Published in final edited form as:
J Am Chem Soc. 2006 March 15; 128(10): 3128–3129. doi:10.1021/ja060018v.

Enantioselective Total Synthesis of FD-891

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Abstract

FD-891 (**1**)

The enantioselective synthesis of FD-891 has been achieved with a longest linear sequence of 21 steps. The synthetic strategy involves the use of aldol additions of a chlorotitanium enolate of N-acylthiazolidinthiones as the key reaction to establish 6 of the 10 stereogenic centers. A key cross-metathesis and a late stage Julia olefination serve to assemble three key subunits.

FD-891, a 16-membered macrolide isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890, has been shown to have cytotoxic activity in vitro against several tumor cell lines.[1] 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 after extensive spectroscopic analysis and partial degradation.[5] The structure was subsequently revised based on x-ray analysis of partial structures.[6] While substantial synthetic accomplishments have been made on related plecomacrolides,[7] to date only three reports of synthesis of fragments of FD-891 have appeared.[8]

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 macrocyclic core. The late-stage installation of the C19–C25 fragment **4** would be accomplished via a Julia olefination. The three key fragments would derive from synthons **5** and **6** accessible through the application of the versatile aldol additions of chlorotitanium enolates of *N*-acylthiazolidinethiones recently advanced in our laboratory.[9]

The synthesis of the C3–C12 unit **2** began with addition of known aldehyde **7**[10] to the chlorotitanium enolate of thioimide **8** to deliver the protected *Evans syn* adduct **5** after silylation

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of the alcohol (Scheme 2). Reductive removal of the auxiliary directly gave aldehyde **9**, which was rapidly transformed to pivaloate **10** in three steps. Selective removal of the primary silyl ether[11] followed by Sharpless epoxidation[12] gave epoxide **11** in 72% yield. Dess-Martin[13] oxidation of alcohol **11**, and subsequent chelate-controlled allylation of the resultant aldehyde[14] delivered the expected epoxyalcohol as single detectable diastereomer (dr >20:1). Protection of the alcohol as its TBS ether produced the required C3–C12 unit **2**.

The synthesis of fragment **3** commenced with an aldol addition between 3-butenal[15] and the enolate of thiazolidinethione **8** under conditions[9a] to give the *non-Evans syn* aldol adduct **6** in 73% yield (>15:1 dr) (Scheme 3). Protection of the alcohol delivered silyl ether **12** whereupon reduction of the *N*-acylthiomide gave alcohol **13**. Homologation of alcohol **13** was accomplished by displacement of the hydroxyl with cyanide under Mitsunobu conditions[16] to provide nitrile **14**. Two-stage reduction gave the corresponding diol, which underwent selective protection to provide alcohol **15**. 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 aldehyde 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 to provide the corresponding Weinreb amide[17] followed by protection of the alcohol and addition of methylmagnesium chloride. Chelation-controlled[18] reduction of the ketone provided 75% of the alcohol 18 along with 15% of the C25 isomer, which could be recycled by oxidation-reduction. Methylation of the C25 hydroxyl gave the corresponding C25 methyl ether. Acid catalyzed deprotection of the MOM and TES groups followed by exposure of the diol to dimethoxypropane and *p*-TsOH provided acetonide **19**. Ozonolysis with reductive work-up followed by a Mitsunobu reaction gave the desired sulfide, which was oxidized to sulfone **4**.

With the three key fragments in hand, their assembly was undertaken. A cross-metathesis[19] between terminal alkenes **2** and **3** was performed with the Grubbs catalyst (Scheme 5). The nature of the protecting group on the C15 alcohol had a profound influence on the selectivity of the cross metathesis. The best *E:Z* ratio was obtained with the C15 acetate compared to other esters or the free hydroxyl. The desired *E* olefin **20** was obtained in 68% yield along with 10% of the *Z*-isomer.

