A Concise and Enantioselective Synthesis of a C-6 O-Acyl Side Chain Equivalent of Zaragozic Acid A

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An optically pure C-6 O-acetyl side chain equivalent of zaragozic acid A, (2E,4S,6S)-4,6-dimethyl-2-octenoic acid, which features a 1,3-syn-dimethyl-substituted carbon chain, has been readily synthesized from (S)-2-methylbutanal using a combination of the Evans aldol reaction and the Ireland deoxygenation method.

Key words zaragozic acid A; acyl side chain; Evans aldol reaction; Ireland deoxygenation method

Zaragozic acids and squalestatins, recently isolated from various fungal cultures by respective researchers at Merck and Glaxo, have been shown to be picomolar competitive inhibitors of squalene synthase. In addition to their therapeutic potential for the treatment of hypercholesterolemia, these natural products possess a novel, densely oxygenated 4,6,7,8-tetrahydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core, differing only in regard to the nature of the C1 alkyl and C6 O-acyl side chains. It is therefore not surprising that the zaragozic acids (squalestatins) have elicited considerable attention from numerous synthetic chemists. The Nicolaou and Heathcock groups have accomplished the total synthesis of zaragozic acid A (squalestatin S1), while efforts of the groups of Carreira, Evans, and Armstrong, as well as ours, have culminated in the total synthesis of zaragozic acid C. Accordingly, our attention has now been turned to the total synthesis of zaragozic acid A. Herein we wish to report the easy and efficient access to (2E,4S,6S)-4,6-dimethyl-2-octenoic acid (1), the C-6 O-acyl side chain equivalent.

The α,β-unsaturated acid 1 was reported to be elaborated from (2S,4S)-2,4-dimethyl-1-hexanol (2) via oxidation and Wittig-type olefination. Thus, alcohol 2 became a focal intermediate which features a minimum carbon chain with skip 1,3-syn-dimethyl stereogenic centers. Of a variety of approaches considered for the enantioselective synthesis of 2, a route proceeding through the asymmetric alkylation of a chiral propionate-derived enolate with readily available (S)-2-methyl-1-iodobutane (3) was deemed highly attractive from the standpoint of conciseness and convergency. In this context, it has been well documented that Evans’ chiral oxazolidinone-derived carboximide enolates do not possess sufficient nucleophilicity toward β-branched alkyl halides such as 3. Although Decicco and Grover recently demonstrated that the enolates did react with β-branched alkyl triflates to give all four possible diastereomers with excellent stereocontrol, a large excess of the electrophile (25 eq) was required in the reaction. In the synthesis of (+)-bourgeanic acid, White and Johnson reported that asymmetric alkylation of an enolate derived from (S)-prolinol N-propionanamide with 3 gave a 17:1 mixture of the adducts with the desired syn product as the major constituent, which, after saponification, was purified to optical homogeneity by recrystallization of the salt of the carboxylic acid and cinchonidine. In the synthesis of zaragozic acid A, Nicolaou and co-workers synthesized 2 via (2S,4S)-2,4-dimethyl-1-hexanal (4) of 92% de, which was obtained by the alkylation of Enders’ chiral hydrazono enolate with 3. In the same context, Heathcock and co-workers who were cognizant of the shortcoming of Evans’ chiral oxazolidinone-derived carboximide enolates, as described above, addressed an alternative alkylation and found access to optically pure 2; methylation of the imide prepared from Evans’ chiral oxazolidinone and (S)-4-methylhexanoic acid, derived from 3, provided the diastereomers in a 17:1 ratio of syn to anti isomers, from which the syn isomer was separated by flash chromatography. Thus, the asymmetric alkylation approach to optically pure 1, employing well-established chiral auxiliaries, has suffered from tedious separation of the diastereomers.

