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 estereoseletiva de um fenilciclopropil carbinol utilizando o catalisador de Pearlman (1 atmosfera de H2) em metanol contendo 2% de ácido trifílico.

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 H2) 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; 29 - 78 pM) isolated by researchers at Merck and Glaxo. 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. In addition to inhibiting the first committed step in cholesterol biosynthesis, a modified zaragozic acid has been reported to inhibit post-translational farnesylation of the ras gene product. 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. Herein, we describe the preparation of the C(1)-C(6’) subunit 4 (Scheme 1) of zaragozic acid C. 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.

In contrast to the reported enantioselective Ti(IV)-catalyzed addition of distilled MeTi(OiPr)3 to benzaldehyde...
(enantioselection > 98:2), the derived 4-pentenyli-
titanium reagent with 20% catalyst afforded in 65% yield and 50% enantiomeric excess. The corresponding alkylzinc reagents were then investigated (Scheme 2). Generation of 4-pentenyllithium (Scheme 2) (1-iodo-4-pentene, 2.0 equiv tert-BuLi, Et₂O, 15 min, -78 °C), transmetalation (1 equiv ZnCl₂ in Et₂O, 1 h, 23 °C) and filtration of the resulting suspension gave a solution of a 4-pentenyli-
titanium reagent. Use of this reagent in the transmetalation (1 equiv ZnCl₂ in Et₂O, 1 h, 23 °C) and filtration of the resulting suspension gave a solution of a 4-pentenyli-
titanium reagent which was used directly in the formation of 4-pentenyllithium.

The optimal reaction conditions involved coupling of the 4-pentenyli-
titanium reagent in Et₂O, 15 min, -78 °C), and removal of the precipitates then afforded a solution of 4-pentenyllithium. This procedure, the addition of 4-pentenylzinc to phenylpropynal has been conducted routinely on large scale (50 mmol) without diminution in yield or enantiose-
lectivity.

Having established the C(4') carbinol stereocenter, 11 was selectively ozonolyzed and the resulting hydroperox-
ide subjected to reductive work-up (NaBH₄) to give diol in 92% yield (Scheme 3). Semi-hydrogenation of alkynediol yielded the desired adduct. The optimal reaction conditions involved coupling of the 4-pentenyli-
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lectivity.
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$_2$O, DMAP, 80% yield). Desilylation (HF, aq CH$_3$CN, 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 phenyl-cyclopropyl carbinol.

Acknowledgment

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References and Notes


2. Nineteen additional squalestatins containing different alkyl and O-acyl side chains as well as the first report of five related structures containing the 6-deoxy, 7-deoxy, or 6,7-dideoxy dioxabicyclooctanone core have been recently described, see: Blows, W.M.; Foster, G.; Lane, S.J.; Noble, D.; Piercy, J.E.; Sidebottom, P.J.; Webb, G. J. Antibiots. 1994, 47, 740.


10. Throughout this letter TADDOL refers specifically to (4S, 5S)-α,α,α'-pentaphenyl-1,3-dioxolane-4,5-dimethanol 10 (Scheme 2), see: Beck, A.K.; Bastani, B.; Plattner, D.A.; Seebach, D.; Braunschweiger, H.; Gysi, P.; La Vecchia, L. Chimia 1995, 45, 238.

11. The reagent was prepared by treatment of 4-pentenyl-lithium 9 with 1.0 equiv of TiCl(OiPr)3 in Et2O at -78 °C for 1 h; removal of the precipitate by filtration under an inert atmosphere then affords a solution of 4-pentenyl-1-tri-isoproxy-titanium.

12. The enantiomeric purity was assayed by 1H-NMR analysis of the diastereomeric triplet resonances (5.73-major and 5.81-minor ppm in CDCl3) observed for the carbinol proton of the derived Mosher ester for the carbinol proton of the derived Mosher ester.