The completion of the macrolactone required the extension at C3 to the dienoate. To this end, reductive removal of the pivaloate preceded oxidation of the allylic alcohol with manganese dioxide, and Horner-Wadsworth-Emmons olefination to deliver the dienoate **21**. Hydrolysis of ester **21** followed by Yamaguchi macrolactonization[20] gave the desired macrocycle **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 olefination[21] between aldehyde **23** and sulfone **4** provided exclusively the *E*-olefin **24** (Scheme 5). Global deprotection by the action of H_2SiF_6[22] 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 macrolide FD-891 in **21** steps (longest linear sequence). The versatile aldol reaction of *N*-acylthiazolidinethione **8** was used to create eight of the twelve stereocenters with the same enantiomer of the chiral auxiliary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by a research grant from The National Cancer Institute (CA63572). We are grateful to professor T. Eguchi for providing authentic ^{1}H and ^{13}C spectra of the natural product.

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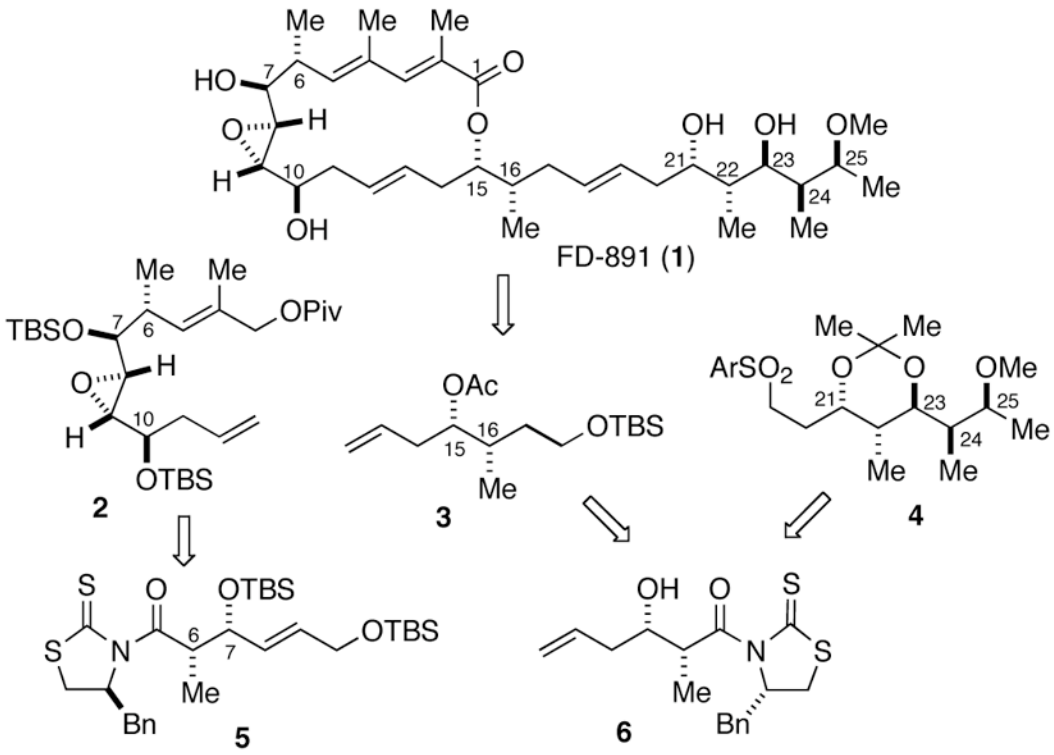
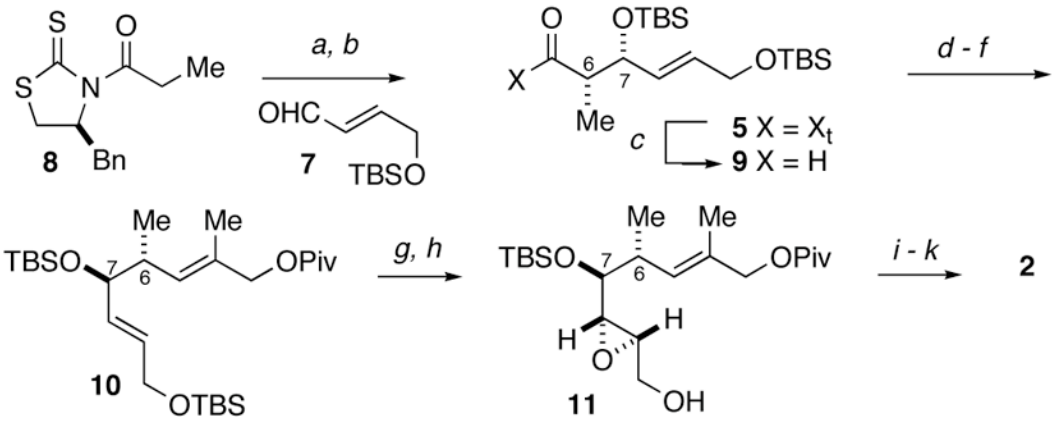


