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A flexible route to immunosuppressive agent FR252921. Asymmetric total synthesis of its (13*R*,14*R*,19*R*)-isomer

Shouyun Yu, Feng Liu and Dawei Ma*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, PR China

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Abstract—A flexible route to the proposed structure of FR252921, a novel immunosuppressive agent, is developed. The key elements include the assembly of its two β-hydroxy acid residues via asymmetric aldol condensation of *N*-acylthiazolidinethinones with aldehydes, and its triene part via a CuI/*N*,*N*-dimethylglycine catalyzed Sonogashira coupling and subsequent isomerization. Using this strategy (13*R*,14*R*,19*R*)-FR252921 is elaborated.

FR252921 (**1**) is a novel immunosuppressive agent that was isolated from the cultured broth of *Pseudomonas fluorescence* No. 408813 by Fujine et al.[1] In in vitro studies, this compound displayed a strong inhibition to both FK 506 sensitive (stimulated by anti-CD3 mAb) and FK506-insensitive (stimulated by lipopolysaccharide (LPS)) splenocyte proliferations by blocking AP-1 pathway. Further investigations revealed that FR252921 acts dominantly against the antigen presenting cell (APC) rather than T cell. In the murine skin allograft model, although FR252921 alone did not have a strong efficacy in transplantation, it showed synergy with FK506 as that combination of FR252921 with FK506 was noticed to be able to prolong an allograft survival by four days comparing to FK506 alone.[1c] These results indicated that FR252921 or related AP-1 inhibitors may serve as excellent members of combination therapy for rejection control in clinical use.

Through NMR studies, the gross structure of FR252921 was established as shown in Figure 1. However, its stereochemistry at the three chiral centers was still unknown.[1a] Interestingly, from the same strains, a antimicrobial substance, named as pseudotrenic acid B (Fig. 2), was isolated by Pohanka et al. quite recently. Treatment of this acid with TFA provided a lactone, which was proposed to have a similar structure with FR252921.[2]

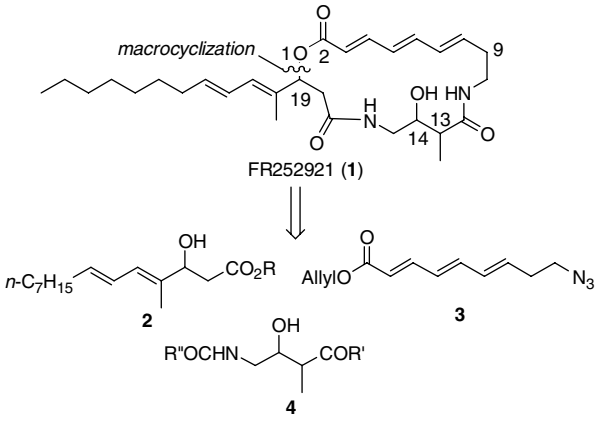

Figure 1. Structure of FR252921 and its retrosynthetic analysis.

The important biological activity displayed by FR252921 and the unsolved structural problem prompted us to develop a flexible protocol to assemble this molecule and its isomers. As depicted in Figure 1, our synthetic plan was based on the degradation of the target molecule into three residues via two amide formation reactions and a macrocyclization. They are two β-hydroxy acid units **2** and **4**, and a triene part **3**. Intermediates **2** and **4** could be elaborated via asymmetric aldol condensation of Crimmins' *N*-acylthiazolidinethinones with corresponding aldehydes,[3] while azide **3** could be constructed by a CuI/*N*,*N*-dimethylglycine-catalyzed coupling of an alkyne with allyl β-iodoacrylate[4] and subsequent isomerization.

