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A Domino 10-Step Total Synthesis of FR252921 and Its Analogues, Complex Macrocyclic Immunosuppressants

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Supporting Information

ABSTRACT: FR252921, FR252922, and FR256523 are a family of potent macrocyclic polyene immunosuppressive agents with a novel mode of action. However, the lack of an efficient and flexible synthesis has hindered further biological studies, mostly due to the fact that the natural products appear to be kinetic isomers regarding the triene moiety. Herein, we report the development and application of an unprecedented, unique domino Suzuki−Miyaura/4π-electrocyclic ring-opening macrocyclization, resulting in a concise, unified, and stereoselective synthetic route to these complex targets in only 10 steps. This in turn enables ready access to a range of unnatural analogues, among which several compounds showed inhibition of T-lymphocyte proliferation at levels equal or superior to those of the natural products themselves.

Immunosuppressive drugs are widely used in the treatment of allograft repulsions and autoimmune-associated diseases. Although a range of immunosuppressive agents have been developed and are available for clinical uses, virtually all of the currently used immunosuppressants carry severe adverse effects and limitations.[1,2] Therefore, the discovery of new immunosuppressants with novel and distinct mode of action (MoA) is of considerable urgency in order to improve the safety and efficiency of immunosuppressive therapy.

In 2003, during their pursuit of novel immunosuppressants acting on antigen presenting cells (APC), researchers from the then Fujisawa Company isolated three novel compounds termed FR252921, FR252922, and FR256523 (henceforth "FR molecules"; see Figure 1C) from the culture broth of *Pseudomonas fluorescens* No. 408813.[3a] Structurally, these molecules share a unique 19-membered (*E,E,E*)-trienic bislactam-lactone core and differ solely at the polyene side chains. Compared to clinically used drugs CsA and FK506, the FR molecules inhibited both lipopolysaccharide (LPS) and anti-CD3 mAb-stimulated murine splenocyte proliferation, with IC_{50} as low as 2.9 and 3.9 ng/mL, respectively. Additional studies on FR252921 showed that it inhibited the production of interleukin-2 (IL-2) and interleukin-12 (IL-12), whereas FK506 and CsA inhibited exclusively the production of IL-2.[3b] Besides that, FR252921 was found to demonstrate strong synergistic effects when concomitantly used with the drug FK506.[3c] These initial biological studies clearly suggested that the FR molecules could have a MoA distinct from that of the known immunosuppressant FK506.

Not surprisingly, since their isolation, the FR molecules have sparked great interest among the synthetic community.[4] The first and so far only total syntheses were reported in 2007, when the groups of Falck[4b] and Cossy[4c] concurrently disclosed their approaches to FR252921, which also led to unambiguous establishment of the relative and absolute stereochemistry of that target. Both teams chose a late-stage Shiina macrolactonization from *seco*-acid **1** to close the 19-membered ring. The group of Falck reported 10%−15% yield for this transformation.[4b] In contrast, Cossy et al. found that this reaction afforded less than 5% yield of FR252921, the major side product being the C2−C3 *Z*-isomer **2** (Figure 1A). Despite screening many conditions and different macrolactonization protocols, *E*/*Z* isomerization at C2−C3 proved to be unavoidable.[4c,d] In order to understand the reason for the isomerization, we have undertaken computational studies regarding the stability of the different isomers which reveal, inter alia, opportunities for intramolecular hydrogen bonding, stabilizing undesired triene isomers (see Supporting Information (SI) for further details).

Polyene natural products form a privileged class of bioactive compounds.[5] Common methods to assemble polyene motifs include carbonyl-based olefinations and transition metal-mediated coupling reactions.[5,6] Recently, Burke et al. reported a series of bifunctionalized *N*-methyliminodiacetic acid (MIDA) boronates and elegantly assembled them en route to polyenic natural products.[7] However, these methods typically mandate the pre-installation of geometrically defined coupling precursors, apart from the need to tune conditions for hydrolysis of the MIDA fragment.

