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Enantioselective Total Synthesis of FD-891

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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]

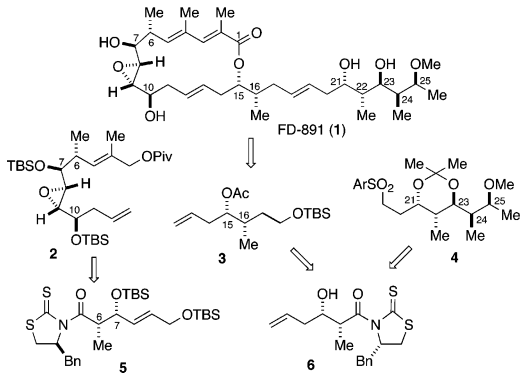
The relative and absolute configuration of FD-891 was elucidated after extensive spectroscopic analysis and partial degradation.[5] The structure was subsequently revised based on X-ray analysis of partial structures.[6] While substantial synthetic accomplishments have been made on related plecomacrolides,[7] 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]

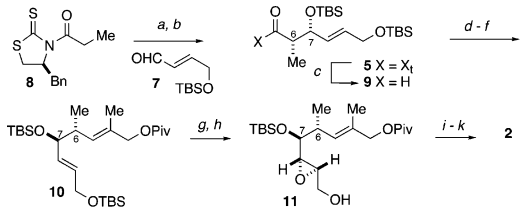
The synthesis of the C3−C12 unit **2** began with addition of known aldehyde **7**[10] to the chlorotitanium enolate of thioimide **8** to deliver the protected *Evans syn* adduct **5** after silylation of the alcohol (Scheme 2). Reductive removal of the auxiliary directly gave aldehyde **9**, which 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 a 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 (dr >15:1) (Scheme 3). Protection of the alcohol delivered silyl ether **12** whereupon reduction of the *N*-acylthioimide 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**.

Scheme 1. Retrosynthetic Analysis of FD-891

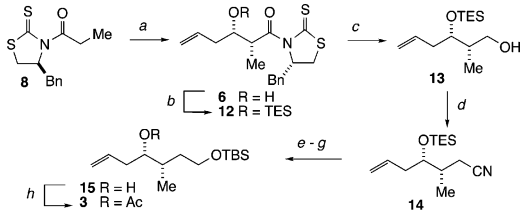


Scheme 2. Synthesis of Epoxide **2**[a]



[a] 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 4 Å, 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, imidazole, DMAP, CH_2Cl_2, 99%.

Scheme 3. Synthesis of the C13−C18 Fragment **3**[a]



[a] 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 room temperature, 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%.

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

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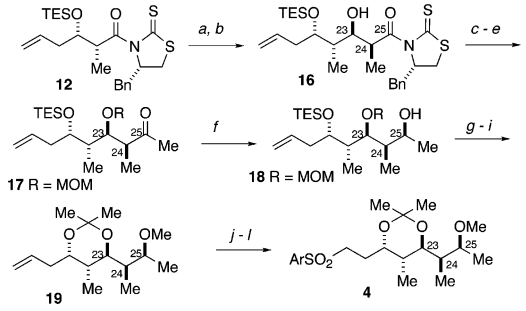
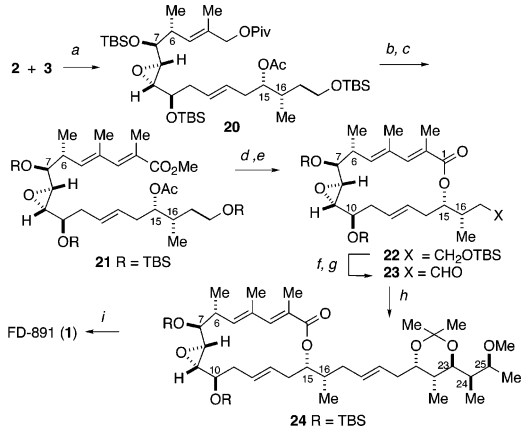
Scheme 4. Synthesis of Sulfone **4**[a]



[a] 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 room temperature, 81%; (h) HCl (concentrated), 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%, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, 89%.

Scheme 5. Completion of FD-891[a]



[a] 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%.

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 workup 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 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 ^{13}C 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

(1) (a) Seki-Asano, M.; Okazaki, T.; Yamagishi, M.; Sakai, N.; Hanada, K.; Mizoue, K. *J. Antibiot.* **1994**, *47*, 1226. (b) Seki-Asano, M.; Tsuchida, Y.; Hanada, K.; Mizoue, K. *J. Antibiot.* **1994**, *47*, 1234.
(2) (a) Muroi, M.; Shiragami, N.; Nagao, K.; Yamasaki, M.; Takatsuki, A. *Cell Struct. Funct.* **1993**, *18*, 139. (b) Drose, S.; Bindseil, K. U.; Bowman, E. J.; Siebers, A.; Zeeck, A.; Altendork, K. *Biochemistry* **1993**, *32*, 3902.
(3) Kataoka, T.; Shinohara, N.; Takayama, H.; Takaku, K.; Kondo, S.; Yonehara, S.; Nagai, K. *J. Immunol.* **1996**, *156*, 3678.
(4) Kataoka, T.; Yamada, A.; Bando, M.; Honna, T.; Mizoue, K.; Nagai, K. *Immunology* **2000**, *100*, 170.
(5) Egushi, T.; Kobayashi, K.; Uekusa, H.; Ohashi, Y.; Mizoue, K.; Matsushima, Y.; Kakinuma, K. *Org. Lett.* **2002**, *4*, 3383.
(6) Egushi, T.; Kamamoto, K.; Mizoue, K.; Kakinuma, K. *J. Antibiot.* **2004**, *57*, 156.
(7) Review: Dai, M.; Guan, Y. C.; Jin, J. *Curr. Med. Chem.* **2005**, *21*, 1947.
(8) (a) Murga, J.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Synlett* **2004**, 2830. (b) Murga, J.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2004**, *45*, 7499. (c) Hang, S. S.; Xu, J.; Loh, T. P. *Tetrahedron Lett.* **2003**, *27*, 4997.
(9) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (b) Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810.
(10) Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *33*, 6227.
(11) Schinzer, D.; Bohm, O. M.; Altmann, K.-H.; Wartmann, M. *Synlett* **2004**, 1375.
(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, Y. S.; Masamune, H.; Sharpless, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(14) (a) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (b) Howe, G. P.; Wang, S.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2629.
(15) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.
(16) Andrus, M. B.; Hicken, E. J.; Meredith, E. L.; Simmons, B. L.; Cannon, J. F. *Org. Lett.* **2003**, *5*, 3859.
(17) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1997**, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(18) Ancerewicz, J.; Vogel, P. *Helv. Chim. Acta* **1996**, *79*, 1393.
(19) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(20) Inanada, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(21) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.
(22) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.

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