* Corresponding author. Tel.: +86 2164163300; fax: +86 2164166128; e-mail: madw@mail.sioc.ac.cn

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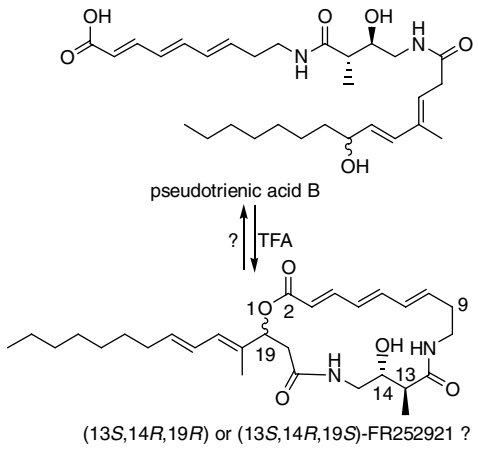
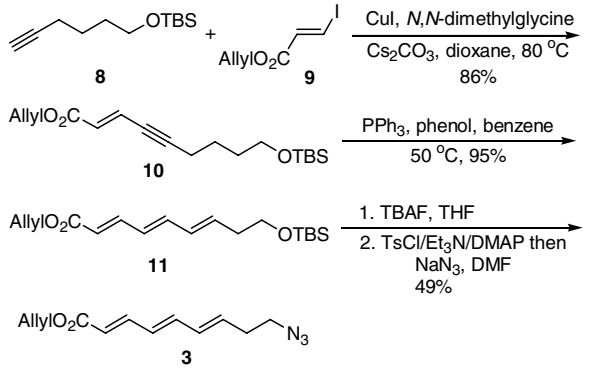


Figure 2. Structure of pseudotrienic acid B and its conversion to (13*S*,14*R*,19*R*) or (13*S*,14*R*,19*S*)-FR252921.

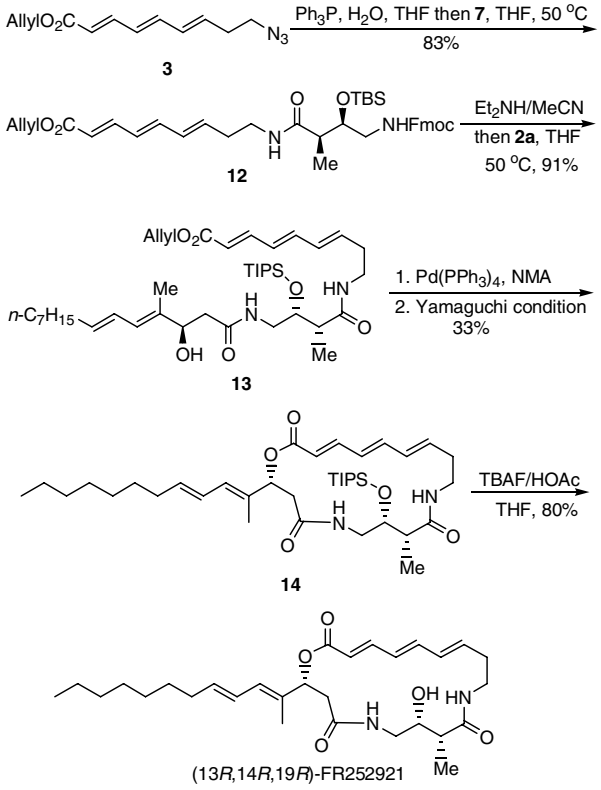
We next tested our strategy by carrying out the total synthesis of (13*R*,14*R*,19*R*)-FR252921. As shown in Scheme 1, the addition of 2-methyl-(2*E*,4*E*)-dodecadienal to a solution of the chlorotitium enolate of *N*-acylthiazolidinethione **5** provided aldol adduct **2a** (68%, >95:5 dr).[3] Similarly, from Fmoc-protected 2-aminoethal and *N*-propionylthiazolidinethione **6** aldol adduct **4a** (82%, >95:5 dr) was obtained, which was treated with TIPSCl to afford silyl ether **7** in a 94% yield. Since it was reported that *N*-acylthiazolidinethione aldol adducts could easily undergo transamination,[3c] we envisaged that both **2a** and **7** could be directly employed for further amidation manipulations. Noteworthy is that by switching the chiral auxiliaries and running Mitsunobu inversion of the 14-hydroxy group in a later stage, we would be able to obtain all building blocks with the required stereochemistry for assembling FR252921 and its isomers.

