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A New Synthetic Route for Construction of the Core of Zaragozic Acids

Haruta Koshimizu, Tomo Baba, Takehiko Yoshimitsu, and Hiroto Nagaoka*

Meiji Pharmaceutical University, Noshio, Kiyose, Tokyo 204-8588, Japan

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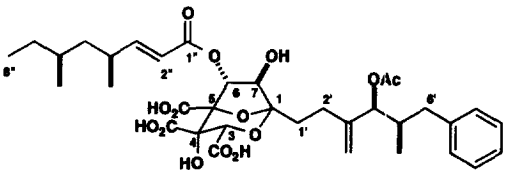
Abstract

A new synthetic route for construction of the core moiety of zaragozic acids from 2,5-furandimethanol (**2**) is described. This synthesis involves highly stereocontrolled transformation of **2** into 7-oxabicyclo[2.2.1]heptane derivative **13**, and the Grob fragmentation-reduction-iodo acetalization reaction (one-pot process) of **13** as a key step to give **16**.

Keywords: Diels-Alder reactions; furans; fragmentation reactions; zaragozic acids

Zaragozic acids (squalestatins), a family of structurally related fungal metabolites isolated from different organisms by three independent groups in 1992, have been found to be potent inhibitors of squalene synthase and farnesyl-protein transferase [1]. These compounds share a common 2,8-dioxabicyclo[3.2.1]octane core and differ in two lipophilic side chains (e.g., zaragozic acid A (**1**)). A number of reports about their synthesis reflected their unique structures and biological activities. Their most characteristic feature is the highly oxygenated hydrophilic core bearing six contiguous chiral carbon atoms. Total syntheses of zaragozic acids have been reported by six groups [2-7], however, various synthetic approaches continue to be investigated [1,8]. In this communication, we would like to report



Zaragozic Acid A (1)

a new synthetic route for construction of the core moiety of zaragozic acids from a furan derivative. This synthesis involves two crucial steps for the regio- and stereoselective introduction of oxygen functionalities into the C(3), C(4), C(6) and C(7) positions [9] on 7-oxabicyclo[2.2.1]hepta-2,5-diene derivative **4** (mp 84-85 °C), and Grob fragmentation-reduction-iodo acetalization reaction of 7-oxabicyclo[2.2.1]heptane **13** to give 2,8-dioxabicyclo[3.2.1]octane ring system **16**.