Pericyclic reactions generally exhibit excellent regio- and stereocontrol as a consequence of stringent frontier orbital requirements.[8] In particular, 4π-electrocyclic ring-opening reactions are a predictable[9] and efficient platform for the

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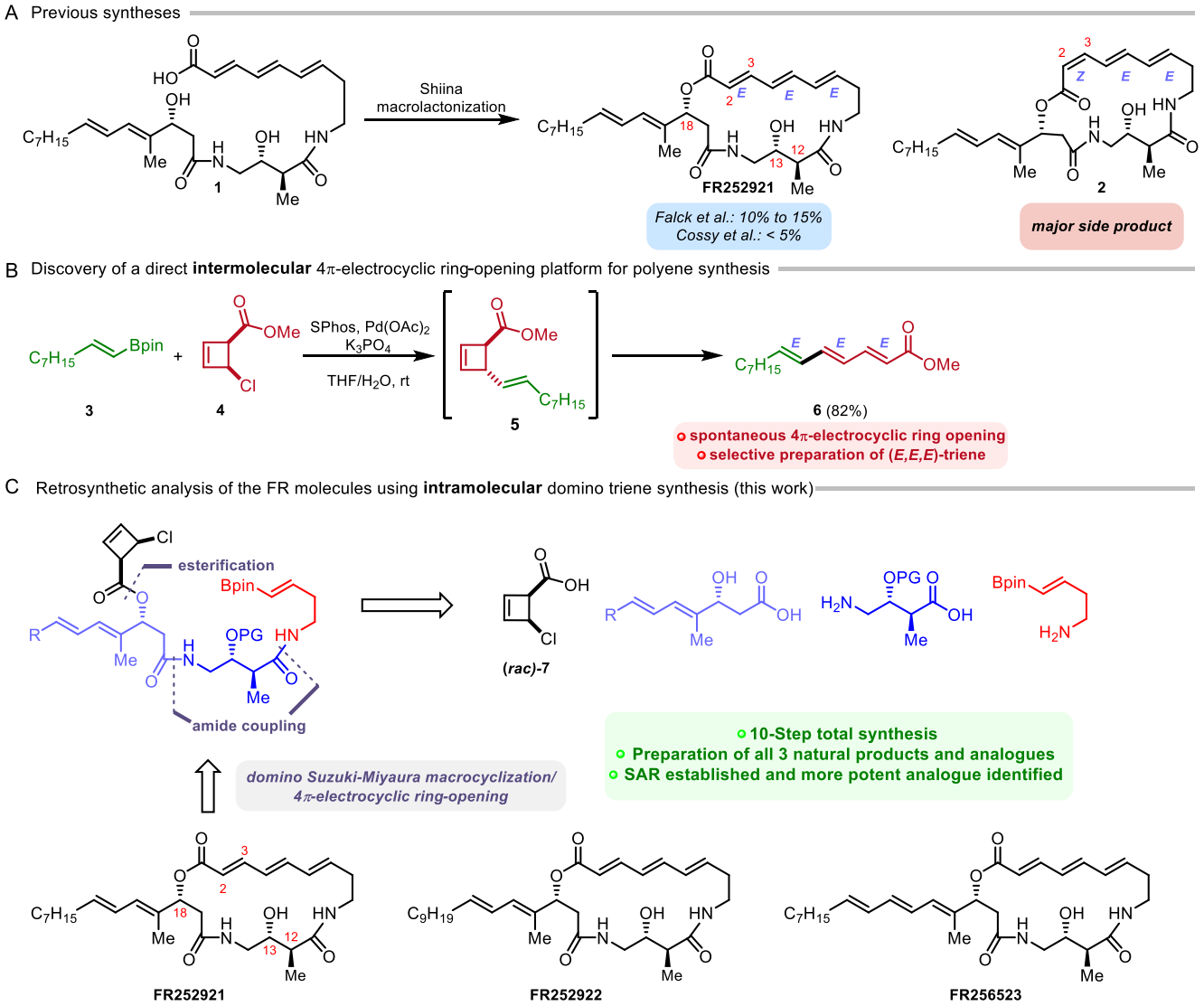

Figure 1. Background of FR molecules and retrosynthetic strategy. (A) Previous syntheses of FR252921 featuring a macrolactonization strategy. (B) Discovery of a direct 4π-electrocyclic ring-opening process as a platform for stereoselective polyene synthesis. (C) Retrosynthetic analysis of the FR molecules.

