J|A|C|S
COMMUNICATIONS

Published on Web 03/17/2007

Structure Elucidation and Enantioselective Total Synthesis of the Potent HMG-CoA Reductase Inhibitor FR901512 via Catalytic Asymmetric Nozaki−Hiyama Reactions

Masahiro Inoue and Masahisa Nakada*

Department of Chemistry, Faculty of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

Received February 5, 2007; E-mail: mnakada@waseda.jp

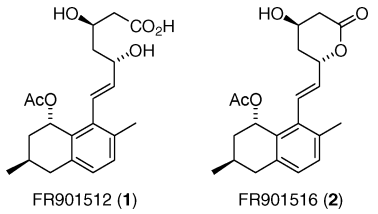
FR901512 (**1**) and FR901516 (**2**) (Figure 1), isolated from the fermentation broth of agonomycete strain No. 14919,[1] are new specific and strong inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (IC_{50} values of 0.95 and 14.0 nM, respectively), and **1** inhibits cholesterol synthesis from [^{14}C]-acetate in Hep G2 cells with an IC_{50} of 1.0 nM. Single oral administration of **1** strongly inhibits sterol synthesis in rats, and daily oral administration of **1** to beagle dogs decreases plasma cholesterol levels; hence, **1** is expected to have a hypolipidemic effect in humans. Compared to the previously reported naturally occurring HMG-CoA reductase inhibitors,[2] **1** and **2** possess a unique tetralin core with two stereogenic centers instead of the hexahydronaphthalene ring found in mevastatin and lovastatin.[3] Furthermore, the side chain, 3,5-dihydroxy-6-heptenoic acid in both compounds, differs from 3,5-dihydroxyheptanoic acid found in mevastatin and lovastatin.

The potent bioactivity and unique structural features of **1** make this compound an attractive target, and we report herein the enantioselective total synthesis of **1** as well as elucidation of the absolute structures of both compounds.

Although **1** was chemically correlated to **2**, the absolute structure of **1** has not been elucidated[1a] and only a limited amount of **1** was available. Hence, we decided to elucidate the structure of **1** through asymmetric total synthesis. We have previously developed the catalytic asymmetric Nozaki−Hiyama reactions,[4] which were widely applicable and reliable, providing both enantiomers of the product with high enantiomeric excess because both enantiomers of the chiral ligand are readily available. Therefore, we outlined our retrosynthetic analysis of **1** as shown in Scheme 1.

We envisioned that the side chain moiety of **1** would be connected at the benzylic position, and that both diastereomers of the tetralin moiety **3** would be derived from **4** via a diastereoselective hydrogenation. We expected to obtain alkene **4** from **5** via the ring-closing metathesis, and both enantiomers of **5** were thought to be prepared by the catalytic asymmetric Nozaki−Hiyama methallylation of **6**. Consequently, we decided to first elucidate the absolute structure of the tetralin moiety **3** and commenced with the catalytic asymmetric preparation of **5**.

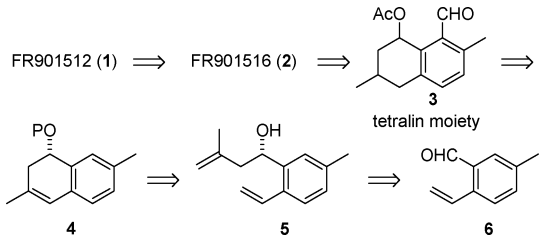
Aldehyde **6** was prepared from readily available **7**[5] via lithiation and formylation (Scheme 2). The catalytic asymmetric Nozaki−Hiyama methallylation of **6** successfully provided **5** with excellent yield and enantioselectivity (93%, 92% ee).[6] We employed Grubbs second generation catalyst[7] for the ring-closing metathesis of **5** to generate the trisubstituted alkene **9** (96%). The hydroxyl group directed hydrogenation of **9** with Crabtree's catalyst[8] in CH_2Cl_2 to produce **10** with >50/1 dr; however, the yield was 59% because the competing dehydration reaction occurred, generating the naphthalene derivative in 33% yield.[9] Conducting the reaction in DME improved the yield (94%).[10] The regioselective lithiation of



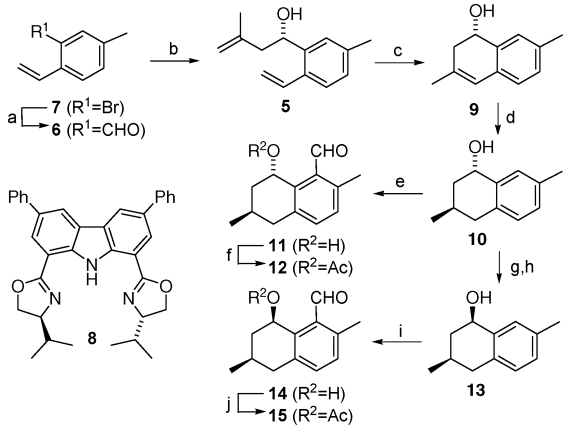
FR901512 (**1**) FR901516 (**2**)

Figure 1. Structure of FR901512 (**1**) and FR901516 (**2**).