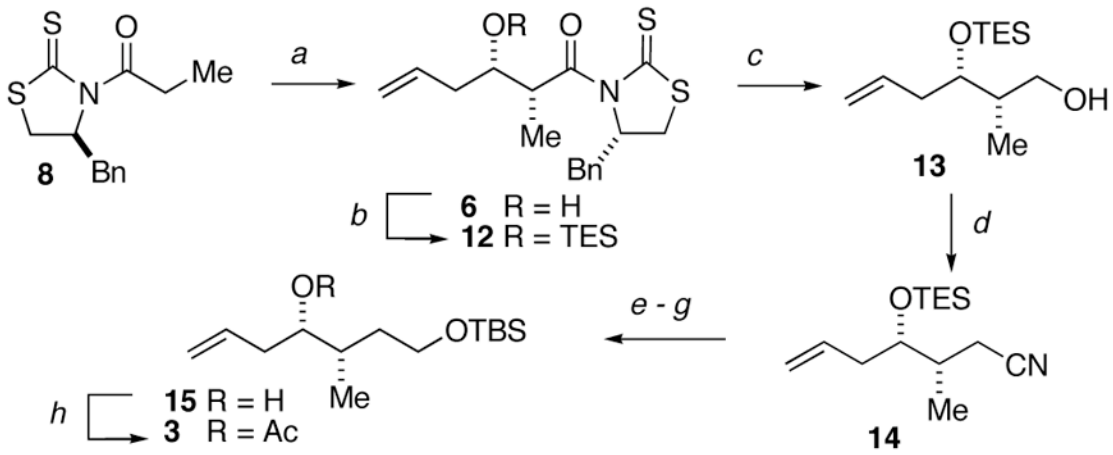
Scheme 1.
Retrosynthetic analysis of FD-891.



Scheme 2.

