nm UV light (**15**: 37%; **16**: 20%); (l) **14a**, **11**, NaH, THF (**15**: 31%; **16**: 52%); (m) NaH, THF (54%); (n) H_2, $Pd(OH)_2$, MeOH; (o) SO_2Cl_2, EtOAc; (p) Ac_2O, DMAP, EtOAc (66%, 3 steps).

In the event, ethyl 2-(hydroxymethyl)acrylate was dibrominated and protected as the THP ether, giving dibromide **25** in excellent yield for the two-step process (78% overall).[26,27] Stereoselective elimination of the α-bromide with tetrabutylammonium fluoride in HMPA provided acryloyl bromide **26** in 85% yield and excellent stereoselectivity (>20:1 *E*/*Z*). Stille coupling of vinyl bromide **26** with tributyl(vinyl)tin yielded dienoate **27** in 93% yield.[28] Using this route, we were able to prepare multigram quantities of **27** in 62% overall yield over four steps from commercially available ethyl 2-(hydroxymethyl)acrylate. Hydrolysis of ester **27** afforded the dienoic acid **28** (>95%), which was esterified as before with alcohol **19**. This time, the THP-protected primary alcohol could be selectively removed with ethanolic PPTS to yield the target northern fragment alcohol **5** in 45% yield (2 steps) with no observable degradation of the TBS or BPin functionalities.



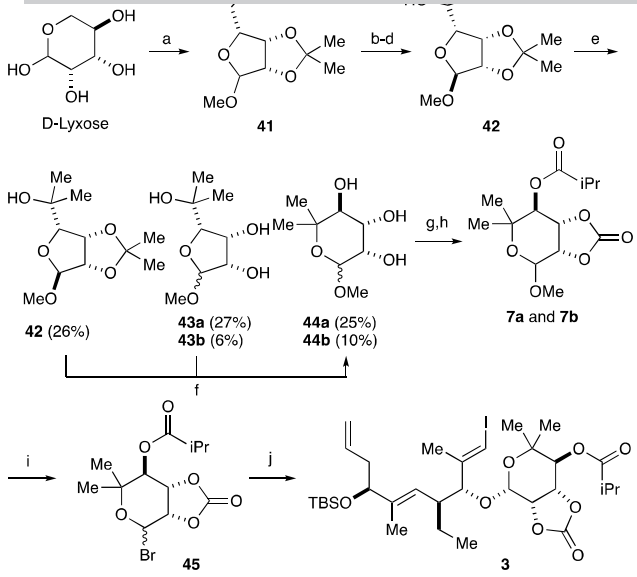
Scheme 3. Synthesis of northern fragment borylated ester **5**. Reagents and conditions: (a) $Ti(OiPr)_4$, D-DIPT, DCM, TBHP, 4Å MS; (b) TBSCl, imidazole (38%, 2 steps); (c) propyne, *n*BuLi, BF_3•OEt_2 (90%); (d) CuCl, PCy_3, NaO^tBu, B_2Pin_2, MeOH, PhMe (81%); (e) *rac*-BINAP, $Rh(COD)_2OTf$, **21**, Ph_3CCOOH, H_2, DCE; then MnO_2, DCM (70%); (f) MeOTf, MeCN; then KOTMS, Et_2O (82%); (g) **19**, Et_3N, DMAP, 2,4,6-trichlorobenzoyl chloride, PhMe (60%); (h) Br_2, $CHCl_3$ (93%); (i) dihydropyran, PPTS, DCM (84%); (j) TBAF, HMPA (85%, >20:1 dr); (k) $Pd_2(dba)_3$, P(2-furyl)$_3$, tributyl(vinyl)tin, THF (93%); (l) LiOH, H_2O, THF, EtOH (>95%); (m) **19**, Et_3N, DMAP, 2,4,6-trichlorobenzoyl chloride, THF; (n) PPTS, EtOH (45%, 2 steps).