Scheme 1. Retrosynthetic Analysis of FR901512 (**1**) via **3**



Scheme 2. Enantioselective Synthesis of **12** and **15**[a]

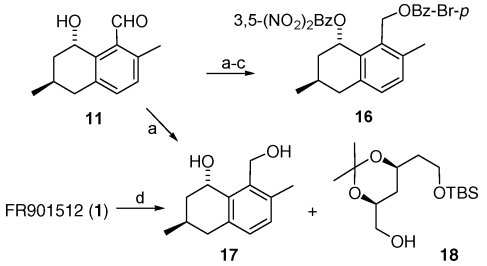


[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; DMF, 96%; (b) methallyl chloride, $CrCl_2$ (5 mol %), **8** (6 mol %), Mn, DIPEA, TMSCl, THF, rt, 93%, 92% ee; (c) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$ (3 mol %), PhMe (0.03 M), 50 °C, 96%; (d) H_2, $[Ir(cod)PCy_3Py]PF_6$ (4 mol %), DME, 0 °C, 94%, dr = >50/1; (e) *s*-BuLi, TMEDA, hexane, −10 °C; DMF, THF, −40 to 0 °C, 43%; (f) Ac_2O, DMAP, THF, −78 °C, 70% (94% brsm); (g) Dess−Martin periodinane, CH_2Cl_2, 0 °C; (h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 100% (2 steps), dr = >50/1; (i) *s*-BuLi, TMEDA, hexane, −10 °C; DMF, THF, −40 to 0 °C; (j) Ac_2O, DMAP, THF, −78 °C, 13% (14% conv, 2 steps).

10 and subsequent formylation were crucial, providing **11** in 43% yield under the optimized conditions. Acetylation of **11** above 0 °C was low-yielding due to the formation of an unidentified byproduct, but performing the acetylation at −78 °C improved the yield (94%, 74% conversion).[11]

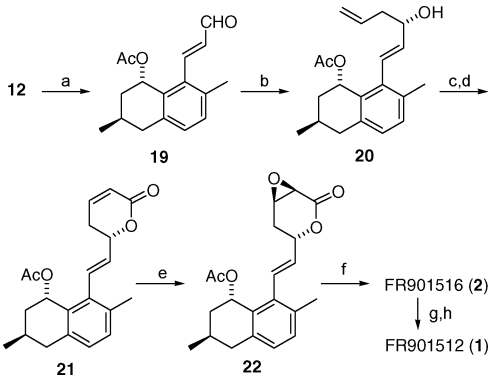
10.1021/ja070812w CCC: $37.00

Scheme 3. Structure Elucidation of FR901512 (**1**)[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 100%; (b) *p*-bromobenzoyl chloride, DIPEA, CH_2Cl_2, 10 °C; (c) 3,5-dinitrobenzoyl chloride, NEt_3, DMAP, CH_2Cl_2, 75% (2 steps); (d) see Supporting Information.

Scheme 4. Enantioselective Total Synthesis of FR901512 (**1**) and FR901516 (**2**)[a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CH{=}N$-*c*Hex, KHMDS, THF, −78 to −30 °C; aq. oxalic acid, 88%; (b) allyl bromide, $CrCl_2$ (15 mol %), **8** (16 mol %), Mn, DIPEA, TMSCl, THF, 3 °C, 99%, 90% de; (c) acryloyl chloride, DIPEA, CH_2Cl_2, 10 °C, 94%; (d) $Cl_2(Cy_3P)_2Ru{=}CHPh$ (10 mol %), CH_2Cl_2 (0.005 M), reflux, 100%; (e) TBHP, Triton B, PhMe, 0 °C, 70%; (f) PhSeSePh, $NaBH_4$, AcOH, THF/EtOH, 0 °C, 100%; (g) MeOH, PhMe, rt; (h) TMSOK, THF, 0 °C, 95% (2 steps).

The diastereomeric acetate **15** was successfully prepared from **10** via **13**. Dess−Martin oxidation of **10** and subsequent highly diastereoselective reduction with $NaBH_4$ and $CeCl_3$ (100%, >50/1 dr, two steps) provided **13**, which was converted to **15** by the transformations identical to those of the method for **12** from **10**.

Comparison of the ^{1}H NMR spectra of **12**, **15**, and **1** clearly indicated that the relative configuration of the tetralin moiety of **1** would be *trans*. Furthermore, alcohol **11** was gratifyingly transformed to crystalline **16** via three steps (Scheme 3), and its X-ray crystallographic analysis established the absolute structure of **16** as shown in Scheme 3. At the same time, we succeeded in preparing **17** and **18** from **1**,[12] and the alcohol prepared by reduction of **11** with $NaBH_4$ was spectroscopically identical to **17** in all respects, while the absolute structure of **18** was determined by comparison with known *ent*-**18**.[13] Consequently, we elucidated the entire structure of FR901512 (**1**) as shown in Figure 1.