Synthesis of epoxide **2.**

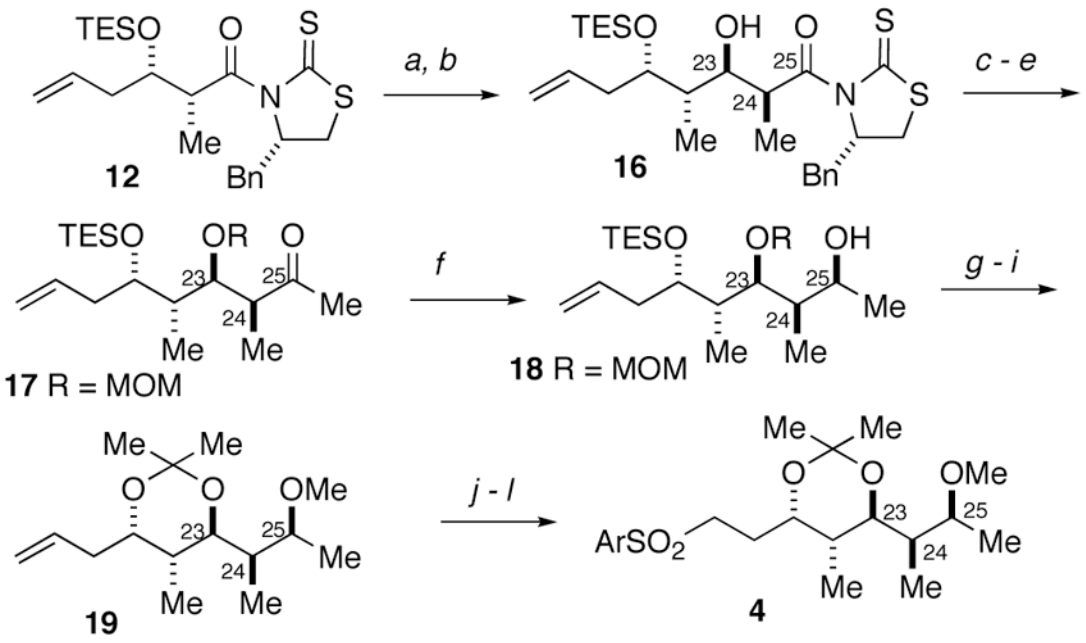
Conditions: (a) $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2, −78 to −40 °C, 78% (dr >20:1); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 92%; (c) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 74%; (d) $Ph_3P{=}C(CH_3)CO_2Et$, toluene, 80 °C, 92%; (e) *i*-Bu_2AlH, THF, −78 °C, 98%; (f) pyridine, PivCl, CH_2Cl_2, 99%; (g) NH_4F, MeOH, 85%; (h) (+)-DET, (*i*-PrO)$_4$Ti, *t*-BuOOH, molecular sieves 4Å, CH_2Cl_2, −23 °C, 72% (dr 15:1); (i) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 97%; (j) $MgBr_2(Et_2O)$, $CH_2{=}CHCH_2SiMe_3$, CH_2Cl_2, −20 to −10 °C, 70% (dr >20:1); (k) TBSCl, imid., DMAP, CH_2Cl_2, 99%.



Scheme 3.

