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A Formal Enantioselective Total Synthesis of FR901483

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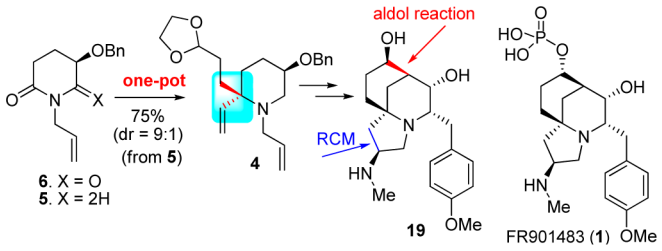
ABSTRACT



A formal enantioselective total synthesis of the potent immunosuppressant FR901483 (1) has been accomplished. Our approach features the use of chiron 6 as the starting material, the application of the one-pot amide reductive bisalkylation method to construct the chiral aza-quaternary center (dr = 9:1), regio- and diastereoselective intramolecular aldol reaction to build the bridged ring, and ring closing metathesis to form the 3-pyrrolin-2-one ring.

FR901483 (**1**, Figure 1) is a potent immunosuppressant isolated from the fermentation broth of the *Cladobotryum* sp. No. 11231 by a research group at the Japan Fujisawa Pharmaceutical Company in 1996.[1] Due to its promising biological activity and challenging structure, this molecule has attracted the attention of many research groups. To date, six enantioselective total syntheses/formal total syntheses[2,3] and numerous synthetic studies[4,5] toward FR901483 (**1**) have been reported. As a continuation

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(1) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot*. **1996**, *49*, 37–44.

(2) For enantioselective total syntheses, see: (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc*. **1999**, *121*, 7778–7786. (b) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed*. **2000**, *39*, 4593–4596. (c) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett*. **2001**, *3*, 765–767. (d) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc*. **2001**, *123*, 7534–7538. (e) Ma, A.-J.; Tu, Y.-Q.; Peng, J.-B.; Dou, Q.-Y.; Hou, S.-H.; Zhang, F.-M.; Wang, S.-H. *Org. Lett*. **2012**, *14*, 3604–3607. For formal total syntheses, see: (f) Brummond, K. M.; Hong, S. P. *J. Org. Chem*. **2005**, *70*, 907–916. (g) Carson, C. A.; Kerr, M. A. *Org. Lett*. **2009**, *11*, 777–779.

(3) For racemic total syntheses, see: (a) Maeng, J.; Funk, R. L. *Org. Lett*. **2001**, *3*, 1125–1128. (b) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett*. **2004**, *6*, 2729–2731. (c) Ieda, S.; Asoh, Y.; Fujimoto, T.; Kitaoka, H.; Kan, T.; Fukuyama, T. *Heterocycles* **2009**, *79*, 721–738.

(4) For enantioselective synthetic studies, see: (a) Puigbó, G.; Diaba, F.; Bonjoch, J. *Tetrahedron* **2003**, *59*, 2657–2665. (b) Diaba, F.; Ricou, E.; Solé, D.; Teixidó, E.; Valls, N.; Bonjoch, J. *ARKIVOC* **2007**, *4*, 320–330. (c) Kaden, S.; Reissig, H.-U. *Org. Lett*. **2006**, *8*, 4763–4766. (d) Seike, H.; Sorensen, E. J. *Synlett* **2008**, 695–701. (e) Ieda, S.; Kan, T.; Fukuyama, T. *Tetrahedron Lett*. **2010**, *51*, 4027–4029. (f) Puppala, M.; Murali, A.; Sundarababu, B. *Chem. Commun*. **2012**, *48*, 5778–5780.

(5) For racemic synthetic studies, see: (a) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem*. **1997**, *62*, 8280–8281. (b) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391–1402. (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem*. **1999**, *7*, 2891–2897. (d) Wardrop, D. J.; Zhang, W. *Org. Lett*. **2001**, *3*, 2353–2356. (e) Brummond, K. M.; Lu, J.-L. *Org. Lett*. **2001**, *3*, 1347–1349. (f) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett*. **2001**, *42*, 3013–3015. (g) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett*. **2003**, *44*, 8387–8390. (h) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem*. **2006**, *71*, 2046–2055. (i) Simila, S. T. M.; Martin, S. F. *J. Org. Chem*. **2007**, *72*, 5342–5349.