preparation of stereodefined dienylcarboxylate arrays[10] which are widely found in bioactive polyene natural products.[5] During unrelated studies, we discovered that the Suzuki–Miyaura cross-coupling of vinylboronic ester **3** and the *cis*-chlorocyclobutene ester **4** delivered the (*E,E,E*)-trienoate ester **6** in 82% yield instead of the anticipated cyclic product (Figure 1B). The (*E,E,E*)-configuration of **6** belies the intermediacy and spontaneous electrocyclic ring-opening of a *trans*-configured cyclobutene **5**, the product of a stereoinvertive (consecutive invertive oxidative addition, retentive trans-metalation, and retentive reductive elimination)[11] Suzuki-type coupling of **3** and **4**. This discovery prompted the interrogation of a novel approach to the total syntheses of the FR molecules via a challenging, intramolecular variant of this domino reaction. Herein, we report a concise and highly convergent, diversity-oriented[12] 10-step total synthesis of the FR molecules and a range of unnatural analogues leveraging this strategy, ultimately enabling the establishment of a structure–activity relationship (SAR) as well as the identification of a more potent analogue.

As shown in Figure 1C, dissection of the FR molecules to an acyclic precursor by applying the domino Suzuki-type-coupling/4π-electrocyclic ring-opening transform allowed simple deconstruction into four relatively small fragments. Figure 2 outlines their preparation and union toward the natural products.

The first fragment which was addressed is the boryl-amine **11** (Figure 2A). It was built in a simple three-step sequence starting from commercially available 4-pentynoic acid **8** and featuring Curtius rearrangement in *tert*-butanol to deliver N-Boc-protected amine **9**. Zirconium-promoted *E*-selective hydroboration[13] and N-Boc deprotection using trifluoroacetic acid delivered salt **11**, used directly in the next step after freebasing. Each of these steps delivered nearly analytically pure product after workup, thus facilitating upscaling to deliver salt **11** in >8 g scale in a single batch (Figure 2A).

A challenge of this synthesis was the efficient preparation of the chiral γ-amino acid fragment **16**, a structural motif found in a large number of natural products[3a,4a,14] and drugs.[15] Previous syntheses of this fragment proved to be cumbersome and low-yielding.[4,16] We thus sought to develop a novel, short, and

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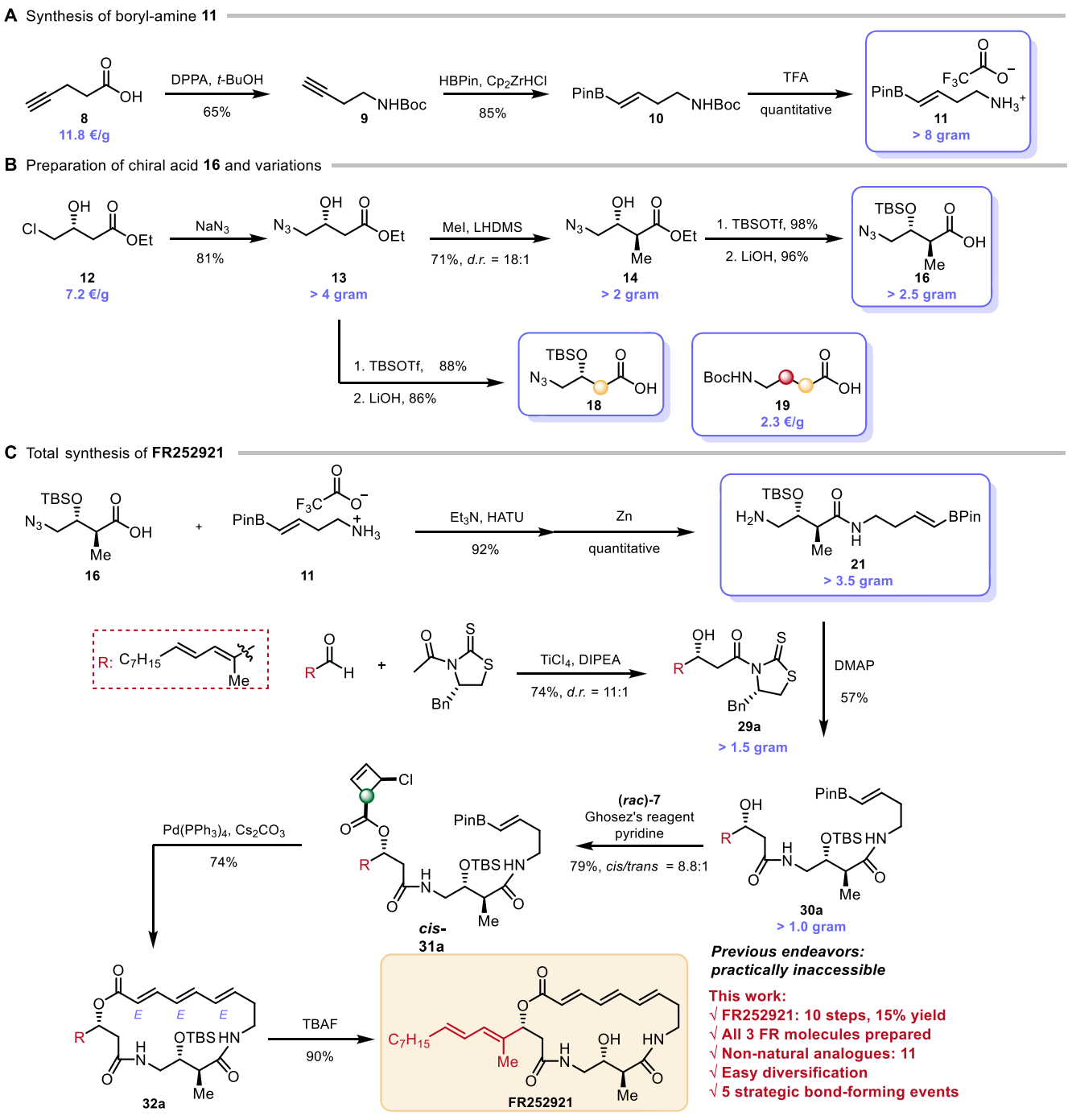