We next turned our focus to the preparation of southern fragment **6** (Scheme 4). Our work on mangrolide A disclosed a route to polyketide fragment **6** utilizing a 2,3-Wittig rearrangement[29] to establish the C10-C11 stereochemistry and a late stage bis-functionalization of an alkyne to prepare the required *E*-vinyl iodide.[14b,15] A related rearrangement has subsequently been utilized by the Roulland group to elegantly set this same stereochemical diad.[12d] As shown in scheme 4A, our route commenced with L-lactate-derived aldehyde **29**. Wittig homologation of the aldehyde afforded *Z*-olefin **30** in 83% yield (*Z*/*E* > 20:1). Methanolysis (*p*TSOH) of the THP-ether was followed by alkylation with propargyl bromide **31** (KO^tBu, THF) to afford [2,3]-Wittig precursor **32** in 76% (2 steps). Deprotonation with *n*BuLi in THF induced a smooth rearrangement to the corresponding alcohol which was trapped in situ with methoxymethyl chloride to provide **33** in 88% yield and with excellent stereoselectivity. The relative stereochemistry was predicted to result from [2,3]-rearrangement occurring via cyclic TTS-A. The stereochemistry was unambiguously assigned via comparison of fragment **6** resulting from this route, to the identical material reported previously by us and others.[12c,14a] Careful selective ozonolysis of the alkene in **33** (Me_2S work-up) was followed by homologation of the resultant aldehyde with stabilized ylide **34** to afford *E*-configured α,β-unsaturated ester **35** in 79% yield (2 steps). To set the stage for subsequent alkyne functionalization, ester **35** was reduced, followed by a TIPS deprotection, and TES protection sequence. The resultant terminal alkyne **36**, obtained in 76% for this 3-step sequence, was subjected to a one-pot stannocupration/methylation/iodination to yield the vinyl iodide with simultaneous cleavage of the TES the primary alcohol gave aldehyde **37**. A diastereoselective Brown allylation was followed by TBS protection of the resultant alcohol to afford intermediate **38** in 65% yield and excellent stereoselectivity (>20:1 dr). A final boron trifluoride mediated cleavage of the methoxymethyl ether afforded target secondary alcohol **6** in 77% yield.