Departing from the alkylation route, we then directed our attention to an approach capitalizing on the aldol reaction between chiral N-propionyl-2-oxazolidinone 5 and (S)-2-methylbutanal (6) followed by deoxygenation, because the Evans aldol reaction provides the most reliable means for the controlled creation of vicinal syn stereogenic centers, irrespective of the absolute configuration of α-branched aldehydes. Indeed, condensation of the boron enolate derived from 5 with 6 provided the crystalline syn aldol adduct 7 as a single diastereomer in 78% yield, the homochirality of which was confirmed by 500 MHz 1H- and 100 MHz 13C-NMR. Removal of the oxazolidinone auxiliary from 7 by reduction with lithium borohydride, followed by selective silylation of the resultant diol, furnished the secondary alcohol 8 in 84% yield. While a number of methods for deoxygenation were reported, we initially explored a combination of mesylation formation and reduction with lithium aluminium hydride. However, reduction of the mesylate was found not to take place even under harsh conditions, which might be accounted for by steric hindrance due to a syn/syn relationship.

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in the C2–C4 stereotriad. We then chose the Ireland deoxygenation procedure\(^{23}\) in preference to the Barton–McCombie reaction,\(^{20}\) because the latter method has demonstrated the formation of toxic tin byproducts difficult to remove completely from the product. Treatment of the alcohol 8 with \(n\)-butyllithium, followed by condensation with \(N,N,N',N'\)-tetramethylphosphorodiamic acid chloride, gave the corresponding phosphorodiimide 9 in 80% yield, which was found to be more stable than the corresponding diethyl phosphate and is easily handled. The reduction of 9 with lithium in ethylamine at 0 °C proceeded cleanly to give a deoxygenated product, which, upon desilylation, produced the alcohol 2, \([\alpha]_D^{27} -4.56^\circ \ (c=1.64, \text{CHCl}_3) \) [lit.\(^{10}\) \([\alpha]_D^{27} -4.5^\circ \ (c=1.60, \text{CHCl}_3)\)], in 81% overall yield. Oxidation of 2 under standard Swern conditions, followed by immediate condensation with Ph\(_3\)P under standard Swern conditions, followed by immediate oxidation of the alcohol with 2,4-dimethylhexan-3-ol (8) afforded exclusively the (E)-\(\alpha,\beta\)-unsaturated ester 10 in 84% yield. Finally, the saponification of 10 furnished the target acid 1, \([\alpha]_D^{27} +58.6^\circ \) (neat) [lit.\(^{27}\) \([\alpha]_D^{27} +55^\circ \) (neat)], in 98% yield, which exhibited identical spectroscopic data with those reported for a sample by the degradation of zaragozic acid A.

In summary, we have achieved the synthesis of an optically pure C-6 \(\alpha\)-acyl side chain equivalent of zaragozic acid A with an overall yield of 35% for the nine-step sequence. The present protocol, employing a combination of an Evans aldol reaction and an Ireland deoxygenation method, has the advantages of providing a practical entry to 1,3-dimethyl-substituted carbon chains with virtually complete enantio- and diastereoccontrol, and thus represents a potent alternative to an asymmetric alkylation strategy.\(^{17}\)

**Experimental**

Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. NMR spectra were measured with JEOL JNM-EX270 (\(1^H\) at 67.8 MHz), JEOL JNM-AL400 (\(1^H\) at 100 MHz) or Bruker ARX-500 spectrometers (\(1^H\) at 500 MHz), with tetramethylsilane (\(0.0\) ppm, \(1^H\)) or chloroform-\(d_2\) (\(\delta 7.70, \ 1^C\)) as internal standards. Infrared spectra were recorded on a Jasco FT/IR-5300 spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Electron impact (EI) mass spectra were obtained on a JEOL DX-303 spectrometer, operating with an ionization energy of 70 eV. FAB-MS were obtained on a JEOL JMS-HX100 spectrometer. Column chromatography was performed on Merck silica gel 60 (70—230 mesh). Bulb-to-bulb distillation was performed using a Büchi Kugelrohr apparatus, and the oven temperature is recorded as the boiling point. Di-\(n\)-butylboron triflate\(^{29}\) and \((S)-4\)-benzyl-3-propionyl-2-oxazolidinone \((S)\) \(^{50}\) were prepared according to literature procedures.

