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Stereoselective Synthesis of the Cytotoxic Macrolide FD-891†

Jorge García-Fortanet,‡ Juan Murga,‡ Miguel Carda,*,‡ and J. Alberto Marco*,§

Departamento de Química Inorgánica y Orgánica, Universitat Jaume I, Castellón, E-12080 Castellón, Spain, and Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain

alberto.marco@uv.es

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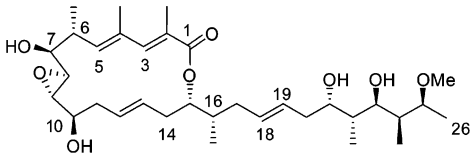
ABSTRACT



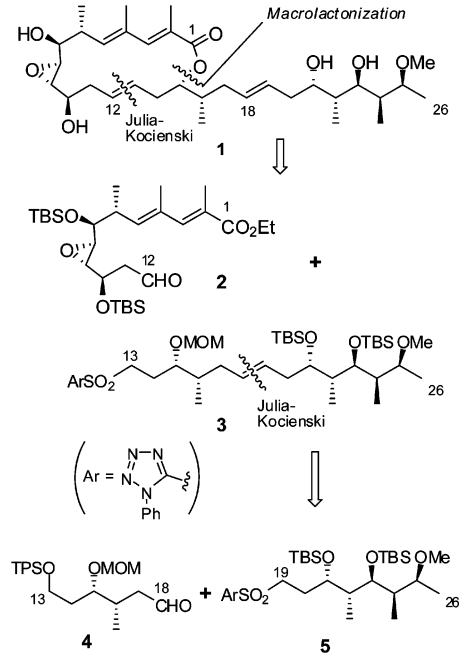
FD-891

A total synthesis of the naturally occurring, cytotoxic macrolide FD-891 is described. Three fragments were first stereoselectively constructed using mainly asymmetric aldol and allylation reactions. The complete framework was then assembled using two Julia–Kocienski olefinations to connect the three fragments and a Yamaguchi reaction to close the macrolactone ring.

The cytotoxic macrolide FD-891 (**1**) was isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890 and was found to be active against several tumor cell lines. In addition, it was found to potently prevent both perforin- and FasL-dependent CTL-mediated killing pathways. In contrast to the structurally related concanamycin A, however, it was unable to inhibit vacuolar acidification.[1] According to the results of chemical degradation, NMR studies, and X-ray diffraction analyses of some degradation products, an erroneous structure for FD-891 was initially proposed,[2] which was subsequently corrected by the same authors to that depicted in Scheme 1.[3]

For our synthesis of this bioactive metabolite, we have chosen the retrosynthetic plan shown in Scheme 1. According to it, the molecule of macrolide FD-891 is disconnected to fragments **2** (C1−C12) and **3** (C13−C26) via a macrolactonization and a Julia−Kocienski olefination. A subsequent disconnection of **3** through a second olefination converts it into fragments **4** (C13−C18) and **5** (C19−C26). In two previous communications, we have published a stereoselective synthesis of **2**,[4] as well as of a fragment structurally

Scheme 1. Retrosynthetic Analysis of FD-891



† Dedicated to the memory of Prof. M. Moreno-Mañas (deceased February 20, 2006).

‡ Universitat Jaume I.

§ Universidad de Valencia.

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(3) Eguchi, T.; Yamamoto, K.; Mizoue, K.; Kakinuma, K. *J. Antibiot.* **2004**, *57*, 156−157.