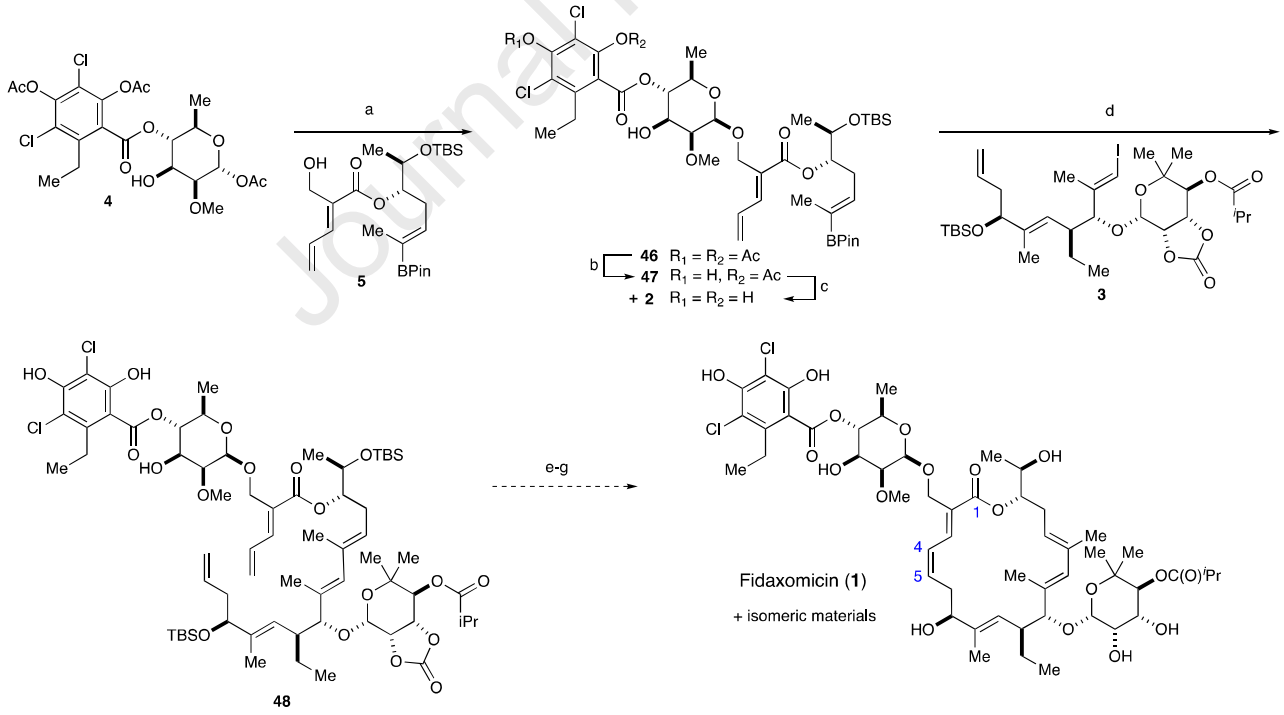
Scheme 4. Two alternative syntheses of southern fragment **6**. Reagents and conditions: (a) *n*PrPPh$_3$Br, *n*BuLi, THF (83%); (b) *p*TsOH, MeOH; (c) **31**, ^{t}BuOK, THF, (76%, 2 steps); (d) *n*BuLi, THF; then MOMCl (88%); (e) O_3, DCM; then Me_2S (93%); (f) **34**, toluene (85%); (g) DIBAL, DCM; (h) TBAF, THF; (i) TESOTf, lutidine, DCM (76%, 3 steps); (j) CuCN, $(Bu_3Sn)_2$, *n*BuLi, MeI; then I_2, THF (80%); (k) DMP, DCM (91%); (l) (–)-Ipc$_2$B-allyl, Et_2O; then H_2O_2, NaOH; (m) TBSOTf, lutidine, DCM (65%, 2 steps); (n) BF_3•OEt_2, Me_2S (77%); (o) $[Ir(COD)Cl]_2$, (*R*)-Cl-MeO-BIPHEP, Cs_2CO_3, *m*NO_2BzOH, allyl acetate, THF (57%, >20:1 dr).

During the course of our synthesis of mangrolide D, we developed an alternative approach to **6** utilizing an Oppolzer sultam mediated aldol reaction (Scheme 4B).[12a,14a] For this work, we exploited primary alcohol **39** to explore a Krische-type iridium catalyzed allylation from the alcohol oxidation state to further streamline this synthetic sequence. Gratifyingly, allylic alcohol **39** directly provided homoallylic alcohol **40** with excellent stereoselectivity (>20:1 dr) using the reported conditions.[31] A straightforward protection/deprotection sequence then revealed key intermediate **6**, which was identical to material produced according to Scheme 4A and previous syntheses.[12c,14a]



Scheme 5. Synthesis of protected novioside **7** and fully glycosylated southern fragment **3**. Reagents and conditions: (a) HCl, MeOH, acetone (75%); (b) TEMPO, KBr, $NaHCO_3$, NaOCl, EtOAc, H_2O (>95%); (c) MeI, K_2CO_3, DMF (66%); (d) MeMgBr, THF (>95%); (e) TFA, MeOH, H_2O; (f) TFA, MeOH, H_2O (70% yield of **44a** and **44b** after 3 cycles); (g) **44a** or **44b**, CDI, THF; (h) $(^iPrCO)_2O$, Et_3N, DMAP, DCM (76% from **44a**, 82% from **44b** over 2 steps); (i) **7b**, HBr, AcOH, DCM; (j) **6**, $HgBr_2$, HgO, 4Å MS, DCM; then Et_3N (67%, 2 steps, >2:1 β:α).