Figure 2. Total synthesis of FR252921. (A) Three-step synthesis to boryl-amine **11**. (B) Short and high-yielding synthesis of acid **16** and its derivatives. (C) Completion of the total synthesis of FR252921.

scalable sequence for its preparation. Our concise four-step route begins with chloride displacement of commercially available enantiopure ester **12** using sodium azide, followed by a Fráter-Seebach alkylation[17] to install the C12-methyl group in excellent diastereoselectivity (*d.r.* = 18:1). Silyl protection and ester hydrolysis afforded **16** on multigram scale in an overall yield of 54%. To the best of our knowledge, this represents the most efficient synthesis of this fragment in the literature and is likely to be of considerable use in several natural product syntheses well beyond those reported herein. Diversion of this route toward acid **18** and the commercially available N-Boc-γ-butyric acid **19** was used for analogue synthesis (Figure 2B).

Fragments **11** and **16** were then coupled, and the azide functionality was reduced to afford the key intermediate **21** in >3.5 g scale over six steps. The aldol adduct **29a** was prepared in 74% yield by Crimmins's procedure,[18] whereby a simple change in the aldehyde partner ("R" in Figure 2C) allowed preparation of a range of analogues (see Figure S4 for an overview).

The endgame of the synthesis reserved a number of critical steps. We found that the acyl transfer reagent DMAP[19] facilitated the direct coupling of **21** and **29a** in one step. The

