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Syntheses of the C-1 alkyl side chains of Zaragozic acids A and C

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Abstract

Asymmetric syntheses of the C-1 alkyl side chains of Zaragozic acids A and C from a common chiral precursor 4 are reported. The stereoselective reduction of unsaturated ketones 8 and 10 is the key step of both syntheses. © 1998 Elsevier Science Ltd. All rights reserved.

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The Zaragozic acids are a family of fungal metabolites which have recently attracted much attention because of their challenging architecture and potential therapeutical use for the treatment of hypercholesterolemia [1]. Two total syntheses of Zaragozic acid A [2,3] and four of Zaragozic acid C [4–7] have already been reported, along with several studies related to the preparation of the bicyclic core [1–11] and the alkyl side chains [1,9,12,13]. We now wish to present a flexible, straightforward, and unified approach to the synthesis of the C-1 alkyl side chains (R¹) of Zaragozic acids A and C.



Since stereoselective reduction of achiral [14-16] and chiral [17] unsaturated ketones with BH₃:SMe₂ in the presence of oxazaborolidine 1 have been extensively studied in our group, it was envisioned that compounds 2 and 3, previously described as suitable protected C-1 alkyl

side chain precursors of Zaragozic acids A and C [12,13], would be available by reduction of proper ketones. According to our previous experience, (S)-1 should be used in the reduction step to obtain the stereochemistry required for 2 and 3, assuming that R would act as the smallest of the two substituents attached to the CO group of the ketones (Scheme 1). These ketones could in turn be obtained from a single Weinreb amide 4.





Chiral Weinreb amide 4 was obtained in a multigram scale by Myers' procedure [18]. Alkylation of the lithium enolate of the (1S,2S)-pseudoephedrine amide 5 with benzyl bromide provided 6 in 82% yield after a single recrystallisation. Acidic hydrolysis of 6 gave (R)-2-methyl-3-phenylpropanoic acid, 7 (97% ee by GC), which was readily converted into the desired amide 4.¹ The overall yield for the three-step sequence leading to 4 was 60%.



Scheme 2. (a) LDA (2 equiv.), LiCl, THF; BnBr, 0 °C, 45 min. (b) H_2SO_4 -dioxane, reflux, 1 h. (c) EDC-HCl MeONHMe·HCl, Et₃N, DMAP cat., CH₂Cl₂, rt, 2 days.

Having in hand Weinreb amide 4, our efforts were focussed on the synthesis of 2 by stereoselective reduction of enone 8.

Addition of the TBS ether of 3-lithio-3-butenol, 9, to amide 4 afforded the desired enone 8^2

¹ Colorless oil. $R_J = 0.47$ (1:1 hexane/AcOEt). $[\alpha]_D = 50.3$ (c 1.75, CHCl₃). IR (film) 1665 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.10 (5H, m), 3.46 (3H, s), 3.20-3.10 (1H, m), 3.12 (3H, s), 3.02 (1H, dd, J = 13.1, 7.8), 2.60 (1H, dd, J = 13.1, 6.7), 1.14 (3H, d, J = 6.7). ¹³C NMR (CDCl₃, 75.4 MHz) δ 177.0, 140.2, 129.0, 128.2, 126.1, 61.2, 39.8, 37.5, 32.1, 17.3. EI-HRMS calculated for C₁₂H₁₇NO₂ 207.1259; found 207.1258.

² Colorless oil. $R_f = 0.62$ (CH₂Cl₂). $[\alpha]_D - 32.9$ (*c* 2.39, CHCl₃). IR (film) 1665 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.10 (5H, m), 5.96 (1H, br s), 5.77 (1H, br s), 3.63-3.53 (2H, m), 3.53-3.43 (1H, m), 2.99 (1H, dd, J = 13.6, 6.6), 2.56 (1H, dd, J = 13.6, 7.8), 2.50-2.40 (2H, m), 1.07 (3H, d, J = 6.9), 0.85 (9H, s), 0.00 (6H, s). ¹³C NMR (CDCl₃, 75.4 MHz) δ 205.1, 145.1, 140.0, 129.0, 128.3, 126.1, 125.6, 61.8, 41.8, 39.7, 34.8, 25.9, 15.25, 17.6, -5.3. CI-MS (NH₃) m/z: [M+1]+ 333 (100), [M+18]+ 350 (22).