Preparation of the southern protected novioside sugar **7** commenced with commercially available D-lyxose (Scheme 5). Treatment of this material with HCl in a mixture of methanol and furanose, anomeric methyl ketal formation, and ketalization of the *cis*-diol to provide compound **41** in 75%.[32] The primary alcohol was then oxidized to the carboxylic acid and alkylated to form the corresponding methyl ester (~65% overall).[33] Addition of excess methylmagnesium bromide afforded tertiary alcohol **42** (>95%). By this four-step sequence up to 9.5 g (41% overall yield) of material was prepared in a single batch with no purifications. This method compared favorably to the previous six-step approach from *O*-methyl mannose reported by Kaufmann.[13a] From **42** onwards our route to **3** followed the sequence reported by Kaufmann et al.[13a] with some minor modifications. Isomerization of **42** to the α- and β-pyranoses, **44a** and **44b** respectively, was performed in a mixture of trifluoroacetic acid and methanol. All four possible isomers of deprotected material were individually isolated and characterized along with recovered starting material **42** in the indicated quantities. In two subsequent iterations, furanose isomers **43a** and **43b** and recovered **42** were combined and resubmitted to the reaction conditions to generate a similar distribution of products. The total combined yield of isolated **44a** and **44b** was 70%. We next took advantage of an improved acylation protocol reported by Kaufmann[8b] to install the cyclic carbonate and the isobutyrate, which provided noviosides **7a** and **7b** from **44a** and **44b** respectively (~76-82% yield). Glycosylation of **6** with unstable glycosyl bromide **45** was performed using a slight modification of the previously reported method.[13a] Thus treatment of **7b** with HBr in acetic acid afforded the unstable glycosyl bromide **45**, which was isolated but not purified.[35] A Helferich type Koenigs-Knorr glycosylation of **6** with crude **45** provided the desired β-anomer **3** as the major product and with better than 2:1 stereoselectivity.[36]



Scheme 6. Synthesis of fully glycosylated northern fragment **2**, cross-coupling with fully glycosylated southern fragment **5**, and exploration of the final steps. Reagents and conditions: (a) **4**, HBr, AcOH, DCM; then **5**, Ag_2CO_3, 4Å MS, DCM (35% + 44% recovered **5**, >3:1 β:α); (b) **46**, K_2CO_3, MeOH (**2**: 35%; **47**: 34%); (c) **47**, K_2CO_3, MeOH (48%); (d) TlOEt, $Pd(PPh_3)_4$, THF, H_2O (38%); (e) Grubbs II, PhMe; (f) NaH, ethylene glycol, THF; (g) HF•Et_3N, THF.

Glycosylation of the northern fragment **5** was best performed with the crude glycosyl bromide derived from acetate **4** (HBr, HOAc, DCM) and mediated by silver carbonate to yield the desired β-anomer **46** in 35% isolated yield (α/β of crude mixture >3:1) along with recovered alcohol **5** (44%). This approach differs from previously reported methods for the installation of this challenging β-mannose type glycosidic bond in the fidaxomicin literature.[37] Methanolysis of the phenolic acetates (K_2CO_3, MeOH) provided target fragment **2** (32%) along with an equal amount of monoacetate **47** (34%). The reaction time had to be kept short to avoid degradation of the sensitive pinacol ester. Purified **47** could be resubmitted to the same reaction conditions

to des. sought to explore macrolide formation using this fully glycosylated northern fragment **2**. Gratifyingly, Suzuki coupling of this material with glycosylated southern fragment **3** using conditions described for coupling of a non-glycosylated northern fragment (cf. **24**) provided the desired hindered diene **48**, albeit with lower efficiency (38% versus published 88% for coupling of **3** with **24**).[13a]

