Asymmetric Synthesis of the Squalene Synthase Inhibitor Zaragozic Acid C

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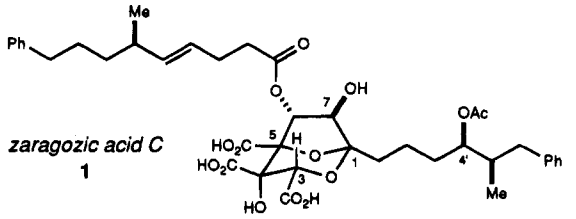
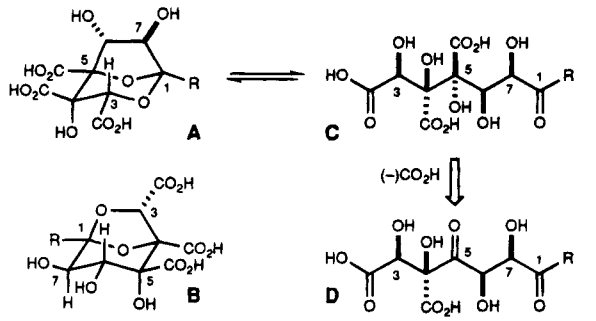
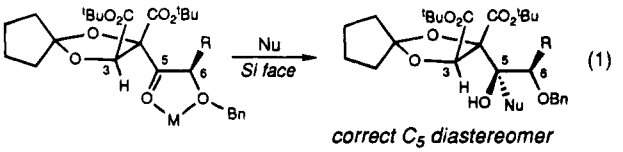
The recently discovered fungal metabolites known both as the squalestatins[1] and zaragozic acids[2] have become attractive targets for synthesis[3] as a consequence of their picomolar inhibition of the enzyme squalene synthase (EC 2.5.1.21), the first committed step in the biosynthesis of sterols. Members of this family of natural products have also been found to be potent inhibitors of farnesyl−protein transferase.[4] In independent studies from Merck[2] and Glaxo,[1] a number of closely related structures sharing the common 2,8-dioxabicyclo[3.2.1]octane core have been isolated and characterized to date. The purpose of this communication is to disclose a route to the synthesis of zaragozic acid C (**1**)[5] which is amenable to the synthesis of the other members of this family of natural products.[6]



In the successful synthesis plan, we have presumed that the bicyclic ketal core **A** would be accessible from acyclic precursor **C** and that the obligatory internal ketalization would lead to the desired ketal rather than its structural isomer **B** (Scheme 1).[7] In another critical step, we planned to introduce the C_5 nucleophilic carboxylate fragment into intermediate **D** through a chelate-orchestrated Grignard addition with stereocontrol evolving from the C_6 oxygen (eq 1). The reduction of this plan to practice is summarized below.

Scheme 1





(1)

The synthesis was initiated with the chiral glycolate aldol reaction between the boron enolate derived from imide **2**[8] and cinnamaldehyde to provide aldol adduct **3** in excellent yield (Scheme 2). A series of routine steps transformed this intermediate into aldehyde **4**, which served as the component of the bicyclic core containing the C_6 and C_7 oxygen-bearing stereogenic centers. Di-*tert*-butyl D-tartrate (**5**)[9] was next employed for the balance of the carbon framework of the core less the C_5 carboxyl moiety. Enolization of ketal **6**[10] with *in situ* silylation (LiHMDS, TMSCl)[11] afforded the silylketene acetal **7** that underwent a stereoselective Lewis acid-catalyzed aldol addition [(^{i}PrO)$TiCl_3$, CH_2Cl_2, −78 → −40 °C, 5 h] with aldehyde **4** to give adduct **8** as a single isomer in 76% yield. After Dess−Martin oxidation[12] of **8** → **9**, addition of vinylmagnesium bromide (6:1 CH_2Cl_2/THF, −78 °C) proceeded to give **10** with at least 10:1 selectivity to introduce the latent C_5 carboxyl moiety in the form of the vinyl substituent. It should be noted that reaction diastereoselection is strongly solvent dependent.[13] The stereochemical outcome of this transformation[14] is consistent with chelate control through the C_6 benzyloxy substituent (eq 1). Although the indicated chelate-derived stereocontrol is speculative, it is noteworthy that the other obvious chelate option accessible to the C_5 carbonyl group predicts the opposite sense of asymmetric induction (eq 2).