**Chart 1**

\[(\text{2.5S,3R,4S,4'R,3'-Hydroxy-2',4'-dimethylhexanoyl-4-benzyl-2-oxazolidinone})\]

To a stirred solution of 5 (12.4 g, 53 mmol) in CH\(_2\)Cl\(_2\) (130 ml) at 0 °C was added di-\(n\)-butylboron triflate (18.0 ml, 71 mmol), followed by triethylamine (12.0 ml, 86 mmol). After 0.5 h of stirring at 0 °C, the mixture was cooled to −78 °C and a solution of (S)-2-methylbutanal (6) (5.9 g, 69 mmol) in CH\(_2\)Cl\(_2\) (15 ml) was added. The mixture was stirred at −78 °C for 1 h, and then at 0 °C for another 2 h. The reaction was quenched with pH 7 phosphate buffer (60 ml), and the mixture was diluted with MeOH (100 ml). A 2:1 mixture of MeOH–30% aqueous H\(_2\)O (200 ml) was added at 0 °C, and the whole was stirred vigorously for 1 h. After the volatile elements were removed in vacuo, the residue was diluted with EtOAc (60 ml) and the layers were separated. The organic layer was washed successively with saturated aqueous NaHCO\(_3\) (40 ml), 10% aqueous Na\(_2\)SO\(_4\) (40 ml) and brine (2 × 10 ml), then dried over anhydrous Na\(_2\)SO\(_4\). Filtration and evaporation in vacuo furnished the crude product (18.1 g), which was purified by column chromatography (silica gel 50 g, 5 : 1 hexane–EtOAc) to give aldox adduct 7 (13.2 g, 78%) as colorless needles, mp 90.0—90.5 °C (hexane), \([\alpha]_D^{27} +43.1^\circ \ (c=1.07, \text{CHCl}_3)\). IR (Nujol) cm\(^{-1}\) : 3522, 2924, 1777, 1692, 1456, 1300. \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) : 0.91 (3H, t, \(J=7.3\) Hz, CH\(_3\)), 0.98 (3H, d, \(J=6.5\) Hz, CH\(_3\)), 1.14 (1H, m, CH), 1.27 (3H, d, \(J=7.0\) Hz, CH\(_2\)), 1.43—1.56 (2H, m, CH\(_2\)), 1.55 (1H, d, \(J=3.3\) Hz, CH), 1.79 (1H, dd, \(J=9.5, 13.4\) Hz, PhCH\(_3\)), 3.26 (1H, dd, \(J=3.3, 13.4\) Hz, PhCH\(_2\)). EI–MS \(m/z\) : 319 (M\(^+\), 10), 301 (8), 262 (22), 244 (33), 178 (100), 143 (26). HR-EI–MS \(m/z\) : 319.1757 (Calcd for C\(_{18}\)H\(_{25}\)NO\(_4\): 319.1784).

To a solution of zaragozic acid A with an overall yield of 35% for the nine-step sequence. The present protocol, employing a combination of an Evans aldol reaction and an Ireland deoxygenation method, has the advantages of providing a practical entry to 1,3-dimethyl-substituted carbon chains with virtually complete enantio- and diastereoccontrol, and thus represents a potent alternative to an asymmetric alkylation strategy.\(^{17}\)
column chromatography (silica gel 150 g, 60 : 1 CH₂Cl₂–MeOH) to give a colorless oil, [α]D₁⁰ +56.6° (neat, d24 = 0.954) [lit.²⁷] [α]D₂⁰ +55° (neat). IR (film) cm⁻¹: 2963, 1698, 1420, 1287, 988. 1H-NMR (CDCl₃) δ: 0.83—0.88 (6H, m, CH₃), 3.51 (1H, dd, J₅,₆ = 11.1, 5.5 Hz, CH₂), 3.43 (1H, dd, J₅,₆ = 5.5, 5.7 Hz, OCH₂), 6.94 (1H, dd, J = 8.4, 15.6 Hz, CH₃CO). 13C-NMR (CDCl₃) δ: 11.1 (CH₃), 31.9 (CH₃), 43.4 (CH₃), 60.1 (CH). 119.6 (CH), 154.7 (CH), 166.9 (C=O). EI-MS m/z (rel. int. %): 198 (M⁺, 2), 169 (30), 153 (30), 141 (44), 69 (100). HR-EL-MS m/z: 198.1626 (Calcd for C₉H₁₈O₂: 198.1620).