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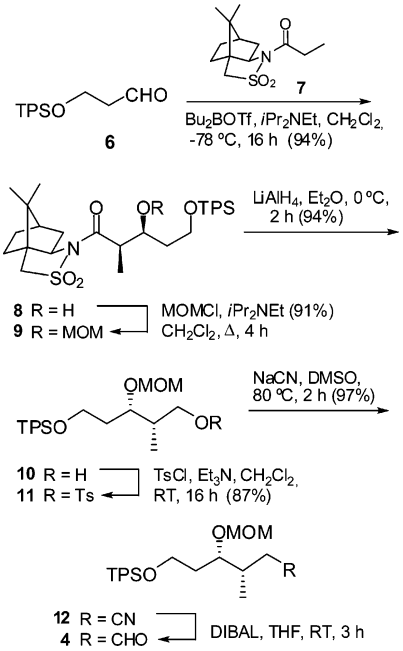
related to **3**[5] but aimed at the synthesis of the wrong structure initially published for FD-891.[2]

Aldehyde **4** was synthesized as depicted in Scheme 2. The known aldehyde **6**[6] was subjected to asymmetric aldol reaction using the *Z* enolborane derived from Oppolzer's chiral propionate[7] equivalent **7**. This provided aldol adduct **8** as a single stereoisomer (dr was ≥98%, as the minor stereoisomer was not detected by means of high-field $^{1}H/^{13}C$ NMR). Introduction of the MOM[8] protecting group and functional manipulation gave nitrile **12**, reduction of which afforded aldehyde **4** (used directly in crude form in the reaction with **5**).

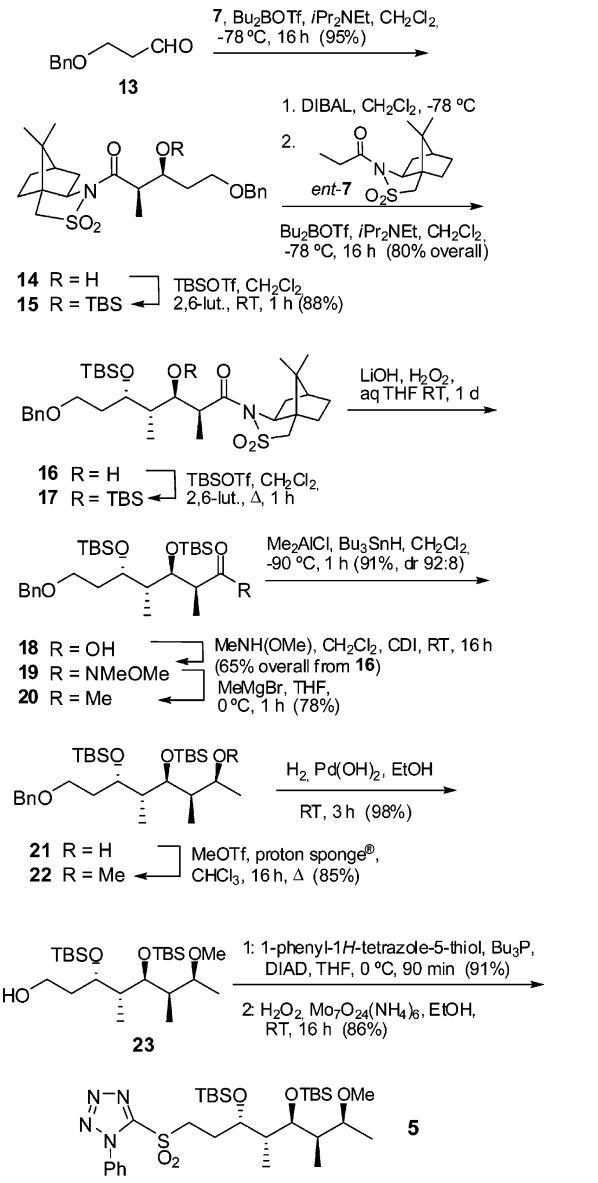
Scheme 2. Synthesis of Fragment **4**[a]



[a] Acronyms and abbreviations: TPS, *tert*-butyldiphenylsilyl; Tf, trifluoromethanesulfonyl; MOM, methoxymethyl; DIBAL, diisobutylaluminum hydride.

