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Stereoselective synthesis of the C_{14}–C_{26} fragment of the cytotoxic macrolide FD-891

Juan Murga,[a,*] Jorge García-Fortanet,[a] Miguel Carda[a] and J. Alberto Marco[b,*]

[a]*Depart. de Q. Inorgánica y Orgánica, Univ. Jaume I, Castellón, E-12080 Castellón, Spain*
[b]*Depart. de Q. Orgánica, Univ. de Valencia, E-46100 Burjassot, Valencia, Spain*

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Abstract—A stereoselective synthesis of the C_{14}–C_{26} fragment of the naturally occurring, cytotoxic macrolide FD-891, is described. Asymmetric Evans aldol reactions and aldehyde Brown allylations are key steps of the synthesis.
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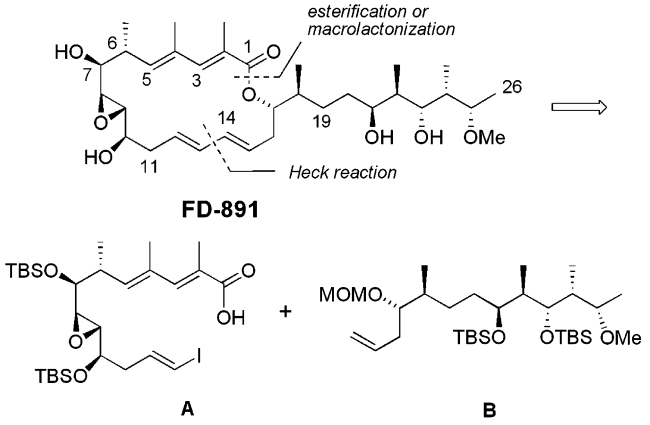
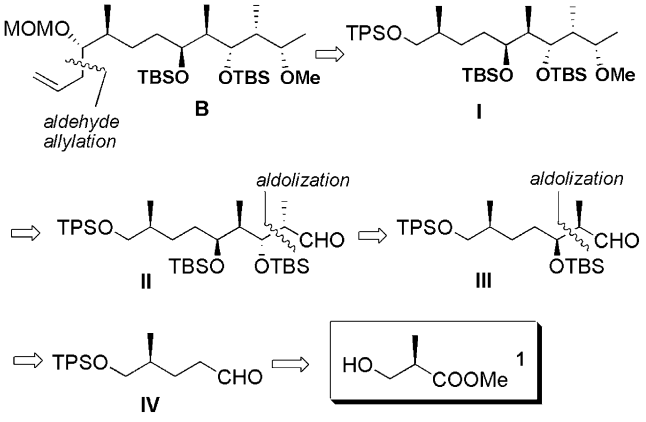
The cytotoxic metabolite FD-891 was isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890 and was found active against several tumor cell lines. In addition, it was found to potently prevent both perforin- and FasL-dependent CTL-mediated killing pathways. In contrast to the structurally related concanamycin A, however, it was unable to inhibit vacuolar acidification.[1] We have now faced the problem of synthesizing this bioactive metabolite and have chosen the convergent retrosynthesis shown in Scheme 1. According to it, the molecule of FD-891 is disconnected to fragments **A** (C_1–C_{13}) and **B** (C_{14}–C_{26}) via an esterification and a Heck coupling. Which one of these two reactions will be the final macrocyclization process still remains an open issue to be decided at a later stage. Indeed, both macrolactonizations[2] and intramolecular Heck reactions[3] are amply represented in the literature.



Scheme 1. Structure of FD-891 and main retrosynthetic disconnection.

In the present communication, we will describe the synthetic work performed to achieve the preparation of fragment **B**, which carries the protecting groups R = TBS (*t*-butyldimethylsilyl) and MOM (methoxymethyl).[4] This fragment, which contains 7 of the 12 stereocenters of the molecule, was further retrosynthetically disconnected as shown in Scheme 2. One key structural transformation in this retrosynthesis (**B** → **I**) is the



Scheme 2. Retrosynthetic disconnection of fragment **B**.