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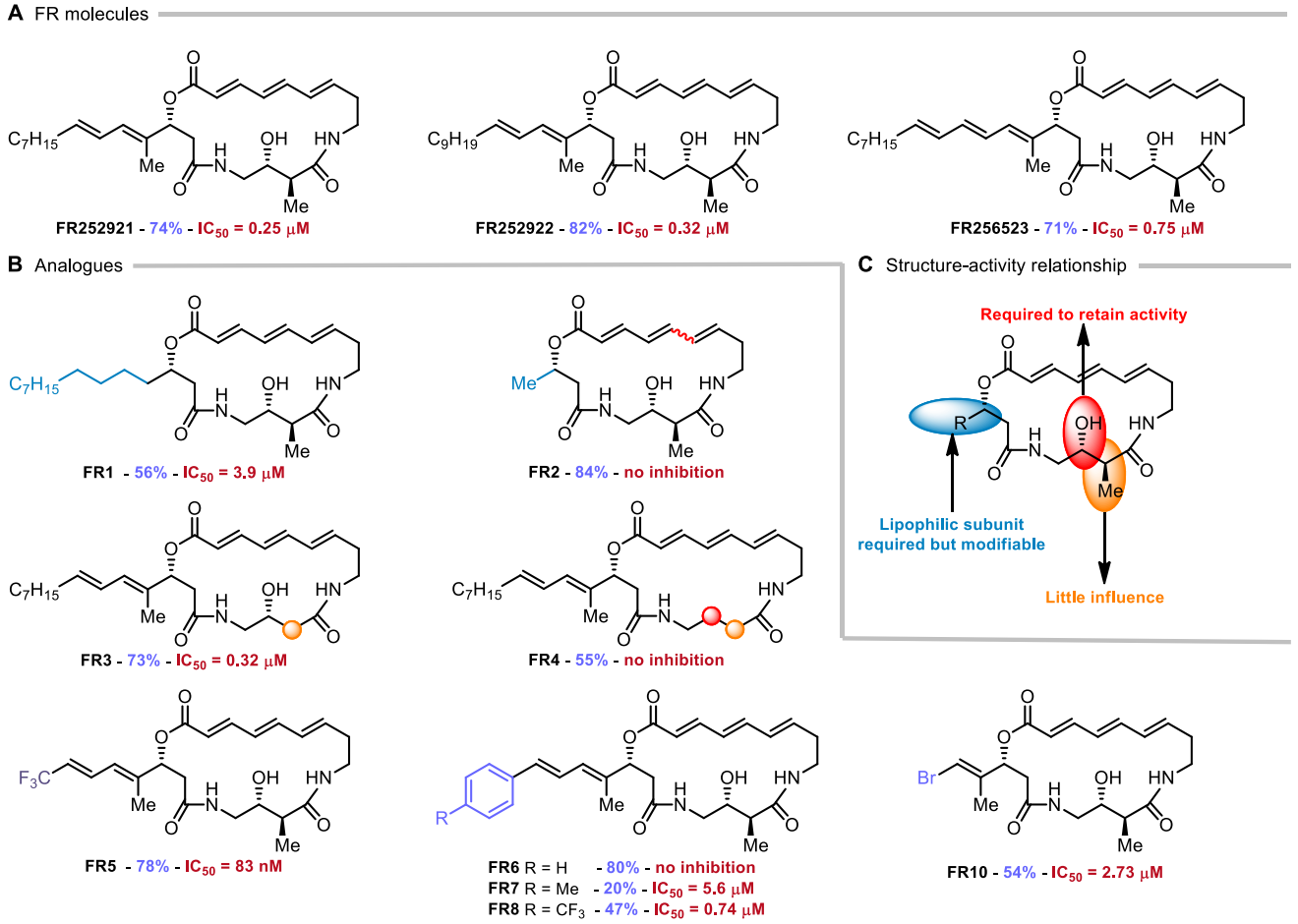

Figure 3. Biological activities of all FR molecules and analogues prepared. (A) FR molecules and (B) analogues. Yields are for the macrocyclization step; IC_{50} are the inhibition values on T-lymphocyte cell line *EL4* proliferation. **FR2** was obtained as a 1.2:1 mixture of (*E,E,E*) and (*E,E,Z*) isomers during purification. (C) Structure−activity relationship deduced.

free alcohol moiety of **23** was then esterified with the (*rac*)-*cis*-chlorocyclobutene acid **7** to give ester **31**. This seemingly simple transformation proved very challenging. Indeed, exposure of *cis*-configured chloroacid **7** to standard carboxylic acid activating agents (see Table S2 for a comprehensive list) led to rapid isomerization to the thermodynamically more stable *trans*-isomer (not shown). This posed a serious threat to our synthetic approach, since only a *cis*-arrangement of the substituents around the cyclobutene moiety of *cis*-**31a** would result in the desired (*E,E,E*)-triene geometric isomer upon domino stereoinvertive Suzuki-type coupling and conrotatory torquoselective 4π-electrocyclic ring-opening.[20] Control experiments revealed that, once the *cis*-chlorocyclobutene ester *cis*-**31a** was formed, it was kinetically stable under the reaction conditions (see Figure S9). After extensive optimization, we found that the combination of Ghosez's reagent[21] and pyridine selectively gave the desired *cis*-chlorocyclobutene ester *cis*-**31** in 79% yield and a reproducible *cis*/*trans* ratio of 8.8:1 (Figure 2C).