(6) (a) Xu, C.-P.; Xiao, Z.-H.; Zhuo, B.-Q.; Wang, Y.-H.; Huang, P.-Q. *Chem. Commun*. **2010**, *46*, 7834–7836. (b) Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem., Int. Ed*. **2010**, *49*, 3037–3040. (c) Xiao, K.-J.; Wang, Y.; Ye, K.-Y.; Huang, P.-Q. *Chem.—Eur. J*. **2010**, *16*, 12792–12796. (d) Liu, X.-K.; Zheng, X.; Ruan, Y.-P.; Ma, J.; Huang, P.-Q. *Org. Biomol. Chem*. **2012**, *10*, 1275–1284. (e) Liao, J.-C.; Xiao, K.-J.; Zheng, X.; Huang, P.-Q. *Tetrahedron* **2012**, *68*, 5297–5302. (f) Wang, Y.-H.; Ye, J.-L.; Wang, A.-E; Huang, P.-Q. *Org. Biom. Chem*. **2012**, *10*, 6504–6511. (g) Xiao, K.-J.; Wang, A.-E; Huang, P.-Q. *Angew. Chem., Int. Ed*. **2012**, *51*, 8314–8317. (h) Xiao, K.-J.; Wang, A.-E; Huang, Y.-H.; Huang, P.-Q. *Asian J. Org. Chem*. **2012** 10.1002/ajoc.201200066.

of our endeavor to develop step-economical[6] and 3-benzyloxyglutarimide[7]-based synthetic methodologies for the asymmetric synthesis of piperidine ring-containing alkaloids,[8] we have embarked on the enantioselective total synthesis of FR901483. We report herein a formal enantioselective total synthesis of FR901483 (**1**).

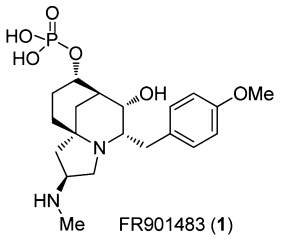
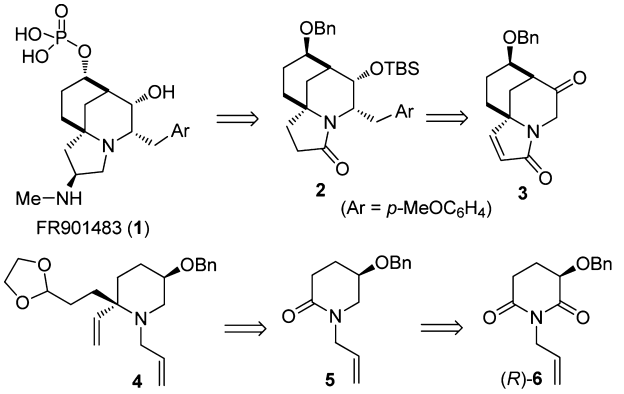


Figure 1. Potent immunosuppressant FR901483 (**1**).

As illustrated retrosynthetically in Scheme 1>, our synthetic plan is based on two key synthetic methodologies developed from our laboratory, namely, the use of chiron **6**[8] as the starting point and the amide reductive bisalkylation method[6b] for a one-pot conversion of piperidin-2-one **5** to piperidine **4** with the formation of two C−C bonds.

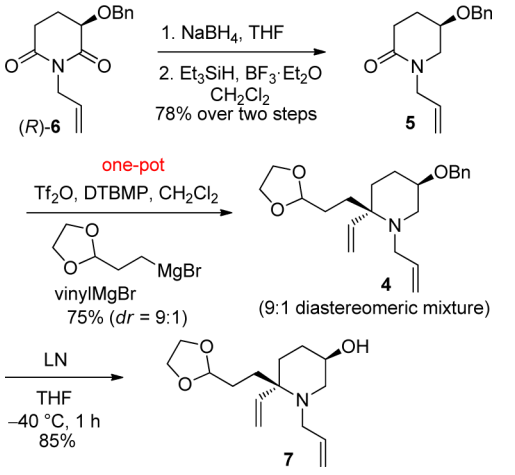
Scheme 1. Retrosynthetic Analysis of FR901483 (**1**)



The synthesis commenced with the partial and regioselective reduction[8b] of (3*R*)-benzyloxyglutarimide **6** with $NaBH_4$ followed by reductive dehydroxylation (BF_3•OEt_2, Et_3SiH, CH_2Cl_2) via an iminium ion intermediate[8a,c] (Scheme 2). The subsequent bisalkylation of lactam[6b] **5** (Tf_2O, DTBMP, CH_2Cl_2; then successive addition of two Grignard reagents) proceeded as planned to produce the desired lactam **4** in 75% yield. Remarkably, the reaction proceeded with high diastereoselectivity (*dr* = 9:1, determined by ^1H NMR of the crude sample). The stereochemistry of the major diastereomer was deduced to be *trans* on the basis of the mechanistic consideration that the vinyl group approaches the iminium ion intermediate from the α-side opposing the benzyloxy group, which was confirmed at a latter stage. It is worth mentioning that, among various synthetic approaches for the synthesis of FR901483 (**1**), this is the first example utilizing the one-pot amide reductive bisalkylation method to construct the chiral aza-quaternary center.

