Synthesis of (+)-Zaragozic Acid C

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Contribution No. 8980
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Received August 31, 1994

The zaragozic acids and the squalestatins constitute a class of mammalian squalene synthetase inhibitors (K_i = 29−78 pM) which have been recently isolated by research groups at Merck[1] and Glaxo.[2] These natural products share a common [3.2.1]-dioxabicyclooctane core, differing exclusively at the C(1) alkyl and C(6) acyl side chains. The structural and stereochemical complexities of these compounds coupled with their potential use as therapeutic agents for the treatment of hypercholesterolemia make the zaragozic acids important targets for synthesis.[3,4] This communication describes the first synthesis of (+)-zaragozic acid C, **1**.

Preparation of the dioxabicyclooctane core commenced with the condensation of D-erythronic γ-lactone **2** with Me_2NH (MeOH, 0 °C), affording the derived trihydroxybutyramide, which was protected to give **3** (Scheme 1).[5] Addition of 1-ethoxyvinyllithium (ethyl vinyl ether, ^{t}BuLi) to amide **3** yielded an intermediate ketone which underwent chelate-controlled addition with TMSC≡CMgBr to give a 20:1 mixture of alcohol diastereomers **4** as determined by ^{1}H NMR.[6] Vinyl ether **4** was converted to diol **6** following ozonolysis, ester reduction ($NaBH_4$, MeOH), and alkyne desilylation (K_2CO_3, MeOH). Differential protection of the primary and tertiary alcohols with ^{t}BuMe$_2$SiCl and Me_3SiCl, respectively, furnished **7**. Intermediate **7** has been routinely prepared on a 30−40 g scale.

Initial attempts to couple lithium acetylide **8** with aldehyde **9**[4b] gave 40% yield of the desired adduct, with recovered acetylene **7** accounting for the remaining mass balance. Transmetalation of **8** to less basic acetylides with either $MgBr_2$ or $CeCl_3$ had little effect on the product distribution. However, addition of 0.5 equiv of anhydrous LiBr to the solution of **8** prior to addition of aldehyde **9** gave the coupled product as a mixture of alcohol epimers in 95% yield.[7] Dess−Martin oxidation of the mixture of propargyl alcohols provided ynone **10**.[8] Known methods for the reduction of α,β-unsaturated ynones to their corresponding *trans* enones (e.g., $CrSO_4$, $CrCl_2$, Red-Al) led to poor isolated yields of **11** (<10%) with extensive decomposition of the starting material **10**.[9] However, following a protocol developed in our laboratories, semireduction with $[Cr(OAc)_2{\cdot}H_2O]_2$ in aqueous THF at 65 °C yielded **11** in 60%.[10]

Osmylation of enone **11** proceeded slowly (10% after 48 h at 23 °C) and nonselectively. After considerable experimentation, it was found that dihydroxylation was best accomplished following deprotection of **11** (Bu_4NF). The resulting diol **12** could be osmylated in the presence of either Sharpless ligand, $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, with NMO as the reoxidant to give a mixture of diastereomers (64:36 desired:undesired, quantitative yield).[11] Treatment of the unpurified osmylation product with HCl in MeOH afforded a mixture of diastereomers (90%, two steps), from which **14** was isolated by chromatography on silica gel following selective protection of both primary hydroxyls as the corresponding silyl ethers. Reaction of the desired diastereomer **14** with trimethylacetyl chloride and subsequent hydrogenolysis of the benzyl ether provided **15**.