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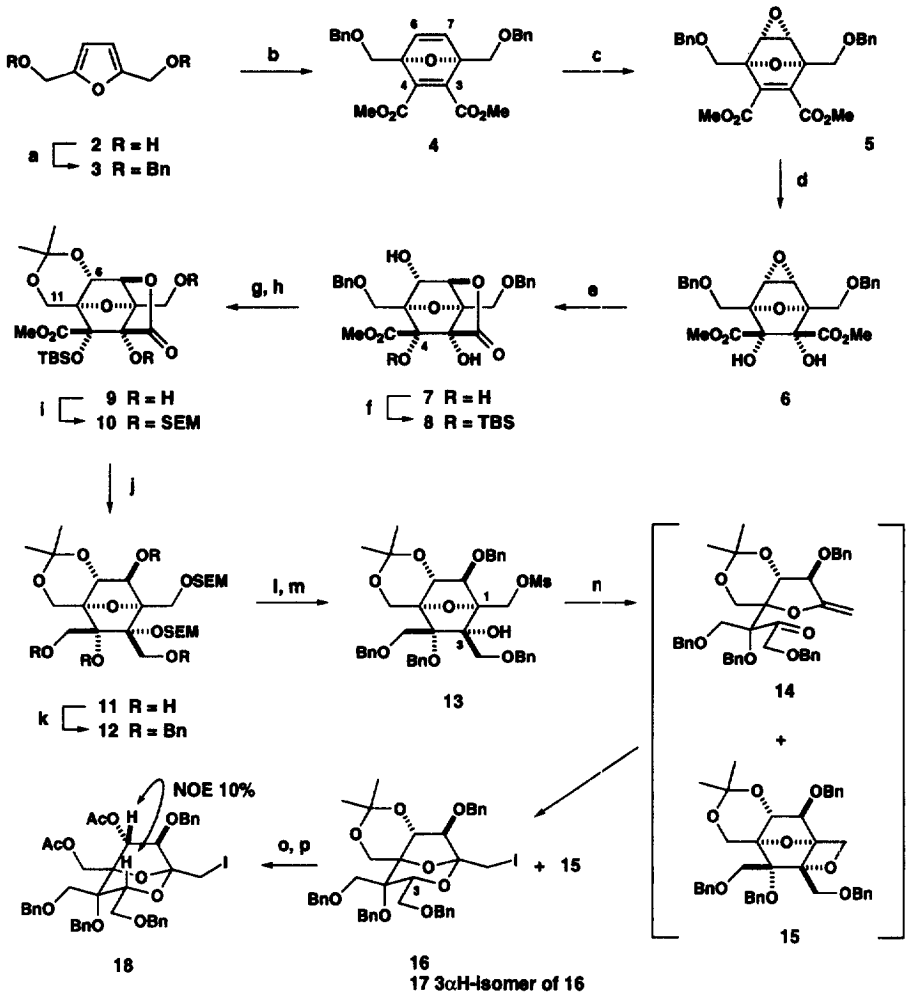
7-Oxabicyclo[2.2.1]hepta-2,5-diene **4** was obtained by Diels-Alder reaction of 2,5-disubstituted furan **3**, easily prepared from 2,5-furandimethanol (**2**), with dimethyl acetylenedicarboxylate in refluxing toluene for 10 h in 83% yield.

Stereoselective introduction of the oxygen functionalities into C(3), C(4), C(6) and C(7) in **4** was achieved as follows. First, the isolated double bond was oxidized with *m*-chloroperoxybenzoic acid (MCPBA) in the presence of 4,4'-thiobis(2-*tert*-butyl-5-methylphenol) [10] in 1,2-dichloroethane at 80°C to predominantly give epoxide **5** (mp 73-74 °C) in 76% yield. Without heating, this epoxidation did not smoothly proceed. The conjugated double bond was then dihydroxylated with osmium tetraoxide to give **6** as a single isomer. The regio- and stereoselectivity during these transformations are explained on the basis of electronic effects and the convex attack of oxidants on the stereochemically rigid 7-oxabicyclo[2.2.1]heptadiene ring system, respectively. The symmetry of all compounds before this process has the potential for asymmetric synthesis of **1** [11]. Acid-catalyzed lactonization of **6**, breaking the symmetry, afforded lactone triol **7** bearing the same relative configuration at C(4), C(5), C(6) and C(7) as that of zaragozic acids.

At this stage, the hydroxyl group at C(3) in **7**, which is necessary for the fragmentation reaction, would be distinguished from the other hydroxyl groups. The most reactive hydroxyl group at C(4) was protected as a *tert*-butyldimethylsilyl (TBS) ether. The benzyl groups in **8** were then removed by hydrogenolysis to give the corresponding tetraol, whose hydroxyl groups at C(6) and C(11) were protected as an acetonide to afford **9**. Hydroxy mesylate **13**, the precursor for the fragmentation reaction, was obtained in a five-step sequence: 1) protection of the two hydroxy groups in **9** as 2-(trimethylsilyl)ethoxymethyl (SEM) ethers; 2) reduction of lactone and ester of **10** with lithium aluminum hydride to give tetraol **11** (TBS was removed during this reduction); 3) protection of all the hydroxy groups in **11** as benzyl ethers; 4) removal of the SEM groups in **12** with tetrabutylammonium fluoride in *N,N'*-dimethylpropyleneurea (DMPU) at 120°C (the resulted diol: mp 161 °C); and 5) selective mesylation of the primary hydroxy group to produce **13**.