Further synthetic studies were continued from **12** (Scheme 4), but all the attempts to assemble the side chain moiety of **1** with **12** failed. However, reaction of **12** with Nagata's reagent[14] provided aldehyde **19** in excellent yield (88%). Although a rather reactive benzylic acetate was incorporated in aldehyde **19**, the catalytic asymmetric Nozaki−Hiyama allylation of **19** fortunately provided **20** with excellent yield and stereoselectivity (99%, 90% de).[15]

The acrylate of **20** was subjected to the ring-closing metathesis with Grubbs second generation catalyst, but unexpectedly, a complex mixture formed. Fortunately, the reaction with Grubbs first generation catalyst[16] afforded **21** in 100% yield. The chemoselective and diastereoselective epoxidation of **21** was well achieved with TBHP and Triton B in toluene, affording **22** as the sole product.[17] The epoxide of **22** was reacted with diphenyldiselenide, $NaBH_4$, and acetic acid[18] in THF/EtOH, providing **2** in 100% yield with complete regioselectivity. Methanolysis of **2** and subsequent cleavage of the resultant methyl ester furnished **1**. The synthesized **1** and **2** were spectroscopically identical to natural FR901512 and FR901516, respectively.

In summary, the structure elucidation and enantioselective total syntheses of FR901512 and FR901516 were accomplished. FR901512 was prepared in 15 steps from the commercially available 2-bromo-4-methylbenzaldehyde in 16.3% overall yield (89% average yield). The catalytic asymmetric Nozaki−Hiyama reactions developed by us proved their applicability and reliability through this work, enabling the concise, efficient, and protecting-group-free enantioselective total syntheses of these new statins.

Acknowledgment. This work is dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday. We thank Drs. Shigehiro Takase, Hidetaka Hatori, and Yuriyo Yamamoto (Astellas Pharmaceutical Co. Ltd.) for kindly donating FR901512 and FR901516. This work was financially supported in part by a Waseda University Grant for Special Research Projects and a Grant-in-Aid for Scientific Research on Priority Areas (Creation of Biologically Functional Molecules (No. 17035082)) from MEXT, Japan. We are also indebted to 21COE "Practical Nano-Chemistry."

Supporting Information Available: Experimental and characterization details (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Hatori, H.; Sato, B.; Sato, I.; Shibata, T.; Tsurumi, Y.; Sakamoto, Y.; K.; Takase, S.; Ueda, H.; Hino, M.; Fujii, T. *J. Antibiot.* **2004**, *57*, 264−270. (b) Hatori, H.; Sato, B.; Sato, I.; Shibata, T.; Ueda, H.; Hino, M.; Fujii, T. *J. Antibiot.* **2004**, *57*, 390−393.

(2) (a) Endo, A. *J. Lipid Res.* **1992**, *33*, 1569−1582. (b) Tobert, J. A. *Nat. Rev. Drug Discovery* **2003**, *2*, 517−526. (c) Gaw, A., Packard, C. J., Shepherd, J., Eds. *Statins: The HMG CoA Reductase Inhibitors in Perspective*, 2nd ed.; Martin Dunitz: London, 2004.

(3) To the best of our knowledge, **1** and **2** are the first naturally occurring statins possessing a tetralin core. Total syntheses of statins incorporating a hexalin core or a octalin core have been reported. For an early review, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909−4951. For a recent total synthesis of (+)-dihydrocompactin, see: Sammakia, T.; Johns, D. M.; Kim, G.; Berliner, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 6504−6505.

(4) (a) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140−1141. (b) Suzuki, T.; Kinoshita, A.; Kawada, H.; Nakada, M. *Synlett* **2003**, 570−572. (c) Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977−2980. (d) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252−255.

(5) Wu, X.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 346−349.

(6) Use of *ent*-**8** afforded *ent*-**5** accordingly.

(7) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(8) Crabtree, R. H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *135*, 395−403.

(9) Hydrogenation of **9** with Wilkinson's catalyst caused dehydration only.

(10) The naphthalene derivative formed only in 3% yield. The reaction in THF provided **10** in 73% yield with 19% of the naphthalene derivative. The basic solvents would reduce the acidity of Crabtree's catalyst.

(11) The acetylation at 0 °C gave **12** in 58% yield (86% brsm).

(12) See Supporting Information.

(13) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672−4685.

(14) (a) Nagata, W.; Hayase, Y. *J. Chem. Soc. C* **1969**, 460−466. (b) Friese, A.; Hell-Momeni, K.; Zündorf, I.; Winckler, T.; Dingermann, T.; Dannhardt, G. *J. Med. Chem.* **2002**, *45*, 1535−1542.

(15) The chiral ligand would induce this stereoselectivity because the reaction of **19** with the racemic ligand **8** showed no selectivity.

(16) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(17) For the precedent synthesis of the β-hydroxy-δ-lactone moiety, see: Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2000**, *65*, 4779−4781.

(18) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469−12486.

JA070812W