Completion of the synthesis of zaragozic acid C required installation of the quaternary center at C(4), oxidation at C(8), C(9), and C(10), and attachment of the C(6) acyl side chain (Scheme 2). Swern oxidation of **15** furnished ketone **16**, to which TMSC≡CLi was added, affording an 86:14 mixture of the desired carbinol along with its diastereomer in 95% yield. The fact that TMSC≡CLi adds to **16** to give the desired C(4) epimer as the major product was unexpected. In related studies, we have observed that the ratio of diastereomeric products from **16** is sensitive to the structure of the nucleophile and the reaction conditions.[12] The mixture of diastereomeric products was separated by silica gel chromatography following alkyne desilylation to give **18**. Removal of all three pivaloyl protecting groups on **18** was effected with Dibal-H. The polyol product was subsequently acetylated to provide **19**, thus installing the requisite C(4′) acetate. Exposure of **19** to mildly acidic conditions led to selective deprotection of the silyl ether at C(8). Semihydrogenation of the terminal acetylene (H_2, Pd−C, C_5H_5N) furnished alkene **20**. Oxidation of the primary alcohol at C(8) was accomplished through a two-step sequence which involved Dess−Martin oxidation to the corresponding aldehyde followed by buffered $NaClO_2$ oxidation and esterification with *N,N′*-diisopropyl-*O*-*tert*-butylisourea to give the *tert*-butyl ester **21**.[13] Following a similar sequence of steps, the silyl ether at C(10) was removed with HF·pyridine (THF, C_5H_5N) to give **22**. Oxidation and esterification afforded the bis(*tert*-butyl) ester **23**. Ozonolysis of **23** and oxidation of the resulting aldehyde with $NaClO_2$ followed by esterification installed the third carboxylate. Selective hydrolysis of the C(6) and C(7) acetates to furnish **25** was effected with a 0.2% solution of K_2CO_3 in MeOH (0.5 h). Coupling of **25** with side chain **26**[1] provided a 1:3 mixture of C(6) and C(7) acylated products, respectively, in 87% combined yield, from which the desired tris(*tert*-butyl) ester of zaragozic acid C was isolated. Spectral data for both

(1) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261 and references therein.

(2) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639.

(3) Chemical modifications of the natural products have been reported, see: (a) Andreotti, D.; Procopiou, P. A.; Watson, N. S. *Tetrahedron Lett.* **1994**, *35*, 1789 and references therein. (b) Biftu, T.; Acton, J. J.; Berger, G. D.; Bergstrom, J. D.; Dufresne, C.; Kurtz, M. M.; Marquis, R. W.; Parsons, W. H.; Rew, D. R.; Wilson, K. E. *J. Med. Chem.* **1994**, *37*, 421 and references therein.

(4) For synthetic studies, see: (a) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Lamont, R. B.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1259. (b) Robichaud, A. J.; Berger, G. D.; Evans, D. A. *Tetrahedron Lett.* **1993**, *34*, 8403. (c) McVinish, L. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **1994**, *35*, 923. (d) Gurjar, M.; Das, S. K.; Saha, U. K. *Tetrahedron Lett.* **1994**, *35*, 2241.

(5) D-Erythronic γ lactone is commercially available and can be prepared from D-isoascorbic acid ($0.04/g), see: Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberg, M.; Liu, Y.−Y.; Thom, E.; Liebmann, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661.

(6) ^{1}H NMR NOE difference experiments for intermediates possessing the dioxabicyclooctane core provided support for the illustrated stereochemical assignments, see supplementary material.

(7) The effect of LiBr on acetylide addition reactions has been noted: van Rijn, P. E.; Mommers, S.; Visser, R. G.; Verkruijsse, H. D.; Brandsma, L. *Synthesis* **1981**, 459.

(8) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899 and references therein.

(9) (a) Castro, C. E.; Stephens, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 4358. (b) Smith, A. B., III; Levenberg, P. A.; Suits, J. Z. *Synthesis* **1986**, 184.

(10) $[Cr(OAc)_2{\cdot}H_2O]_2$ has been used to reduce α-haloketones and α-haloketoximines, see: (a) Williamson, K. L.; Johnson, W. S. *J. Org. Chem.* **1961**, *26*, 4563. (b) Corey, E. J.; Richman, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5276. The scope of $[Cr(OAc)_2{\cdot}H_2O]_2$ as a mild reductant for the conversion of ynones to enones is currently under investigation in our laboratory.