Sonogashira coupling between 1-alkynes and vinyl halides usually worked under the catalysis of Pd/CuI.[6] Recently we discovered that under the promotion of *N*,*N*-dimethylglycine, CuI alone could catalyzed Sonogashira coupling reaction under mild conditions.[4] To our delight, this catalyst system was applicable to our present synthesis, as evidenced from that coupling of alkyne **8** and allyl β-iodoacrylate **9** delivered enyne **10** in an 86% yield. Next, the isomerization of **10** was conducted under the action of phenol and PPh_3 in benzene at 50 °C,[5] giving (*E*,*E*,*E*)-triene **11** in a 95% yield as a single product. The cleavage of the silyl ether in **11** with TBAF afforded an alcohol, which was then converted to the desired azide **3** through its tosylate (Scheme 2).

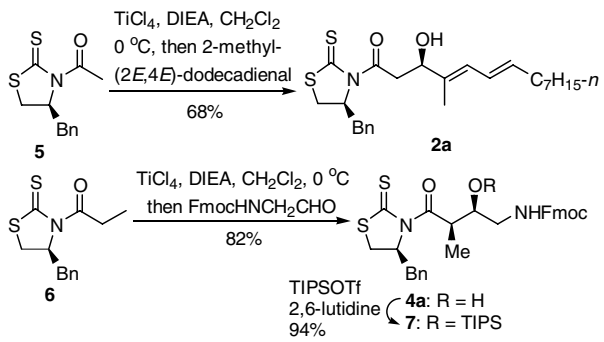
With all required fragments in hand, we started to elaborate the target molecules by connecting them with each other. As outlined in Scheme 3, the reduction of azide **3** under Staudinger condition[7] gave rise to a free amine, which was condensed with thiazolidinethione **7** in THF at 50 °C to afford amide **12** in 83% yield. After cleavage of the Fmoc group in **12**, the liberated amine was condensed with *N*-acylthiazolidinethione aldol adduct **2a** to provide cyclization precursor **13** in an excellent yield. Although transamination between thiazolidine amides and amines has been established for over



Scheme 2.



Scheme 3.



Scheme 1.

three decades,[8] few examples have been reported on its applications in the total synthesis of complex natural products.[9] The present success may stimulate its further utilization.

The removal of the allyl ester in **13** was achieved using $Pd(PPh_3)_4$ as a catalyst and *N*-methylaniline as a base.[10] The resultant hydroxyl acid was then subjected to macrocyclization using Yamaguchi procedure (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP)[11] to produce the desired lactone **14** in a 33% yield. The silyl group in **14** was cleaved with TBAF and acetic acid to finally give (13*R*,14*R*,19*R*)-FR252921 **1a** in an 80% yield.[12] This structure was further confirmed by COSY and HMQC analysis. However, the NMR data of synthetic **1a** were not in agreement with those reported for natural FR252921, and therefore the configuration of 13*R*, 14*R*,19*R* for FR252921 was ruled out.

In summary, we have developed a facile and flexible route to the possible isomers of FR252921. The *N*-acylthiazolidinethinone method not only delivered required enantiopure building blocks, but also led to direct connection of the three residues. Another notable feature for this synthetic protocol is its convergent manner and suitability for a large-scale preparation, which would be of benefit for further structure–activity relationship (SAR) studies and subsequent drug development based on the structure of this novel immunosuppressive agent. Investigations along this direction, as well as the elaboration of the other possible isomers to reveal the exact structure of this molecule, are in progress and will be reported in due course.