Intermediate fragment **5** was prepared as shown in Scheme 3 following the methodology previously described by us.[5] Thus, the known aldehyde **13**[9] was subjected to asymmetric aldol reaction with chiral reagent **7** to yield aldol **14** as a single stereoisomer. Hydroxyl silylation and reductive cleavage (DIBAL) of the chiral auxiliary gave an intermediate

Scheme 3. Synthesis of Fragment **5**[a]



[a] Acronyms and abbreviations: CDI, 1,1′-carbonyldiimidazole; TBS, *tert*-butyldimethylsilyl; 2,6-lut, 2,6-lutidine; DIAD, diisopropyl azodicarboxylate.

aldehyde which was submitted to asymmetric aldol reaction with Oppolzer's reagent *ent*-**7**.[7] This yielded a single crystalline aldol **16**,[10] which was converted into the silyl derivative **17**. The latter was then transformed into methyl ketone **20** via the intermediate acid **18** and the Weinreb[11] amide **19**.[12] Reduction of **20** under chelation control[13] and *O*-methylation using methyl triflate and Proton Sponge[14]

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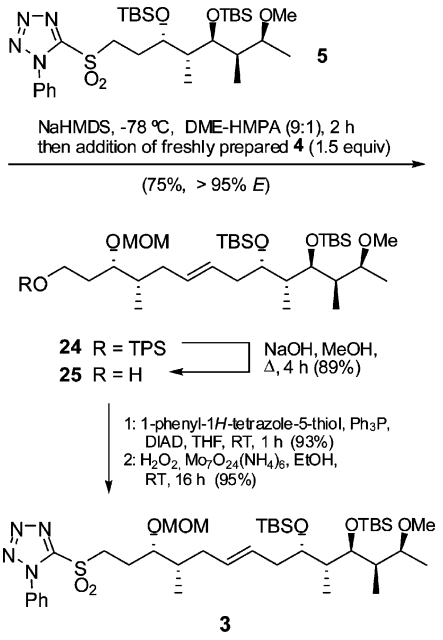
(9) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301−2309.
(10) The absolute configuration of aldol **16** has been secured via X-ray diffraction analysis (see the Supporting Information).
(11) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15−40.
(12) Silylation of **16** required the use of a considerable excess of silylating agent. Therefore, purification of **17** proved difficult. For this reason, the overall yield is given for the three steps **16** → **19**.
(13) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840−10852. See also: Ooi, T.; Morikawa, J.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2993−2996.

stereoselectively afforded compound **22**. Hydrogenolytic *O*-debenzylation to **23**, introduction of the tetrazolylthio[15] moiety via Mitsunobu reaction using PBu_3,[16] and Mo(VI)-catalyzed sulfide−sulfone oxidation[17] gave rise to the desired aryl sulfone **5**.

With all key fragments in hand, the synthesis proceeded as shown in Scheme 4. Connection between **4** and **5** was

Scheme 4. Synthesis of Fragment **3**[a]