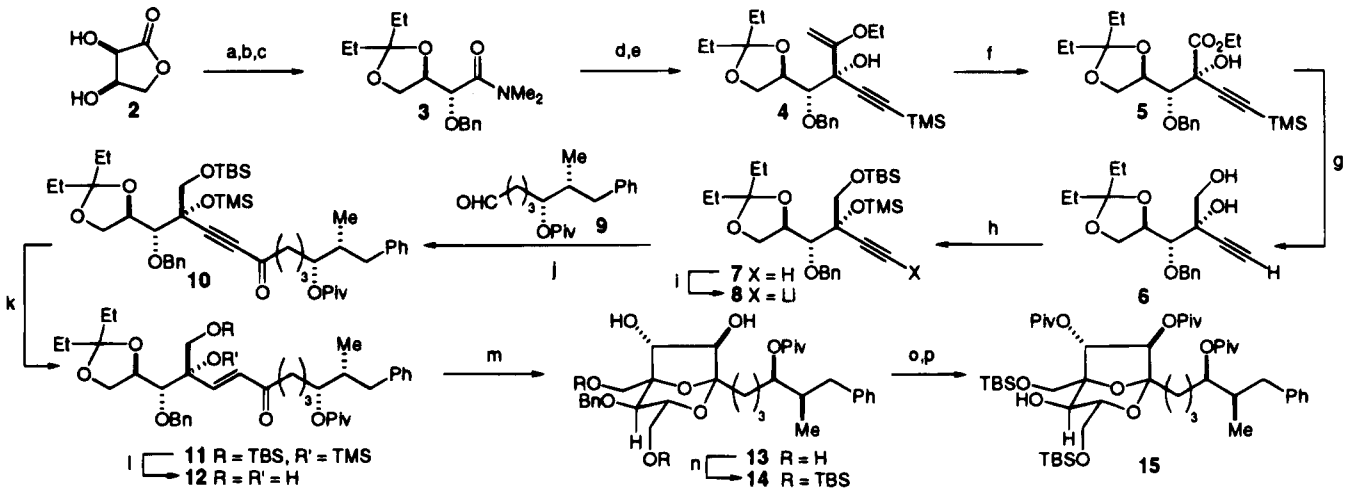
(11) In the absence of $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, dihydroxylation of **12** furnishes a 50:50 mixture of diastereomers. For a recent discussion of the osmylation reaction, see: Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

(12) These studies will be reported at a later time.

(13) For the preparation and use of *N, N′*-diisopropyl-*O*−*tert*-butylisourea, see ref 1.