The indicated six-step refunctionalization sequence of vinyl carbinol **10** (76% yield) afforded lactone **12** as a fully elaborated

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(2) (a) Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151−7158. (b) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L.; Omstead, M. N.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Pelaez, F.; Diez, M. T.; Alberts, A. W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 80−84. (c) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221−10226. (d) Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. *Tetrahedron Lett.* **1993**, *34*, 399−402. (e) Dufresne, C.; Wilson, K. E.; Singh, S. B.; Zink, D. L.; Bergstrom, J. D.; Rew, D.; Polishook, J. D.; Meinz, M.; Huang, L.; Silverman, K. C.; Lingham, R. B.; Mojena, M.; Cascales, C.; Pelaéz, F.; Gibbs, J. B. *J. Nat. Prod.* **1993**, *56*, 1923−1929.

(3) Model studies on the core: (a) Aggarwal, V. K.; Wang, M. F.; Zaparucha, A. *J. Chem. Soc., Chem. Commun.* **1994**, 87−88. (b) Gable, R. W.; McVinish, L. M.; Rizzacasa, M. A. *Aust. J. Chem.* **1994**, *47*, 1537−1544. (c) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1839−1843. Synthesis of the 1′ sidechains of zaragozic acids A and C: (d) Robichaud, A. J.; Berger, G. D.; Evans, D. A. *Tetrahedron Lett.* **1993**, *34*, 8403−8406. Synthesis of the C_6-acyl sidechain of zaragozic acid C: (e) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261−2266.

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(5) X-ray crystallography has been employed to establish the full relative stereochemistry of zaragozic acid A[2a] and C, while the absolute stereochemistry of zaragozic acid C was determined by asymmetric synthesis of the C_6 acyl sidechain: Ref. 3c.

(6) The first synthesis of **1** has recently appeared: Carreira, E. M.; DuBois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825−10826.

(7) This presumption has not been reinforced by molecular mechanics calculations, which indicate that the trimethyl ester derived from **B** is more stable than its corresponding structure **A**.

(8) For the synthesis of **2**, see: Evans, D. A.; Bender, S. W.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526.

(9) Uray, G.; Lindner, W. *Tetrahedron* **1988**, *44*, 4357−4362.

(10) Precedent for the enolization of dimethyl tartrate acetonide has been reported by Seebach: Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030−1031. In our hands, we have found the *tert*-butyl ester analogs of these tartrate ketals to be much more reliable in enolate−electrophile bond constructions.

(11) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495−498.

(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156−4158.

(13) For example, see: Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417−420.

(14) The C_5 stereochemical assignment was made on the C_7 desilylated analog of lactone **11**.

(15) Reaction conditions without a temperature designation were carried out at room temperature.

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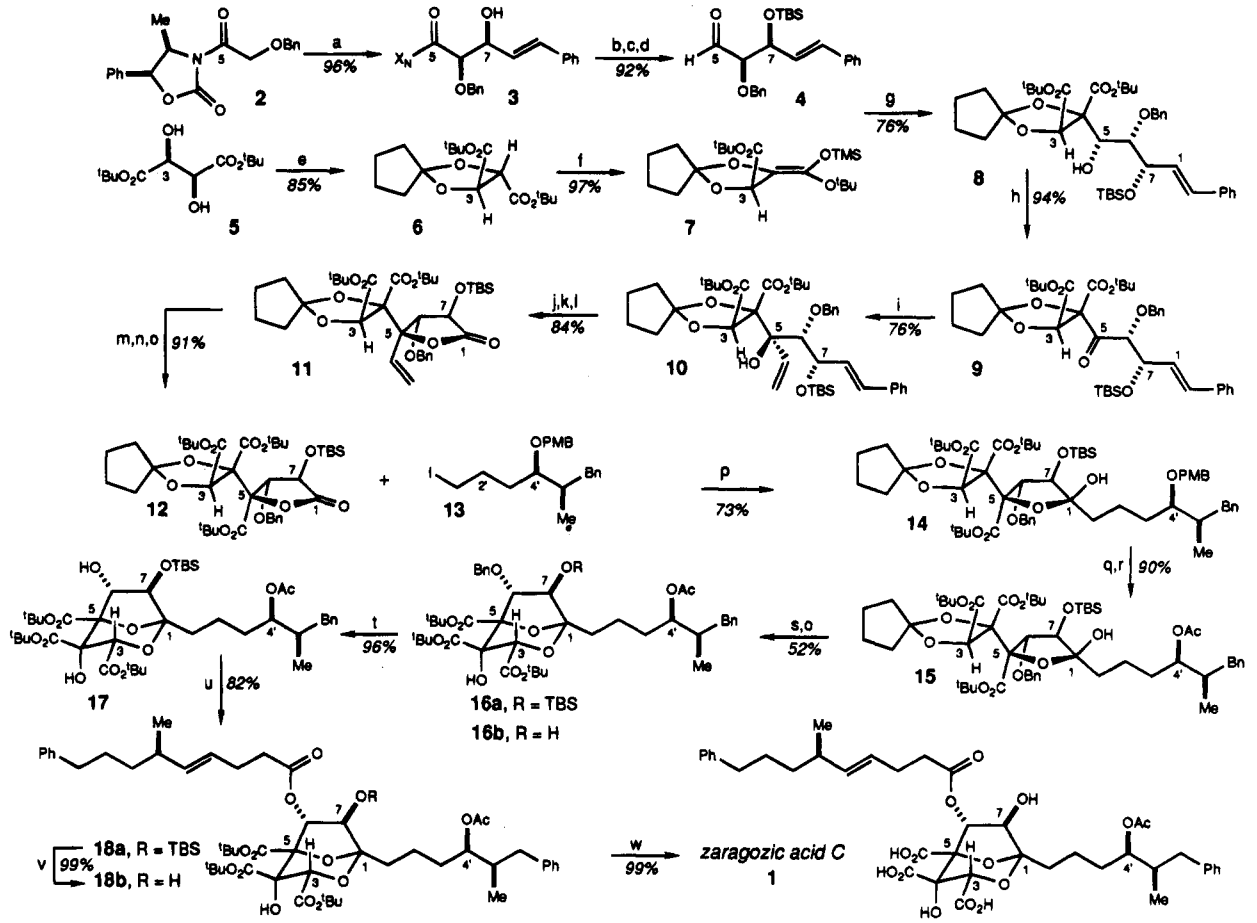
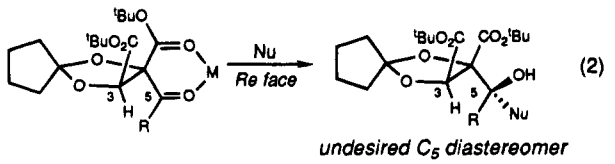
Scheme 2[a]



