FD-891, a 16-membered macrolide isolated from the fermentation broth of Streptomyces graminifaciens A-8890, has been shown to have cytotoxic activity in vitro against several tumor cell lines. The activity is reportedly similar to that of concanamycin A, a specific inhibitor of vascular-type H+-ATPase.2 Recently, concanamycin A has been shown to specifically inhibit perforin-dependent cytotoxic T lymphocyte (CTL)-mediated cytotoxicity, but not affect Fas ligand (FasL)-dependent CTL-mediated cytotoxicity; these two cytotoxic pathways play an essential role in the maintenance of tissue homeostasis.3 Conversely, FD-891 was found to potently prevent both perforin and FasL-dependent CTL-mediated killing pathways, but did not inhibit vacuolar acidification.4

The relative and absolute configuration of FD-891 was elucidated on related plecomacrolides,7 to date only three reports of FD-891 pathways, but did not inhibit vacuolar acidification.4

Herein we report the first total synthesis of FD-891. A convergent strategy exploiting the assembly of three subunits 2, 3, and 4 of similar complexity was anticipated for the synthesis of FD-891 (Scheme 1). Fragments 2 and 3 were envisioned to undergo selective cross-metathesis leading to a subsequent lactonization to give the (Scheme 1). Fragments 2 and 3 were envisioned to undergo selective cross-metathesis leading to a subsequent lactonization to give the

FD-891 fragment. The aldehyde obtained in 98% yield. The aldehyde was subjected to a second epoxidationa) followed by Sharpless epoxidationb) gave epoxide in 97% yield. Protection of the secondary alcohol as its acetate gave the C13 C12 unit.

The synthesis of fragment 3 commenced with an aldol addition between 3-butenalc) and the enolate of thiazolidinethioned) under conditionsd) to give the non-E aldol adduct 6 in 73% yield (dr > 15:1) (Scheme 3). Protection of the alcohol delivered silyl ether 12 whereupon reduction of the N-acyltiothioimide gave alcohol 13. Homologation of alcohol 13 was accomplished by displacement of the hydroxyl with cyanide under Mitsunobu conditions to provide nitrile 14. Two-stage reduction gave the corresponding diol, which underwent selective protection to provide alcohol 15.

Scheme 1. Retrosynthetic Analysis of FD-891

Scheme 2. Synthesis of Epoxide 2e

Scheme 3. Synthesis of the C13–C18 Fragment 3f

Protection of the secondary alcohol as its acetate gave the C13–C18 fragment 3 in 98% yield.

The synthesis of sulfone 4 began with the thioimide 12 also used in the synthesis of the C13–C18 fragment. The aldoldehyde obtained by the direct reduction of thioimide 12 was subjected to a second aldol iteration to provide the aldol adduct 16 in 87% yield. The methyl ketone 17 was obtained by transacylation of the auxiliary
The completion of the macrocycle required the extension at C3 to the dieneocte. To this end, reductive removal of the pivalate preceded oxidation of the allylic alcohol with manganese dioxide and Horner—Wadsworth—Emmons olefination to deliver the dieneocte 21. Hydrolysis of ester 21 followed by Yamaguchi macrolactonization20 gave the desired macrolactone 22. Selective deprotection of the primary silyl ether and oxidation of the resultant alcohol provided aldehyde 23 in 70% yield, ready to be coupled with the C19—C26 fragment 4 via a Julia reaction. Julia olefination21 between aldehyde 23 and sulfone 4 provided exclusively the E-olefin 24 (Scheme 5). Global deprotection by the action of H2SiF622 gave FD-891 in 90% yield. The spectral data of synthetic FD-891 were consistent in all respects with those reported for the natural product.1,5,6

In conclusion, we have completed the first total synthesis of the macroclide FD-891 in 21 steps (longest linear sequence). The versatile aldol reaction of N-acylthiazolidinethione 8 was used to create 8 of the 12 stereocenters with the same enantiomer of the chiral auxiliary.

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Supporting Information Available: Experimental procedures, as well as 1H and 13C NMR spectra for all new compounds, and synthetic FD-891. This material is available free of charge via the Internet at http://pubs.acs.org.

References