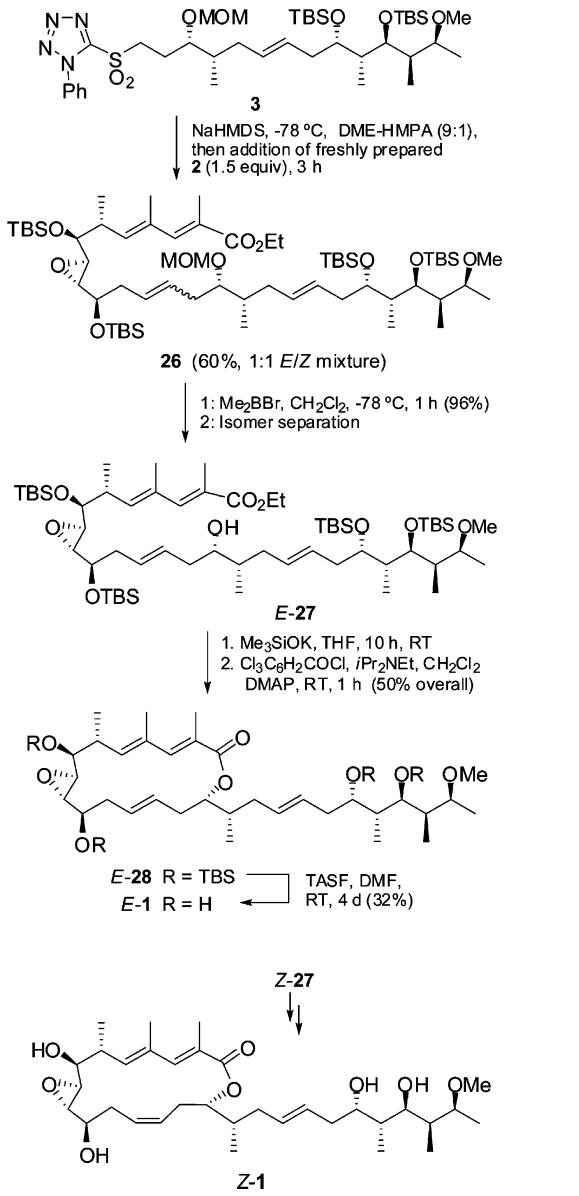


[a] Acronyms and abbreviations: HMDS, hexamethyldisilazide; HMPA, hexamethylphosphortriamide; DME, 1,2-dimethoxyethane.

performed using the Julia−Kocienski[18] olefination protocol, which yielded olefin **24** in good yield (75%, based on recovered **5**) as a single *E* stereoisomer. Selective cleavage of the TPS group[19] gave alcohol **25**, which was converted into aryl sulfone **3** via Mitsunobu reaction (PPh_3 performed better here than PBu_3) and Mo(VI)-catalyzed oxidation.

The final attack toward macrolide **1** was carried out as depicted in Scheme 5. Connection of fragments **2** and **3** was performed as above with the aid of the Julia−Kocienski olefination protocol and gave **26**. The yield was, however, not as high as in Scheme 4, and the reaction was not stereoselective. Changes in various reaction conditions did not lead to improvements.[20] Separation of the *E* and *Z* stereoisomers of **26** was not feasible but could be done after

Scheme 5. Final Steps of the Synthesis of **1**[a]



[a] Acronyms and abbreviations: TASF, tris(dimethylamino)sulfonium difluorotrimethylsilicate.

selective cleavage of the MOM group,[21] which yielded *E*-**27** and *Z*-**27**. Hydrolysis of the ethyl ester group of *E*-**27** was achieved under mild, anhydrous conditions using TMSiOK.[22] Macrolactonization of the resulting hydroxyl acid was performed at high dilution (0.006M) using the Yamaguchi procedure[23] and yielded lactone *E*-**28**. Cleavage of all silyl groups with TASF[24] finally gave macrolide *E*-**1** (FD-891).[25,26]

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(21) (a) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969−3972. (b) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912−3920.
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Following the same series of reactions, lactone *Z*-**27** was transformed into *Z*-**1**, a stereoisomer of the natural macrolide. Its biological properties will also be investigated and compared with those of the natural product.

In summary, a convergent synthesis of the cytotoxic macrolide FD-891 has been achieved. We are presently investigating how to improve the unsatisfactory yield of some of the final steps.[27]

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Supporting Information Available: Experimental procedures for the preparation and tabulated spectral data of all new compounds. Graphical NMR spectra of all new compounds. Crystallographic data of aldol **16** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The identity of the final desilylation product **1** was confirmed through comparison with an authentic sample of the natural product (see the Acknowledgment).

(26) Cleavage of the silyl groups at C-7 and C-10 takes place with ease. In contrast, those allocated at C-21 and C-23 proved unexpectedly reluctant to cleavage under various mild conditions (too harsh conditions caused decomposition). These two groups are thus responsible for the low yield in the final desilylation step. We are presently investigating how to eliminate this unfavorable feature.

(27) While this manuscript was being prepared, a stereoselective total synthesis of macrolide FD-891 (*E*-**1**) appeared: Crimmins, M. T.; Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128−3129.