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

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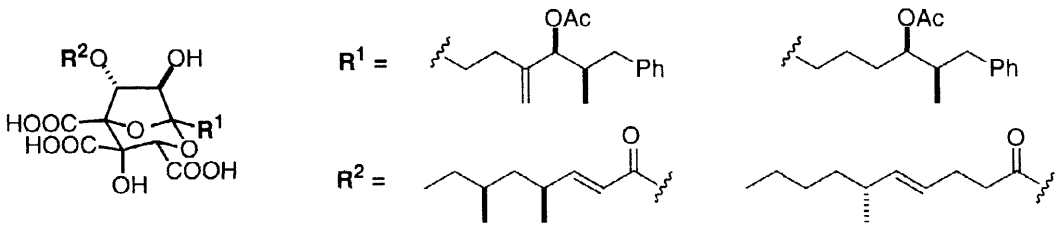
Abstract

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.

Keywords: Natural products; Zaragozic acid; Asymmetric synthesis; Reduction

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 (R^1) of Zaragozic acids A and C.



Zaragozic acid A **Zaragozic acid C**

Since stereoselective reduction of achiral [14–16] and chiral [17] unsaturated ketones with BH_3:SMe_2 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

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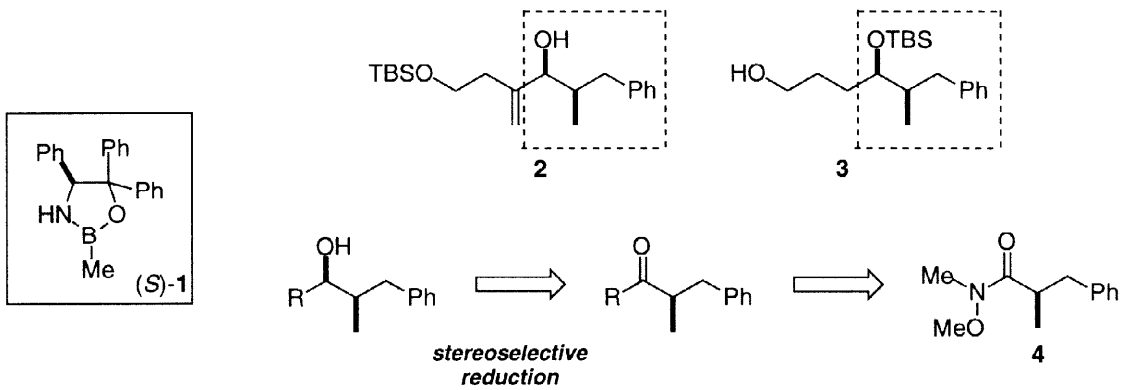
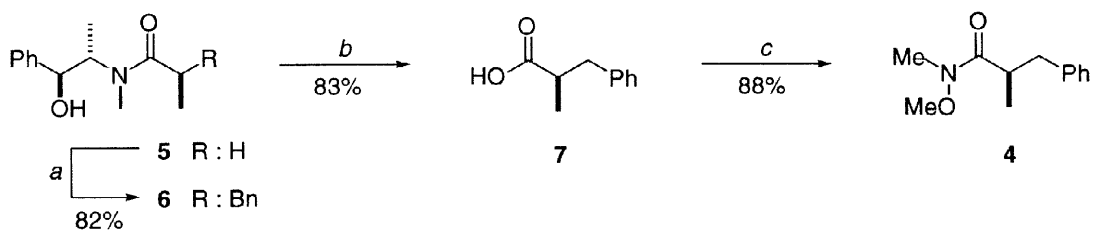
side chain precursors of Zaragozic acids A and C [12,13], would be available by reduction of proper ketones. According to our previous experience, (*S*)-**1** should be used in the reduction step to obtain the stereochemistry required for **2** and **3**, assuming that R would act as the smallest of 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**.