The selective *O*-debenzylation of compound **4** was achieved by treatment of piperidine **4** (diastereomeric mixture) with lithium naphthalenide (LN)[9] in THF at −40 °C for 1 h, which gave, after chromatographic separation, the piperidin-3-ol **7** as a pure diastereomer in 85% yield.

Scheme 2. Stereoselective Synthesis of the Key Intermediate **7**



Next, the piperidin-3-ol **7** needed to be oxidized to the ketone **8** before the key intramolecular aldol ring closure reaction could be commenced. After unsuccessful trials with the Dess-Martin periodinane, and partial success with the Ley oxidation (35% yield), the Swern oxidation was attempted. It was found that by the use of an extreme excess of triethylamine, the desired ketone could be obtained in 90% yield [$(COCl)_2$ 6 equiv, DMSO 12 equiv, CH_2Cl_2, −78 °C, 1 h; and then NEt_3 25 equiv]. After deacetalization of compound **8** with a 4 *N* HCl solution, the resulting keto-aldehyde, in the form of its hydrochloride salt, was heated with ethylene glycol (4.0 equiv)[10] and CSA (0.3 equiv) in toluene at 90 °C. The desired regioselective intramolecular aldol reaction took place smoothly with concomitant acetalization of the ketone to give compound **9** as the solely observable regio- and diastereomer in 53% yield (Scheme 3). The relative stereochemistry of **9** was established on the basis of the observed

(7) Ruan, Y.-P.; Wei, B.-G.; Xu, X.-Q.; Liu, G.; Yu, D.-S.; Liu, L.-X.; Huang, P.-Q. *Chirality* **2005**, *17*, 595–599.

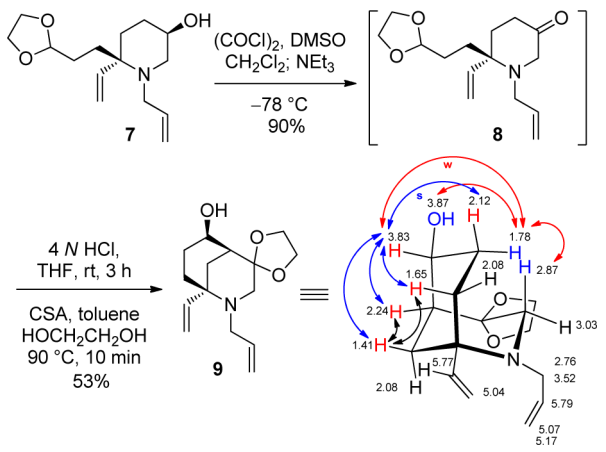
(8) For recent examples, see: (a) Fu, R.; Ye, J.-L.; Dai, X.-J.; Ruan, Y. -P.; Huang, P.-Q. *J. Org. Chem.* **2010**, *75*, 4230–4243. (b) Yang, R.-F.; Huang, P.-Q. *Chem.—Eur. J.* **2010**, *16*, 10319–10322. (c) Tuo, S.-C.; Ye, J.-L.; Wang, A.-E; Huang, S.-Y.; Huang, P.-Q. *Org. Lett.* **2011**, *13*, 5270–5273.

(9) Liu, H.-J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253–2256.

(10) If the hydrochloride salt was neutralized and the mixture was heated in the absence of ethylene glycol, a regiomeric aldol product was obtained in 65% yield as a single diastereomer.

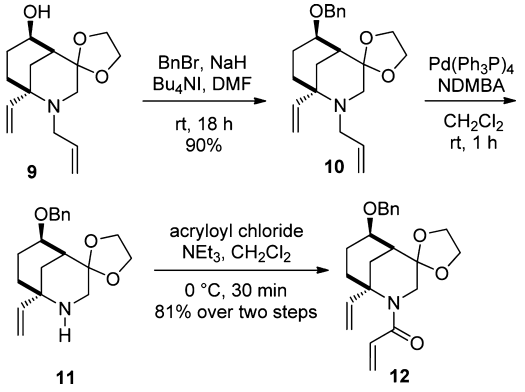
strong correlation between the methine proton (δ 3.83) and the H_{eq} (δ 2.12), and a smaller correlation between the methine proton (δ 3.83) and the H_{ax} (δ 1.78) in its NOESY spectrum (Scheme 3).