2(4E,5S,6S)-4,6-Dimethyl-2-oxo-2-tetradecane (4) Liquid hydroxide monoxide (1.28 g, 31 mmol) was added to a solution of ester 10 (1.98 g, 10.0 mmol) in 3 : 1 MeOH–H₂O (20 ml) at room temperature. After 12 h of stirring at room temperature, the solvent was evaporated in vacuo. The residue was dissolved in H₂O (15 ml) and the whole was washed with hexane (2×10 ml). The aqueous layer was acidified with 10% aqueous HCl (20 ml) and was extracted with EtOAc (20 ml). The organic layer was washed with 1N aqueous HCl (30 ml), saturated aqueous NaHCO₃ (20 ml), and was extracted with 10 : 1 CH₂Cl₂–MeOH (20 ml). The layers were separated and the aqueous layer was washed with brine (2×10 ml) and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo provided the crude product (5.23 g), which was purified by column chromatography (silica gel 150 g, 60 : 1 CH₂Cl₂–MeOH) to give a colorless oil, [α]D₁⁰ +55° (neat). IR (film) cm⁻¹: 3327, 2961, 1426, 1379, 1034. 1H-NMR (CDCl₃) δ: 0.86 (3H, t, J₅,₆ = 7.4 Hz, CH₃), 0.58 (1H, t, J₅,₆ = 6.6 Hz, CH₃CO), 3.16 (1H, d, J = 6.6 Hz, CH₃), 1.72 (CH₂), 1.38 (1H, d, J = 6.6 Hz, 10.5 Hz, CH₃CO), 3.51 (1H, dd, J = 5.1, 10.5 Hz, CH₃). 13C-NMR (CDCl₃) δ: 11.2 (CH₃), 17.3 (CH₃), 19.8 (CH₂), 29.0 (CH₃), 31.6 (CH₃), 33.1 (CH), 40.6 (CH₂), 68.2 (CH₂). EI-MS m/z (rel. int. %): 113 (M⁺–CH₃, 15), 83 (77), 80 (100). HR-EL-MS m/z: 113.1334 (Calcd for C₇H₁₈O: 113.1330). 1H-NMR (CDCl₃) δ: 1.09 (1H, m, CH₃CH₂), 2.06 (1H, m, CH₃CH₂CO), 2.12 (1H, m, CH₃CH₂O), 3.12 (1H, d, J = 6.6 Hz, CH₃CO), 3.51 (1H, dd, J = 5.1, 10.5 Hz, CH₃). 13C-NMR (CDCl₃) δ: 12.1 (CH₃), 17.3 (CH₃), 19.8 (CH₂), 29.0 (CH₃), 31.6 (CH₃), 33.1 (CH), 40.6 (CH₂), 68.2 (CH₂). EI-MS m/z (rel. int. %): 113 (M⁺–CH₃, 15), 83 (77), 80 (100). HR-EL-MS m/z: 113.1334 (Calcd for C₇H₁₈O: 113.1330).

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References and Notes
20) A similar approach to skip 1,3-dimethyl arrays based on the combinational use of Evans aldol reaction and Barton–McCombie deoxygenation has been adopted by Yamada and co-workers, culminating in a total synthesis of doliculide. Ishiwata H., Sone H., Kigoshi H., Yamada K., *Tetrahedron*, 50, 12853—12882 (1994).