Scheme 1

Chiral Weinreb amide **4** was obtained in a multigram scale by Myers' procedure [18]. Alkylation of the lithium enolate of the (1*S*,2*S*)-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, Et_3N, DMAP cat., CH_2Cl_2, 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]

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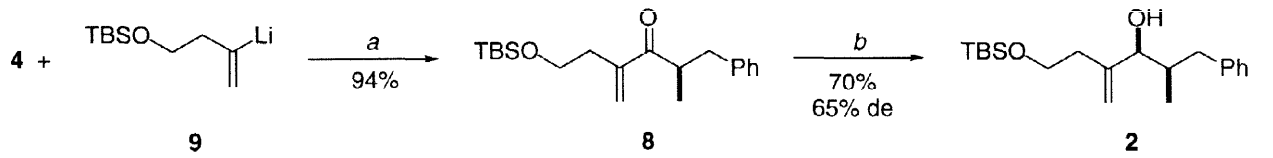
[1] Colorless oil. R_f = 0.47 (1:1 hexane/AcOEt). $[\alpha]_D$ –50.3 (*c* 1.75, $CHCl_3$). IR (film) 1665 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.10 (5H, m), 3.46 (3H, s), 3.20-3.10 (1H, m), 3.12 (3H, s), 3.02 (1H, dd, *J* = 13.1, 7.8), 2.60 (1H, dd, *J* = 13.1, 6.7), 1.14 (3H, d, *J* = 6.7). ^{13}C NMR ($CDCl_3$, 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 $C_{12}H_{17}NO_2$ 207.1259; found 207.1258.

[2] Colorless oil. R_f = 0.62 (CH_2Cl_2). $[\alpha]_D$ –32.9 (*c* 2.39, $CHCl_3$). IR (film) 1665 cm^{-1}. ^1H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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 (NH_3) *m/z*: $[M+1]^+$ 333 (100), $[M+18]^+$ 350 (22).

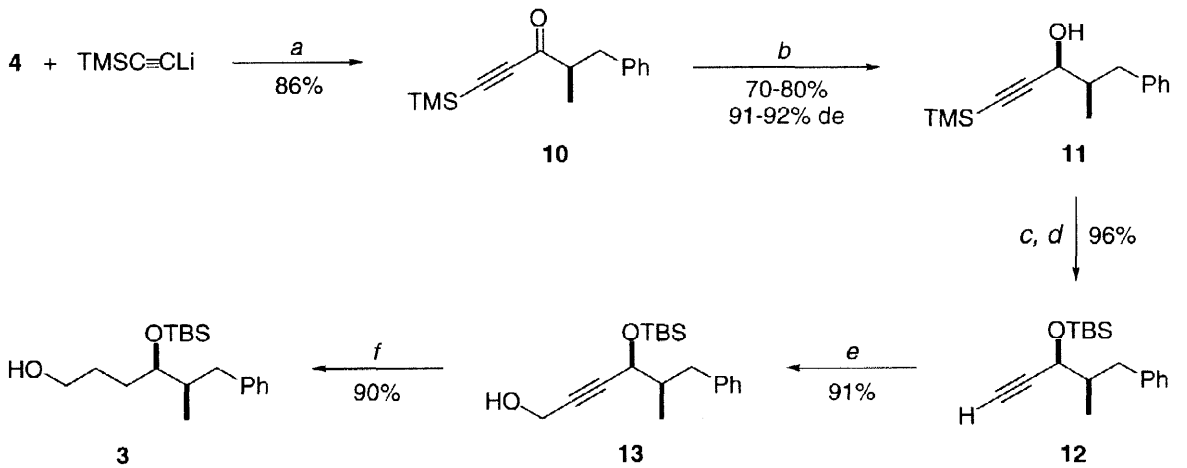
in excellent yield (94%). Reduction of **8** using oxazaborolidine (*S*)-**1** proved to be troublesome. The steric hindrance of the carbonyl precluded its reduction under the standard conditions: conversion was very low when 1 mmol of (*S*)-**1** was used and long reaction times led to products derived from the hydroboration of the double bond.[3] Eventually, reduction of enone **8** was accomplished with an excess of BH_3:SMe_2 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 BH_3:SMe_2, 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 °C to 0 °C, 30 min. (*b*) 1 mmol BH_3:SMe_2, 0.2 mmol (*S*)-**1**, THF, 0 °C, 30 min. (*c*) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min. (*d*) K_2CO_3, wet MeOH, 3 h. (*e*) *n*-BuLi, THF, –78 °C, 45 min; $(CH_2O)_n$, –78 °C to rt, 4 h. (*f*) H_2, 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-aminoethanol [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/CH_2Cl_2). $[\alpha]_D$ –27.0 (*c* 2.06, $CHCl_3$). IR (film) 2150, 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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 (NH_3) *m/z*: [M+1]+ 245 (3), [M+18]+ 262 (100).