All that remained was a penultimate ring closing olefin metathesis (RCM) and removal of the carbonate and silyl protecting groups. The ring closing metathesis of a mono-glycosylated (at C_{11}),[13a] or a non-glycosylated[12b] seco-macrolide diene was reported to yield separable mixtures of *E*/*Z*-macrocycles with the desired natural *E*-isomer dominating (~2:1), and the unwanted *Z*-isomer recyclable after separation and resubjecting to the RCM conditions. Unfortunately, similar conditions with fully glycosylated seco-macrolide diene **48** led to an inseparable 1:2 mixture of double bond isomers with the unnatural *Z*-isomer dominating as determined by ^{1}H NMR of the crude reaction product. Exploration of other RCM catalysts did not provide a satisfying solution. These results underscore the unpredictable influence of peripheral protecting groups and functionality on double bond geometry in the context of ring closing metathesis leading to larger ring systems.[38,39]

While these results were a setback, we hoped to be able to separate the *E*/*Z* isomers at a later stage. At this point, we had only small amounts of crude RCM product mixtures available and subsequent reactions were performed on sub-milligram scale with product mixtures characterized primarily by crude NMR and mass spectrometry, but in insufficient quantities to support a more rigorous structural assignment. Nevertheless, the crude RCM mixture was subjected to carbonate cleavage and fluoride-mediated silyl ether cleavage as described.[8b,13a] Analysis of the crude reaction product by TLC and HPLC revealed three separable products. Each of these three products was isolated in low yield (<15%) by preparative RP-HPLC and independently characterized by ^{1}H NMR and HRMS. Each consisted of an inseparable 2:1 *Z*/*E* mixture of olefin isomers and had a mass (m/z) consistent with that of authentic fidaxomicin. One product coeluted with commercial fidaxomicin in a co-injection experiment, and comparison of the ^{1}H NMR of this material with that of authentic fidaxomicin supported its assignment as a 2:1 mixture of 4,5-*Z*-fidaxomicin and fidaxomicin. The remaining products appear to be constitutional isomers of fidaxomicin (same m/z), presumably isobutyrate migration products in the novioside sugar.[40] However, none of these materials was obtained in sufficient quantity to support a more rigorous structural assignment.

3. Conclusion

We have established robust synthetic routes to key intermediates **2**-**7** en route to fidaxomicin. In particular, the hydrogenative C-C coupling route (scheme 3B) to dienoate **23** represents a favorable route towards this compound. The 2,3-Wittig rearrangement is a less contemporaneous, yet highly efficient approach to install the stereodiad embedded within the southern polyketide fragment **6**. The catalytic Krische-type allylation from the alcohol oxidation stage represents and efficient alternative to classical reagent controlled allylations to install the homoallylic alcohol of fragment **6** with high diastereoselectivity. The preparation of novioside **7** from D-Lyxose represents a substantial improvement in both step count and efficiency over previous approaches. Koenigs-Knorr glycosylations towards both **2** and **3** were efficient and selective Finally, though we demonstrated that the cross-coupling and RCM of fully glycosylated fragments was possible, the yields were adversely impacted because the sugar decoration in the northern fragment reversed the *E*/*Z*-selectivity of the RCM macrocyclization, and these isomers were unfortunately no longer separable.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https:///doi.org/

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HIGHLIGHTS

Efficient stereoselective synthesis of the key polyketide fragments of Fidaxomicin

Efficient stereoselective synthesis of Fidaxomicin's resorcylic rhamnoside and novioside sugar fragments

Efficient and selective glycosylation of the polyketide fragments with the sugar fragments

Krische hydrogenative C-C coupling towards Fidaxomicin's branched dienoic acid fragment

[2,3]-Wittig rearrangement tactic to arrive at a polyketide stereodiad fragment embedded within Fidaxomicin's southern polyketide fragment

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: