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Article

Enantioselective Synthesis of the C(1)-C(6') Subunit of Zaragozic Acid C

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A preparação da subunidade C(1)-C(6') do ácido zaragózigo é descrita. O estereocentro C(5'), contendo uma metila, é instalado através de uma abertura rápida e estereosseletiva de um fenilciclopropil carbinol utilizando o catalisador de Pearlman (1atmosfera de H_2) em metanol contendo 2% de ácido trífilico.

Preparation of the C(1)-C(6') subunit of Zaragozic acid C is described. The C(5') methyl-bearing stereocenter is installed by rapid, regioselective opening of a phenylcyclopropyl carbinol with Pearlman's catalyst (1 atm H_2) in 2% triflic acid/methanol.

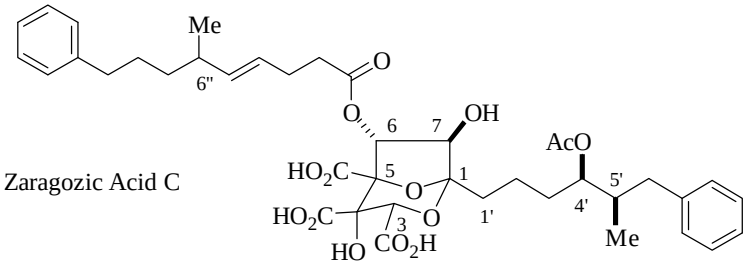
Keywords: *enantioselective synthesis, Zaragozic acid*

Introduction

Zaragozic acid C is a member of a class of mammalian squalene synthetase inhibitors (K_i 29 - 78 pM) isolated by researchers at Merck and Glaxo[1]. These remarkable natural products, which include the zaragozic acids and squalestatins, share a common [3.2.1]-dioxabicyclooctane core but differ exclusively at the C(6) acyl sidechain and C(1) bridgehead subunit[2]. In addition to inhibiting the first committed step in cholesterol biosynthesis[3], a modified zaragozic acid has been reported to inhibit post-translational farnesylation of the *ras* gene product[4]. Thus, these natural products represent important leads in the development of squalene synthetase and farnesyl-protein transferase inhibitors. The great excitement engendered by these natural products has led to numerous studies on their chemistry and pharmacology[5]. Herein, we describe the preparation of the C(1)-C(6') subunit **4** (Scheme 1) of zaragozic acid C[6]. The route described differs considerably from our previously reported syntheses, and documents a novel approach to the construction of propionate subunits exemplified by C(1)-C(6').

In our retrosynthetic analysis, synthon **1** is disconnected into acyl-sidechain **2** and subunits **3** and **4** (Scheme 1). This disconnection strategy incorporates flexibility in the subsequent construction of the C(1)-C(7) bond in zaragozic acid C and related analogs. Central to the synthetic plan for the C(1)-C(6') subunit is the regioselective, reductive opening of cyclopropyl carbinol **5** to afford **4** (Scheme 1). The cis-substituted cyclopropane **5** could be prepared from chiral, allylic alcohol **6**; it was anticipated that **6** could be accessed from the addition product of a 4-pentenylmetal reagent to phenylpropynal[7-10].

In contrast to the reported enantioselective Ti(IV)-catalyzed addition of distilled $MeTi(O^iPr)_3$ to benzaldehyde

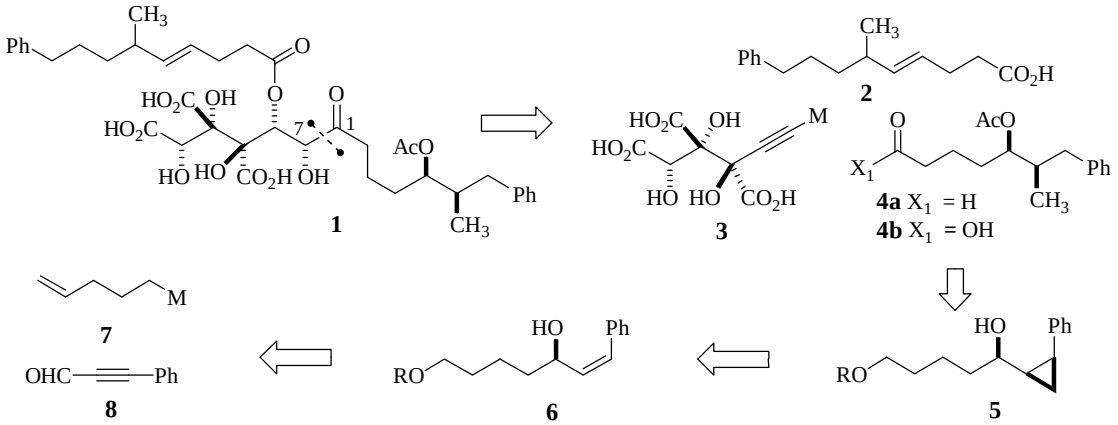


Zaragozic Acid C

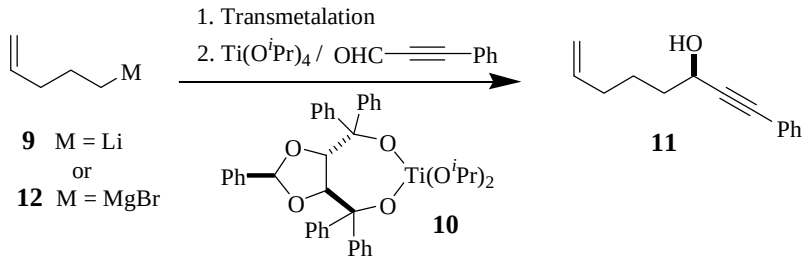
(enantioselection > 98:2),[7b] the derived 4-pentenyltitanium reagent[11] with 20% catalyst **10** afforded **11** in 65% yield and 50% enantiomeric excess[12]. The corresponding alkylzinc reagents were then investigated (Scheme 2). Generation of 4-pentenyllithium **9** (Scheme 2) (1-iodo-4-pentene, 2.0 equiv *tert*-BuLi, Et_2O, 15 min, -78 °C), transmetalation (1 equiv $ZnCl_2$ in Et_2O, 1 h, 23 °C) and filtration of the resulting suspension gave a solution of a 4-pentenylzinc reagent. Use of this reagent in the Ti(O^{i}Pr)$_2$TADDOL-catalyzed addition to phenylpropynal failed to provide the desired adduct. The optimal reaction conditions involved coupling of the 4-pentenylzinc generated from **12** in a manner similar to that described by Seebach[7a]. Preparation of **12** (bromo-4-pentene, Mg, Et_2O, 23 °C, 2 h), transmetalation with zinc chloride (1.0 equiv $ZnCl_2$ in Et_2O, 2 h, 23 °C), and removal of the precipitates formed upon addition of dioxane afforded a solution of 4-pentenylzinc reagent which was used directly in the Ti(O^{i}Pr)$_2$TADDOL-mediated addition (8 h, 0 °C) to give **11** in good yields (70%) and excellent enantioselectivity (94:6). Using this procedure, the addition of 4-pentenylzinc to phenylpropynal has been conducted routinely on large scale (50 mmol) without diminution in yield or enantioselectivity.

Having established the C(4') carbinol stereocenter, **11** was selectively ozonolyzed and the resulting hydroperoxide subjected to reductive work-up ($NaBH_4$) to give diol **13** in 92% yield (Scheme 3). Semihydrogenation of alkyne **13** ($Pd/BaSO_4$, H_2, pyridine, 23 °C) provided allylic alcohol **14** (78%) exclusively. Treatment of **14** with Et_2Zn/CH_2I_2[13] in toluene then furnished cyclopropyl carbinol **15** in 75% yield a single diastereomer as judged by analysis of its ^{1}H NMR spectrum[14].

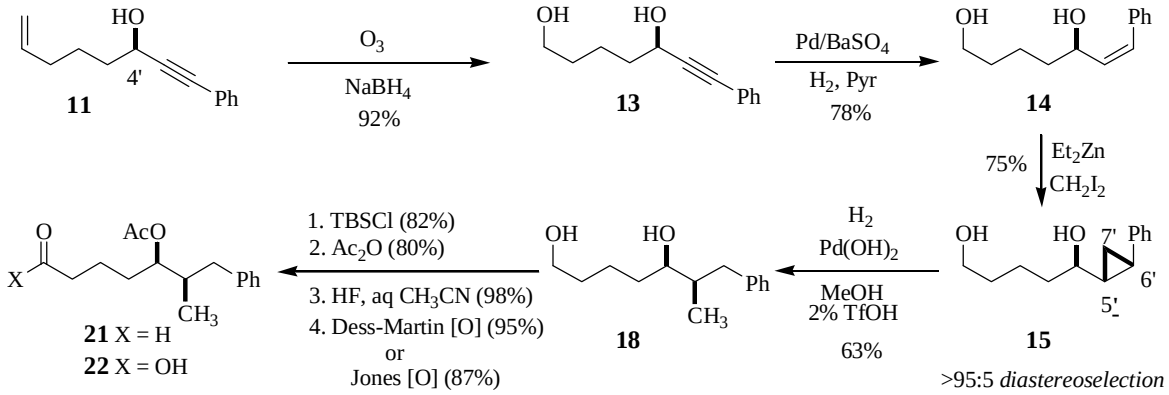
The reductive opening of cyclopropyl carbinol **15** was then addressed. It was expected that conditions could be found to effect regioselective scission of the more accessible C(6')–C(7') cyclopropane bond. Treatment of **15** with $Hg(ClO_4)_2$ in MeOH (23 °C, 12 h)[15] provided an organomercurial intermediate which was then reduced ($LiAlH_4/Et_2O$) to afford a 2:1 diastereomeric mixture of **16** and **17** in only 30% yield (Eq 1). Alternatively, hydrogenolysis of **15** ($Pd(OH)_2/C$, MeOH, 1 atm H_2, 23 °C) proceeded at a slow rate (40% conversion, 24 h) to give a 1:1 mixture of isomeric diols **18** and **19** (Eq 2). Dramatic effects on regioselectivity and rate of the reduction were observed when the reaction was conducted in methanol containing 2% (v/v) triflic acid. Under these strongly acidic conditions, reductive cleavage was complete in 2 h (23 °C) to give **18** as the major product in 63% isolated yield. This result contrasts with the reported cleavage of *cis*-1-methyl-2-phenylcyclopropane with Li in NH_3 at -33 °C which gives exclusively *n*-butylbenzene[16]. It is worth noting that in the absence of $Pd(OH)_2$, treatment of **15** with 2% triflic acid/methanol solution does not yield **17** (Eq 1), but instead produces homoallylic ether **20** at a *slow rate* (40% conversion, 12h) (Eq 3)[17]. Since no intermediates were observed