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* Corresponding authors. Tel.: +34 96 3544337; fax: +34 96 3544328; e-mail: alberto.marco@uv.es

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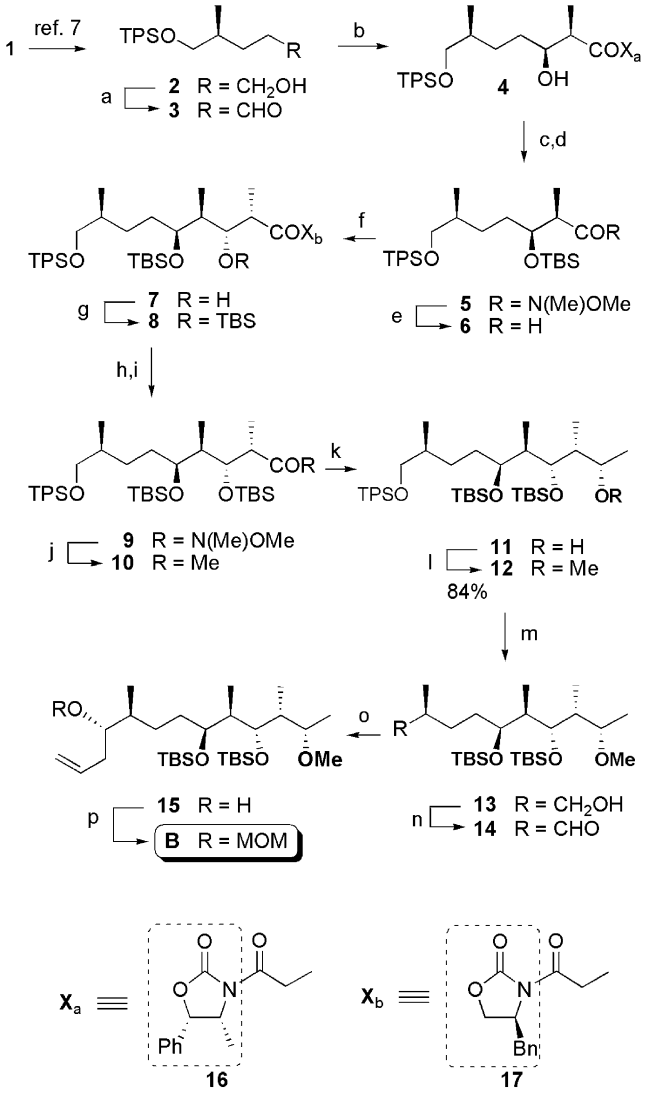
stereoselective allylation of a chiral α-methyl aldehyde and was planned to be performed in an asymmetric way using one of Brown's chiral allylboration reagents.[5] The protecting group TPS (*t*-butyldiphenylsilyl) was selected with the idea in mind of its later selective cleavage in the presence of two TBS groups. The two other key retrotransformations, **II** → **III** and **III** → **IV**, are aldol reactions conceived to create the C_{22}–C_{25} dipropionate segment. In the actual synthesis, both aldol steps were executed with the aid of the chiral oxazolidinones developed by Evans and his group.[6] The ultimate chirality source was the commercially available ester **1**.



Scheme 3. Stereoselective synthesis of compound **B**. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 1 h, 0 °C; (b) **16**, Bu_2BOTf, Et_3N, 0 °C, then **3**, 2.5 h, 0 °C, 89% overall from **2**; (c) MeNHOMe, $AlMe_3$, THF, 3 h, rt, 79%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 92%; (e) DIBAL, THF, −78 °C, 30 min; (f) **17**, Bu_2BOTf, Et_3N, 0 °C, then **6**, 3 h, 0 °C, 75% overall from **5**; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 90%; (h) H_2O_2, aq LiOH, THF, 0 °C → rt, overnight; (i) MeNHOMe, 1,1′-carbonyldiimidazole, CH_2Cl_2, rt, 12 h, 80% overall from **8**; (j) MeMgBr, THF, 0 °C, 1 h, 70%; (k) Me_2AlCl (2.5 equiv), Bu_3SnH, CH_2Cl_2, −90 °C, 1 h, 91% (92:8 diastereoisomeric mixture); (l) MeOTf, 2,6-di-*t*-butylpyridine, $CHCl_3$, Δ, 4 h, 84%; (m) 10% NaOH, MeOH, Δ, 30 h, 84%; (n) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 20 min, 0 °C; (o) allylBIpc$_2$ [from (−)-DIP-Cl and allylmagnesium bromide], Et_2O, 1 h, −90 °C, 55% overall from **13** as a single stereoisomer; (p) MOMCl, EtN*i*-Pr_2, CH_2Cl_2, rt, overnight, 79%.