Cyclobutene *cis*-**31a** was then submitted to the highly anticipated domino macrocyclization/4π-electrocyclic ring-opening process.[22] Importantly, *cis*-**31** also accommodates a highly conjugated allylic ester (in the form of a cyclobutenyl carboxylate moiety) which could be prone to deleterious oxidative addition by a Pd(0) catalyst. In the event, after careful optimization (see Table S5), the desired macrocyclization proceeded smoothly and selectively in the presence of catalytic amounts of $Pd(PPh_3)_4$ and Cs_2CO_3 to deliver macrolactone **32a** encompassing the (*E,E,E*) trienic moiety in 74% yield (for a mechanistic study of this domino process, see pp S52−S55 in the SI). The remarkable chemo- and stereoselectivity of this mechanistically unique macrocyclization maneuver contrasts sharply with the failure of conventional macrolactonization protocols as reported previously by Falck and Cossy.[4b] Final deprotection of **32a** using TBAF at 0 °C for 5 min cleanly led to FR252921 in 90% yield (Figure 2C). Our longest linear sequence (LLS) to this complex macrocyclic natural product thus consists of only 10 steps and delivers FR252921 in 15% overall yield. Notably, among these 10 steps, five steps were strategic bond-forming events, endowing our synthetic route with an ideality score of 50%.[23]

A similar pathway was followed to complete the first total syntheses of the other two members, FR252922 and FR256523, thus providing a unified access to all members of the family for the first time. Our route was further extended to the synthesis of a range of non-natural analogues (for details, see SI). Additionally, deletion of either the C12 methyl group or both the C12 methyl and the C13 hydroxy group allowed the generation of "molecularly edited" analogues of high usefulness for SAR studies. Altogether, using the novel strategy presented herein, the three natural products and 11 non-natural derivatives were accessed (Figure 3).

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The synthesized molecules were tested in a proliferation assay against the T-lymphocyte cell line *EL4*. All three natural products demonstrated potent inhibition of proliferation, with IC_{50} values below 1 μM. When the side chains were alkyl chains, **FR1** with 11 carbon atoms still remained active, although less potent than FR252921. However, **FR2** with only a methyl group on the side chain completely lost activity even at 20 μM, the highest concentration tested. Because **FR2** was isolated as a 1.2:1 mixture of (*E,E,E*) and (*E,E,Z*) isomers, it has not yet been possible to fully differentiate the biological impacts of the methyl side chain versus the alkene geometry in this case. Nonetheless, since this mixture was completely inactive under the conditions tested, we can tentatively conclude that neither of the two compounds possesses appreciable activity. This result showed that the lipophilic side chains are important to maintain the activity. Then, substitution in the macrocycle was evaluated. While C12-methyl deletion had little influence on the activity (cf. FR252921 and **FR3**, Figure 3A,B), further removal of the C13-hydroxy group rendered analogue **FR4** inactive (Figure 3B). Based on these results, several other analogues with halogenated or arylated side chains were synthesized. Among them, **FR5** with a CF_3 substituent was the most potent inhibitor, with an IC_{50} of 83 nM surpassing FR252921 by 3-fold (Figure 3B). Other analogues displayed either inferior activity or poor solubility. Altogether, these results enabled the preliminary establishment of an SAR for this family of compounds as depicted in Figure 3C. The surprisingly strong modulation of biological activity by side-chain modification is a valuable vector for development of these molecules.

A unique domino Suzuki macrocyclization/4π-electrocyclic ring-opening enabled highly efficient and flexible total syntheses of the complex macrocyclic immunosuppressive natural products FR252921, FR252922, and FR256523. Remarkably, the C−C macrocyclization strategy laid out herein largely supersedes conventional approaches featuring C−O macrolactonization methods which are conducive to deleterious C═C bond isomerization. Further highlights of our work include a short and high-yielding synthesis of the useful chiral acid **16**, a common motif found in a range of natural products, as well as the use of Ghosez's reagent for mild, stereoselective esterification of a pivotal *cis*-chlorocyclobutene carboxylate linchpin. Based on this short, 10-step procedure, 14 compounds were synthesized and tested in a proliferation assay against *EL4*-T-lymphocyte cells, enabling the establishment of clear SAR correlations for this family of compounds and the identification of a more potent analogue, **FR5**. Our work showcases the power of this strategy for the preparation of macrocyclic polyene natural products and paves the way for further development of the chemistry and biology of this fascinating class of secondary metabolites.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07185.

Experimental, computational, and characterization data, including Figures S1−S18 and Tables S1−S5 (PDF)

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Notes

The authors declare no competing financial interest.

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