in excellent yield (94%). Reduction of **8** using oxazaborolidine (S)-1 proved to be troublesome. The steric hindrance of the carbonyl precluded its reduction under the standard conditions: conversion was very low when 1 mmol of (S)-1 was used and long reaction times led to products derived from the hydroboration of the double bond.³ Eventually, reduction of enone **8** was accomplished with an excess of BH₃:SMe₂ and (S)-1 (see Scheme 3) in 70% yield and 65% de, recovering 20% of starting material. The stereochemistry of the major component of the alcohol mixture was established by the Kakisawa method [22].



Scheme 3. (a) THF, -20 °C, 20 min. (b) 1.5 mmol BH3:SMe2, 3 mmol (S)-1, THF, 0 °C, 30 min.

We then turned our attention to the synthesis of 3, a precursor of the C-1 alkyl side chain of Zaragozic acid C.

Addition of TMSC=CLi to amide 4 furnished ketone 10^4 in 86% yield along with a small amount of the desilylated ynone (5%). Borane-mediated reduction of 10 using 0.2 equiv. of oxazaborolidine (S)-1 afforded propargylic alcohol 11 (70%, 91% de); stoichiometric amounts of (S)-1 increased the chemical yield (80%, 92% de).



Scheme 4. (a) THF, $-78 \degree$ C to $0\degree$ C, 30 min. (b) 1 mmol BH₃:SMe₂, 0.2 mmol (S)-1, THF, $0\degree$ C, 30 min. (c) TBSOTf, 2,6-lutidine, CH₂Cl₂. $0\degree$ C, 15 min. (d) K₂CO₃, wet MeOH. 3 h. (e) *n*-BuLi, THF, $-78\degree$ C, 45 min; (CH₂O)_n, $-78\degree$ C to rt, 4 h. (f) H₂, 10% Pt/C, AcOEt, 1 h.

³ It is worth noting that alternative chiral reagents capable of reducing unsaturated ketones, such as oxazaborolidines arising from proline [19] and 1,2-diphenyl-2-aminocthanol [20], as well as Noyori's hydride [21], were also investigated, with similar or worse results.

⁴ Colorless oil. $R_f = 0.45$ (1:1 hexane/CH₂Cl₂). $[\alpha]_D - 27.0$ (*c* 2.06, CHCl₃). IR (film) 2150, 1680 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.10 (5H, m), 3.17 (1H, dd, J = 13.7, 6.0), 2.90-2.80 (1H, m), 2.63 (1H, dd, J = 13.7, 8.2), 1.15 (3H, d, J = 7.2), 0.25 (9H, s) ¹³C NMR (CDCl₃, 75.4 MHz) δ 190.8, 139.0, 129.0, 128.4, 126.3, 101.2, 99.25, 50.1, 38.5, 15.6, -0.8. CI-MS (NH₃) *m/z*: [M+1]+ 245 (3), [M+18]+ 262 (100).

Protection of the propargylic alcohol 11 with TBSOTf and desilylation with K₂CO₃/MeOH gave alkyne 12 in 96% overall yield.⁵ Treatment of alkyne 12 with BuLi and (CH₂O)_n followed by catalytic hydrogenation (10% Pt/C, AcOEt) provided the desired precursor 3, $[\alpha]_D = +12.15$ (*c* 2.1, CHCl₃) (lit. [12], $[\alpha]_D = +12.2$ (*c* 2.15, CHCl₃)) in 82% yield (Scheme 4).

In summary, we have disclosed a very efficient synthetic sequence for the preparation of the C-1 alkyl side chains of Zaragozic acids A and C. The strategy takes advantage of the highly stereoselective reduction of unsaturated ketones achieved with a phenylglycine-derived oxazaborolidine. Moreover, both ketones are readily available from the same Weinreb amide.

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⁵ Parallel reduction of the desilylated ketone derived from 10 with BH_3 : SMe_2 in the presence of (S)-1 (1 mmol) gave the corresponding propargylic alcohol (73%, 88% de), which was also converted into 12 with TBSOTf (94%).