Cleavage of the C-C bond between C(1)-C(3) was conducted by treatment of **13** with potassium hexamethyldisilazide (KHMDS) in refluxing dioxane to produce a 3:1 mixture of unstable keto enolether **14** and oxetane **15** [13]. Their ratio was affected by temperature and by solvent; at low temperature (-78°C to 0°C), oxetane **15** was predominantly produced and in refluxing toluene, the ratio of **14** and **15** was 1:4. Without their separation (**14**:**15**=3:1), the mixture, first reduced with sodium borohydride followed by iodine treatment, gave the desired 2,8-dioxabicyclo[3.2.1]octane derivative **16** (30% from **13**) with a small amount of **17** (3αH-isomer of **16**, 7%) and unreactive **15** (13%). The configuration of C3 in **16** was determined based on the NOE experiment of diacetate **18** derived from **16** in two steps. After some attempts to more conveniently obtain compound **16**, it was found that **16** was synthesized from **13** in the following one-pot process which involves a sequential fragmentation-reduction-acetalization reaction. To a hot (100°C) solution of **13** in dioxane was added 1.5 equiv. of KHMDS. After 5 min, the mixture was cooled to 25°C, then methanol and 3 equiv. of sodium borohydride were added. After 1.5 h, 5% aqueous sodium

Scheme 1



Reagents and conditions: **a.** BnBr, NaH, Bu_4NI, THF, 67°C, 2.5 h, 92%; **b.** dimethyl acetylenedicarboxylate, toluene, 110°C, 10 h, 83%; **c.** MCPBA, 4,4'-thiobis(2-*tert*-butyl-5-methylphenol), $ClCH_2CH_2Cl$, 80°C, 40 min, 76%; **d.** OsO_4, NMO, MeCN-H_2O, rt, 30 min, 98%; **e.** *p*-TsOH, MeOH-H_2O, 65°C, 3 h, 95%; **f.** TBSCl, Et_3N, CH_2Cl_2, rt, 3 h, 94%; **g.** H_2, 10% Pd-C, MeOH, rt, 7 h; **h.** acetone, $Me_2C(OMe)_2$, CSA, rt, 2.5 h, 96% (2 steps); **i.** SEMCl, $^iPr_2NEt$, CH_2Cl_2, rt to 40°C, 20 h, 84%; **j.** $LiAlH_4$, THF, 67°C, 2 h, 63%; **k.** BnBr, NaH, Bu_4NI, THF, rt, 38 h, 90%; **l.** TBAF, DMPU, 120°C, 6.5 h, 94%; **m.** MsCl, Et_3N, CH_2Cl_2, rt, 30 min, 85%; **n.** KHMDS, dioxane, 100°C, 5 min / $NaBH_4$, MeOH, 25°C, 1.5 h / I_2, 5% $NaHCO_3$, 25°C, 30 min (**16**: 43%; **17**: 10%; **15**: 18%)(3 steps); **o.** AcOH-H_2O (4:1), 70°C, 5 h; **p.** Ac_2O, pyridine, 50°C, 6 h, 91% (2 steps).

bicarbonate and 1.5 equiv. of I_2 were added, and the mixture was stirred for 30 min at 25°C to furnish **16** in 43% yield together with **17** (10%) and **15** (18%).

In conclusion, suitably functionalized 2,8-dioxabicyclo[3.2.1]octane ring system **16**, the core moiety of zaragozic acids, was synthesized from 2,5-furandimethanol (**2**), which involves highly stereocontrolled synthesis of **13** from **2** and sequential fragmentation-reduction-acetalization reaction of **13**. We are currently investigating the total synthesis of **1** using **16** in this laboratory.

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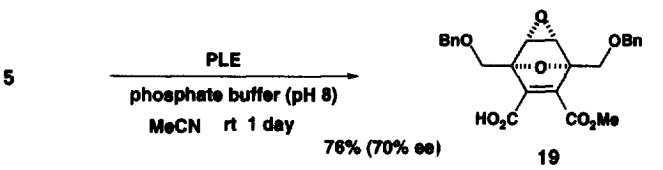

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