Scheme 3. Synthesis and the Observed NOE Correlations of Compound **9**



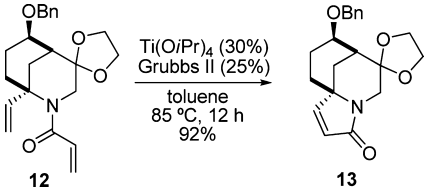
After securing access to the bicyclic core **9**, the conversion of the latter to a precursor for the ring closing metathesis (RCM) reaction was investigated. Thus, the hydroxyl group was protected as its benzyl ether **10** (BnBr, NaH, Bu_4NI, DMF, 90% yield) (Scheme 4). Compound **10** was subjected to Pd-catalyzed *N*-deallylation [$Pd(Ph_3P)_4$ (0.01 equiv), NDMBA (3 equiv), CH_2Cl_2, rt, 1 h],[11] and acryloylation (acryloyl chloride, NEt_3, CH_2Cl_2, 0 °C, 30 min), which gave acrylamide **12** in 81% yield over two steps.

Scheme 4. Synthesis of the Acrylamide Derivative **12**



We next investigated the RCM reaction of **12**. Formation of α,β-unsaturated lactams by the RCM reaction of acrylamides has been well documented using either Grubbs' first or second generation catalyst.[12] The reaction generally proceeded in CH_2Cl_2.[5f,12] However in our case all attempts to perform the RCM reaction of **12** by the use of the Grubbs first or second generation catalyst in CH_2Cl_2 were unsuccessful. Considering the steric hindrance of the substrate, it was envisioned that a higher reaction temperature would favor the reaction. Indeed, when a toluene solution of acrylamide **12** and the Grubbs second generation catalyst (25%) was heated to 85 °C for 12 h, the desired cyclized product **13** was obtained in 30% yield, along with 60% of the recovered starting material. Remarkably, when the reaction (Grubbs II 25%, toluene, 85 °C) was run in the presence of 30% molar equiv of $Ti(OiPr)_4$,[13] the desired cyclic core **13** was obtained in 92% yield (Scheme 5).

Scheme 5. Construction of the Tricyclic Core **13** by the RCM Reaction



Now we were in a position to undertake the functional group exchange and the functionalization of the core structure. Thus, acetal **13** was cleaved by treatment with a solution of 4 *N* HCl in acetone at reflux for 3 h to give the keto-lactam **3** in 85% yield (Scheme 6). Inversed addition[3a] of the enolate, generated from ketone **3** by deprotonation with KHMDS (1 equiv) in THF at −50 °C, with *p*-methoxybenzyl bromide (3.0 equiv) in DMF at 0 °C for 20 min produced compound **14** as the only observable regio- and diastereomer in 75% yield. Pd/C-catalyzed selective hydrogenation of **14** (Pd/C 30 wt %, H_2, 1 atm, EtOAc) produced lactam **15** in 90% yield. Subjection of ketone-lactam **15** to the SmI_2-mediated reduction[3b,14] (SmI_2 5 equiv, HMPA 25 equiv, MeOH 10 equiv, THF, −78 °C, 12 h) yielded the desired *cis*-diastereomer **16** as the only observable diastereomer in 85% yield. The spectral data of our synthetic **16** matched those reported for the racemic **16**,[5d] which confirmed the relative stereochemistry of our synthetic product.

We next turned our attention to the stereoselective α-amination of lactam **16**. Thus, the hydroxyl group in **16** was first protected (TBSOTf, NEt_3, CH_2Cl_2, 93%) as TBS

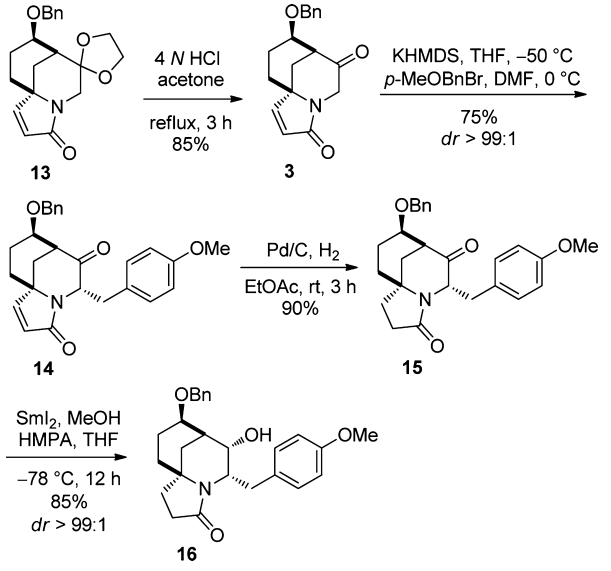
(11) (a) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109–6113. (b) Davies, S. G.; Fenwick, D. R. *Chem. Commun.* **1997**, 565–566.