Protection of the propargylic alcohol **11** with TBSOTf and desilylation with K_2CO_3/MeOH gave alkyne **12** in 96% overall yield.[5] Treatment of alkyne **12** with BuLi and $(CH_2O)_n$ followed by catalytic hydrogenation (10% Pt/C, AcOEt) provided the desired precursor **3**, $[\alpha]_D = +12.15$ (*c* 2.1, $CHCl_3$) (lit. [12], $[\alpha]_D = +12.2$ (*c* 2.15, $CHCl_3$)) 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.

Acknowledgments

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References

[1] Nadin A, Nicolaou KC. Angew. Chem. Int. Ed. Engl. 1996;35:1622-1656.

[2] Nicolaou KC, Yue EW, La Greca S, Nadin A, Yang Z, Leresche JE, Tsuri T, Naniwa Y, De Riccardis F. Chem. Eur. J. 1995;1:467-494.

[3] Stoermer D, Caron S, Heathcock CH. J. Org. Chem. 1996;61:9115-9125.

[4] Carreira EM, Du Bois J. J. Am. Chem. Soc. 1995;117:8106-8125.

[5] Evans DA, Barrow JC, Leighton JL, Robichaud AJ, Sefkow M. J. Am. Chem. Soc. 1994;116:12111-12112.

[6] Sato H, Nakamura S, Watanabe N, Hashimoto S. Synlett 1997;451-454

[7] Armstrong A, Jones LH, Barsanti PA. Tetrahedron Lett. 1998;39:3337-3340.

[8] Hodgson DM, Bailey JM, Harrison T. Tetrahedron Lett. 1996;37:4623-4626.

[9] Paterson I, Feβner K, Finlay RMV. Tetrahedron Lett. 1997;38:4301-4304.

[10] Hegde SG, Myles DC. Tetrahedron Lett. 1997;38:4329-4332.

[11] Kataoka O, Kitagaki S, Watanabe N, Kobayashi J, Nakamura S, Shiro M, Hashimoto S. Tetrahedron Lett. 1998;39:2371-2374.

[12] Robichaud AJ, Berger GD, Evans DA. Tetrahedron Lett. 1993;34:8403-8406.

[13] Parsons JG, Rizzacasa MA. Tetrahedron Lett. 1994;35:8263-8266.

[14] Bach J, Berenguer R, Farras J, Garcia J, Meseguer J, Vilarrasa J. Tetrahedron: Asymmetry 1995;6:2683-2686.

[15] Bach J, Berenguer R, Garcia J, Loscertales T, Vilarrasa J. J. Org. Chem 1996;61:9021-9025.

[16] Berenguer R, Cavero M, Garcia J, Muñoz M. Tetrahedron Lett. 1998;39:2183-2186.

[17] Bach J, Garcia J. Preceding communication in this issue.

[18] Myers AG, Yang BH, Chen H, Gleason JL. J. Am. Chem. Soc. 1994;116:9361-9362

[19] Corey EJ, Baksi RK, Shibata S. J. Am. Chem. Soc. 1987;109:5551-5553.

[20] Quallich GJ, Blake JF, Woodal TM. J. Am. Chem. Soc. 1994;116:8516-8525.

[21] Noyori R, Tomino I, Yamada M, Nishizawa M. J. Am. Chem. Soc. 1984;106:6717-6725.

[22] Ohtani I, Kusumi T, Kashman Y, Kakisawa H. J. Am. Chem. Soc. 1991;113:4092-4096.

[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%).