Acknowledgments

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References and notes

1. (a) Fujine, K.; Tanaka, M.; Ohsumi, K.; Hashimoto, M.; Takase, S.; Ueda, H.; Hino, M.; Fujii, T. *J. Antibiot.* **2003**, *56*, 55; (b) Fujine, K.; Abe, F.; Seki, N.; Ueda, H.; Hino, M.; Fujii, T. *J. Antibiot.* **2003**, *56*, 62; (c) Fujine, K.; Ueda, H.; Hino, M.; Fujii, T. *J. Antibiot.* **2003**, *56*, 68.
2. Pohanka, A.; Broberg, A.; Hohansson, M.; Kenne, L.; Levenfors, J. *J. Nat. Prod.* **2005**, *68*, 1380.
3. (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883; (b) Crimmins, M. T.; Chandhary, K. *Org. Lett.* **2000**, *2*, 775; (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chandhary, K. *J. Org. Chem.* **2001**, *66*, 894.
4. Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934, Detailed studies on the coupling of vinyl iodides with 1-alkynes will be published elsewhere.
5. (a) Ma, D.; Lu, X. *Tetrahedron* **1990**, *46*, 3189; (b) Trost, B. M.; Uli, K. *J. Am. Chem. Soc.* **1992**, *114*, 7933; (c) Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921; (d) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659.
6. Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1999; Vol. 3, p 521.
7. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635; (b) Venturini, A.; Gonzalez, J. *J. Org. Chem.* **2002**, *67*, 9089.
8. Nagao, Y.; Seno, K.; Kawabuta, K.; Miyasaka, T.; Takao, S.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 841.
9. (a) Nagao, Y.; Dai, W. M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211; (b) Wang, L.-X.; Li, C.; Wang, Q.-W.; Hui, Y.-Z. *J. Chem. Soc. Perkin Trans. 1* **1994**, 621; (c) Grillot, A.-L.; Hart, D. J. *Tetrahedron* **1995**, *51*, 11377.
10. Ciommer, M.; Kunz, H. *Synlett* **1991**, 593.
11. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; (b) Makino, K.; Nakajima, N.; Hashimoto, S.-I.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9077.
12. Selected data for **1a**: $[\alpha]_D^{23}$ −89.6 (*c* 0.60, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.93 (s, 1H), 6.96 (dd, $J = 12.8$, 13.9 Hz, 1H), 6.64 (t, $J = 11.5$ Hz, 1H), 6.56 (dd, $J = 11.2$, 14.2 Hz, 1H), 6.28–6.20 (m, 2H), 5.95 (d, $J = 10.9$ Hz, 1H), 5.90–5.86 (m, 1H), 5.71–5.65 (m, 1H), 5.47 (d, $J = 11.5$ Hz, 1H), 5.37 (d, $J = 10.8$ Hz, 1H), 4.64 (br s, 1H), 3.48–3.42 (m, 1H), 3.25–3.15 (m, 1H), 2.97–2.92 (m, 1H), 2.75–2.69 (m, 1H), 2.67–2.59 (m, 1H), 2.50–2.35 (m, 2H), 2.25–2.15 (m, 1H), 2.15–2.5 (m, 1H), 2.05–1.97 (m, 1H), 1.70 (s, 1H), 1.34–1.30 (m, 2H), 1.25 (s, 8H), 0.98 (d, $J = 6.5$ Hz, 3H), 0.87–0.83 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.2, 168.9, 165.2, 142.5, 141.1, 137.2, 135.2, 133.1, 132.8, 127.3, 125.7, 125.2, 117.5, 76.1, 72.5, 45.4, 44.4, 40.2, 38.0, 32.4, 32.3, 31.0, 28.8, 28.6, 28.5, 22.0, 14.0, 13.9, 12.8; ESI-MS *m*/*z* 501.2 $(M+H)^+$, 523.3 $(M+Na)^+$; HRMS (MALDI) calcd for $C_{29}H_{45}N_2O_5$ $(M+H)^+$ 501.3323, found 501.3324.