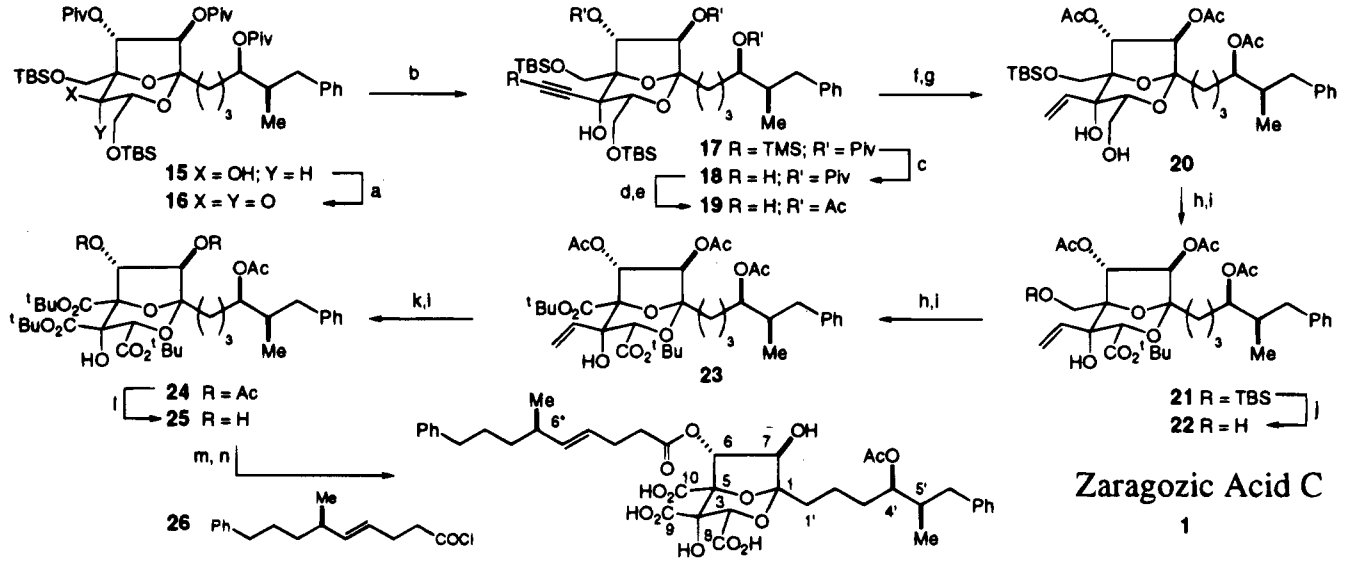
0002-7863/94/1516-10825$04.50/0

Scheme 1[a]



[a] (a) Me_2NH, MeOH, 99%; (b) $(MeO)_2CEt_2$, H^+, 90%; (c) NaH, BnCl, THF, 96%; (d) 1-ethoxyvinyllithium, THF; (e) TMSC≡CMgBr, THF, 84%; (f) O_3, CH_2Cl_2–EtOH, 84%; (g) $NaBH_4$, MeOH then K_2CO_3, MeOH, 78%; (h) ^{t}BuMe$_2$SiCl, Et_3N, DMAP then Me_3SiCl, Et_3N, CH_2Cl_2, 88%; (i) ^{n}BuLi, LiBr then **9**, THF, 93%; (j) Dess-Martin, 93%; (k) $[Cr(OAc)_2{\cdot}H_2O]_2$, THF/H_2O, 60%; (l) Bu_4NF, THF, 93%; (m) OsO_4, NMO, $(DHQD)_2PHAL$, acetone; HCl, MeOH, 90%; (n) ^{t}BuMe$_2$SiCl, Et_3N, DMAP, CH_2Cl_2, 86%; (o) PivCl, DMAP, 50 °C, $ClCH_2CH_2Cl$, 97%; (p) $Pd(OH)_2$–C, Pd–$CaCO_3$, H_2, 99%.

Scheme 2[a]



[a] (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 90%; (b) TMSC≡CLi, Me_3N–Et_2O, 78%; (c) $AgNO_3$, 2,6-lutidine, 95%; (d) DIBAL-H, PhMe, 84%; (e) Ac_2O, DMAP, CH_2Cl_2, 95%; (f) Cl_2CHCO_2H, MeOH, 90%; (g) H_2/Pd–C, py, 99%; (h) Dess-Martin, 94%; (i) $NaClO_2$, NaH_2PO_4, β-isoamylene, THF–H_2O then *N,N'*-diisopropyl-*O*-*tert*-butylisourea, 70–85%; (j) HF·py, THF, 90%; (k) O_3, CH_2Cl_2–MeOH, −78 °C, 97%; (l) K_2CO_3, MeOH, 92%; (m) **26**, DMAP, CH_2Cl_2, 87%; (n) TFA, 100%.

24 and the tris(*tert*-butyl) ester of zaragozic acid C were identical in all respects to those previously reported.[1] Deprotection of the triester was effected with a 25% solution of trifluoroacetic acid in CH_2Cl_2 (12 h). The synthetic (+)-zaragozic acid C, **1**, was identical in all respects (IR, ^{1}H NMR, ^{13}C NMR, HPLC co-injection, MS) to an authentic sample of the natural product.[14]

Acknowledgment. We are grateful to the National Science Foundation for a predoctoral fellowship to J.D.B. This research has been supported by a Beckman Young Investigator Award and a gift from the Medicinal Chemistry Research Unit at The Upjohn Co.

(14) We thank Dr. Conrad Santini (Merck Research Laboratories) for providing us with an authentic sample of zaragozic acid C.

Supplementary Material Available: Spectral data for compounds **3**, **5**, **7**, **11**, **14**, **15**, precursor to **19**, **20**, **21**, and **23** as well as relevant NOE data (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.