(12) For reviews on the applications of the RCM reaction in the synthesis of lactams, see: (a) Hassan, H. M. A. *Chem. Commun.* **2010**, *46*, 9100–9106. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (c) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712. For a recent example, see: (d) Zhang, H.-K.; Li, X.; Huang, H.; Huang, P.-Q. *Sci. Sinica Chim.* **2011**, *41*, 732–740. *Sci. China Chem.* **2011**, *54*, 737–744 (*in Chinese*).

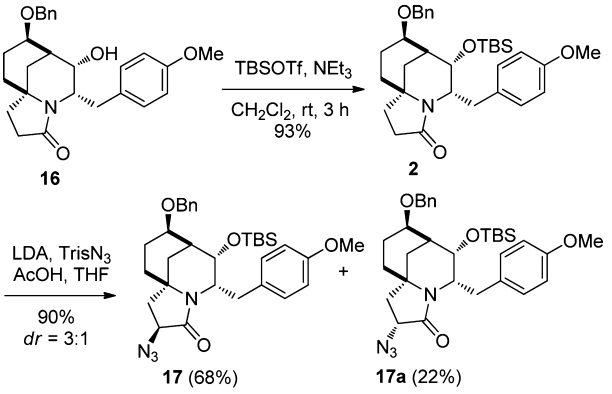
(13) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651–4654.

(14) For recent reviews on SmI_2, see: (a) Procter, D. J., Flowers, R. A., Skrydstrup, T., Eds. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: 2010. (b) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165. (c) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607–637.

Scheme 6. Diastereoselective Synthesis of Compound **16**



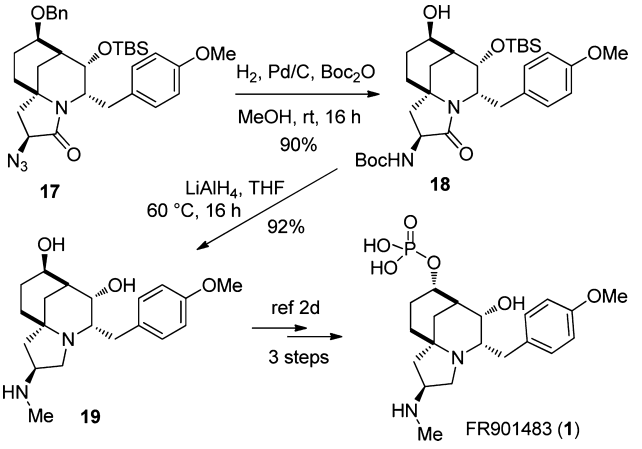
Scheme 7. Synthesis of Compound **17**



ether **2** (Scheme 7). Successive treatment of lactam **2** with LDA (3.0 equiv) and $TrisN_3$ (3 equiv) at −78 °C for 5 min, followed by addition of HOAc, led to the formation of the desired azide **17** as a separable diastereomeric mixture in a 3:1 ratio with a combined yield of 90%. The stereochemistry of the major diastereomer **17**, which was assumed to be formed by approaching the electrophile from the less hindered β-face, was determined by NOESY experiments.

To convert the azido group to the *N*-methylamino group, azide **17** was hydrogenated (10%Pd/C 30 wt %, H_2 1 atm) in the presence of Boc_2O (1.2 equiv), which gave the concomitantly protected compound **18** in 90% yield (Scheme 8). Treatment of compound **18** with a large excess of $LiAlH_4$ (30 equiv) in THF at 60 °C for 16 h afforded the amino-diol **19** in 92% yield. It is worth noting that, in this senario, *N*-Boc reduction to give *N*-Me group, lactam reduction to give pyrrolidine, and *O*-desilylation occurred sequentially. The ^1H and ^{13}C NMR spectral data of compound **19** are in agreement with those reported by Ciufolini.[2d] Since compound **19** has been converted into FR901483 (**1**) in three steps,[2d] our synthetic approach thus constitutes a formal total synthesis of (−)-FR901483 (**1**).

Scheme 8. Synthesis of the Known Precursor (**19**) of FR901483



In summary, starting from the known chiron **6**, we have achieved the synthesis of the advanced intermediate **19** in 18 steps with an overall yield of 4.1%, which constitutes a formal enantioselective total synthesis of FR901483 (**1**).

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Supporting Information Available. Full experimental procedures; ^1H and ^{13}C NMR spectra of all new compounds; NOESY spectra of compounds **9** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.