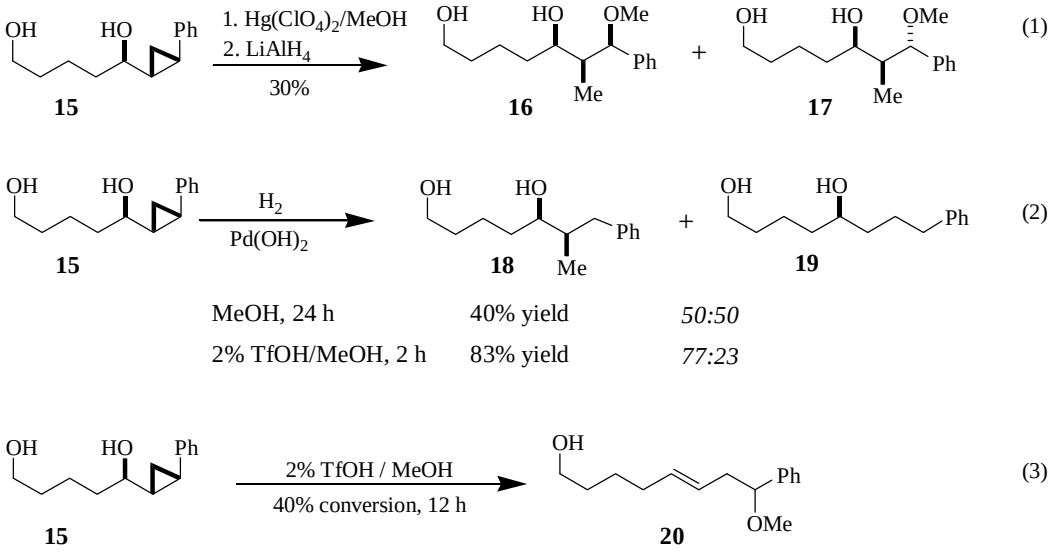
Scheme 1.



Scheme 2.



Scheme 3.



in any of the cyclopropane-opening reactions (Eqs. 2 and 3) an explanation for the combined role of triflic acid, $Pd(OH)_2$, and H_2 awaits further experimentation.

The synthesis was completed (Scheme 3) by selective protection of the primary carbinol in **18** (TBSCl, 82% yield), and acetylation of the resulting secondary alcohol (Ac_2O, DMAP, 80% yield). Desilylation (HF, aq CH_3CN, 98% yield) and subsequent oxidation of the ensuing primary alcohol with the Dess-Martin periodinane furnished aldehyde **21** in 95% yield. Alternatively, oxidation with chromic acid provided the corresponding carboxylic acid **22** in 87% yield (Scheme 3).

In summary, we have prepared the C(1)-C(6') subunit of zaragozic acid C. The regioselective, reductive opening of cyclopropane **15** efficiently incorporates the C(5') methyl-bearing stereocenter. The addition of 2% triflic acid to a suspension of Pearlman's catalyst in methanol (1 atm H_2) effects rapid, regioselective cleavage of a phenylcyclopropyl carbinol.

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12. The enantiomeric purity was assayed by ^{1}H-NMR analysis of the diastereomeric triplet resonances (5.73-major and 5.81-minor ppm in $CDCl_3$) observed for the carbinol proton of the derived Mosher ester (Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512). The absolute configuration was secured by direct correlation to authentic alcohol prepared by (*S*)-Alpine-Borane reduction of the monoprotected ketone corresponding to **13**.
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