Synthesis of the C13–C18 fragment **3.**

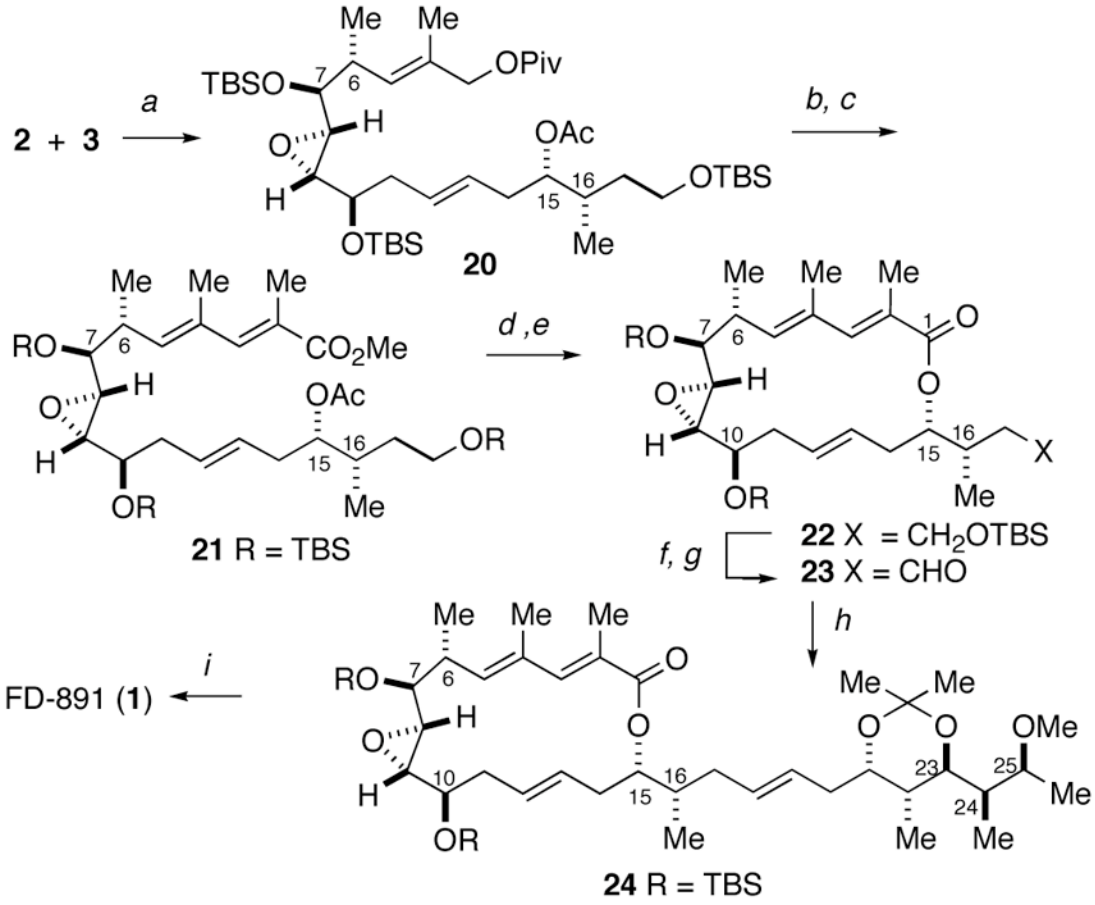
Conditions: (a) $TiCl_4$, (−)-sparteine, 3-butenal, CH_2Cl_2, 0 °C, 73%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 96%; (c) $LiBH_4$, Et_2O, MeOH, 0°C to rt, 98%; (d) acetone cyanohydrin, DEAD, Ph_3P, toluene, 70 °C,90%; (e) *i*-Bu_2AlH, toluene, −78 °C, 88%; (f) $NaBH_4$, CH_2Cl_2, MeOH, then HCl, 84%; (g) TBSCl, imidazole, CH_2Cl_2, 92%; (h) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 to 25 °C, 98%.



Scheme 4.

Synthesis of sulfone **4.**

Conditions: (a) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 84%; (b) Thioimide **8**, $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2, −78 to 0 °C, then add aldehyde, 87% (dr >20:1); (c) $CH_3N(OCH_3)H{\cdot}HCl$, imidazole, CH_2Cl_2, 78%; (d) MOMCl, *i*-Pr_2NEt, DMF, 50 °C, 87%; (e) MeMgCl, Et_2O, 0 °C, 97%; (f) $NaBH_4$, $CeCl_3{\cdot}7(H_2O)$, MeOH, 0 °C, 75% **18** + 15% C25 isomer which was recycled; (g) NaH, MeI, THF, 0 °C to rt, 81%; (h) HCl (conc.), MeOH, 78%; (i) 2,2-dimethoxypropane, *p*-TSA, 88 %; (j) O_3, CH_2Cl_2, MeOH, −78 °C, then $NaBH_4$ –78 to 25 °C, 81%; (k) DIAD, 2 −mercaptobenzothiazole, PPh_3, CH_2Cl_2, 93%; (l) H_2O_2 30%,$(NH_4)_6Mo_7O_{2\,4}{\cdot}4H_2O$, EtOH, 89%.



Scheme 5.

Completion of FD-891.

Conditions: (a) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C, 68% + 10% *Z*-isomer; (b) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 85%; (c) MnO_2, CH_2Cl_2, 40 °C, then BuLi, $Ph_3P(O)C(CH_3)CO_2Me$, THF, 0 to 25 °C, 66% for 2 steps; (d) TMSOK, THF; (e) $Cl_2C_6H_3COCl$, Et_3N, THF; then DMAP, $PhCH_3$, 61% for 2 steps; (f) PPTS, MeOH, 90%; (g) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 82%; (h) Sulfone **4**, KHMDS, THF, −78 °C, then aldehyde **23**, 80%; (i) H_2SiF_6 20% in H_2O, CH_3CN, 90%.