Scheme 3 depicts the actual synthetic sequence, which led to compound **B**. The chiral, commercially available ester **1** was converted into the known primary alcohol **2**[7] via a literature procedure. Swern oxidation of the latter to aldehyde **3** was followed by Evans asymmetric aldolization using the *Z* boron enolate of the chiral oxazolidinone **16**.[6a] This provided aldol adduct **4** as an essentially single stereoisomer. Conversion of **4** into the Weinreb amide[8] and silylation afforded **5**, which was then reduced (DIBAL) to aldehyde **6**. The latter compound was submitted to a second aldolization with Evans oxazolidinone **17**,[6a] followed by silylation and amidation. This yielded Weinreb amide **9**,[9] which was converted into methyl ketone **10** by treatment with methylmagnesium bromide. Stereoselective reduction of the carbonyl group of **10** under chelation control[10–13] to alcohol **11** and subsequent O-methylation with methyl triflate/2,6-di-*tert*-butylpyridine[14] afforded compound **12**. Selective cleavage of the OTPS group in **12** under alkaline conditions[15] provided the primary alcohol **13**, which was then oxidized to aldehyde **14**. Asymmetric allylation of the latter[5] afforded secondary alcohol **15**, which, through protection of the secondary alcohol group as its MOM derivative,[16] afforded the desired fragment **B**.[17]

In summary, a stereoselective synthesis of the C_{14}–C_{26} fragment of the cytotoxic macrolide FD-891 has been achieved. Studies toward the total synthesis of the natural product are underway and will be published in due course.

Acknowledgements

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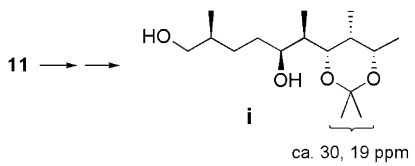

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17. Oil; $[\alpha]_D$ −3.1 (*c* 0.86, $CHCl_3$), ^1H NMR (500 MHz) δ 5.82 (1H, m, H-2), 5.10 (1H, dd, J = 17, 1.5 Hz, H-1t), 5.04 (1H, dd, J = 10, 1 Hz, H-1c), 4.65 (2H, AB system, J = 7 Hz, MOM), 3.81 (1H, dd, J = 5.8, 1.6 Hz, H-10), 3.70 (1H, m, H-8), 3.47 (1H, m, H-4), 3.37 (3H, s, OMe), 3.30 (3H, s, OMe), 3.14 (1H, quint, J = 6.5 Hz, H-12), 2.30 (2H, m, H-3), 1.75–1.50 (5H, br m, H-5/H-6/H-9), 1.45–1.40 (2H, m, H-7), 1.12 (3H, d, J = 6.5 Hz, H-13), 0.94 (3H, d, J = 7 Hz, *Me*-C), 0.91 (3H, d, J = 7 Hz, *Me*-C), 0.90 (9H, s, *t*-Bu), 0.89 (9H, s, *t*-Bu), 0.86 (3H, d, J = 7 Hz, *Me*-C), 0.09 (3H, s, *Me*-Si), 0.07 (3H, s, *Me*-Si), 0.06 (3H, s, *Me*-Si), 0.05 (3H, s, *Me*-Si). ^{13}C NMR (125 MHz) δ 18.5, 18.3 (C), 135.6, 81.4, 79.9, 73.4, 72.6, 43.4, 41.2, 36.6 (CH), 116.7, 96.1, 36.0, 33.4, 27.2 (CH_2), 56.4, 55.6, 26.1 (×3), 26.0 (×3), 16.5, 14.6, 11.1, 10.6, −3.3, −3.5, −4.0, −4.1 (CH_3). HR EIMS *m/z* (% rel. int.) 517.3756 ($M^+ - t$-Bu, 3), 283 (20), 231 (55), 139 (34), 59 (100). Calcd for $C_{31}H_{66}O_5Si_2$-*t*-Bu, 517.3744.