[a] Reagents and conditions:[15] (a) Bu_2BOTf, Et_3N, PhCH=CHCHO, CH_2Cl_2, −78 °C, 1 h → −40 °C, 1.5 h; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; (c) $LiBH_4$, MeOH, THF, 0 °C, 3.5 h; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 30 min → 0 °C, 1 h; (e) 3 equiv of cyclopentanone dimethyl ketal, TsOH, C_6H_6, 65 °C, 200 Torr, 12 h; (f) LiHMDS, TMSCl, THF, −78 °C, 30 min → 0 °C 30 min; (g) $(iPrO)TiCl_3$, CH_2Cl_2, −78 °C 2 h, → −40 °C, 2.5 h; (h) 3 equiv of Dess−Martin periodinane, pyridine, CH_2Cl_2, 8 h; (i) 20 equiv of CH_2=CHMgBr, 6:1 CH_2Cl_2/THF, −78 °C, 10 h; (j) OsO_4, NMO, 10:3:1 *t*-BuOH/THF/H_2O, 40 h; (k) $Pb(OAc)_4$, C_6H_6, 20 min; (l) $[(n\text{-}C_3H_7)_4N][RuO_4]$, NMO 4 Å sieves, CH_2Cl_2, 5 h; (m) O_3, pyridine, CH_2Cl_2, −78 °C, 2 h, then Me_2S, −78 → 23 °C, 2 h; (n) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe, *t*-BuOH, 3.5 h; (o) 7 equiv of *N,N'*-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, 24 h; (p) 1.7 equiv of **13**, 3.4 equiv of *tert*-butyllithium, 1:1 hexane/ether, −78 °C, 5 min, then **12**, −78 °C, 15 min; (q) 2 equiv of DDQ, CH_2Cl_2/H_2O, 1 h; (r) 2 equiv of Ac_2O, DMAP, 1:4 pyridine/C_6H_6, 1 h; (s) 20:10:1 CH_2Cl_2/TFA/H_2O, 14 h; (t) H_2, 750 psi, 10% Pd/C, AcOH, MeOH, 20 h; (u) (4*E*,6*R*)-6-methyl-9-phenylnon-4-enoic acid, DCC, DMAP, CH_2Cl_2, 36 h; (v) TBAF, THF, 0 °C, 15 min; (w) TFA, CH_2Cl_2, 24 h.



undesired C_5 diastereomer (2)

intermediate, to which a nucleophilic C_1 side chain equivalent can be added. Generation of the nucleophilic alkyllithium C_1 side chain derived from primary iodide **13**[16] (2 equiv of *tert*-butyllithium, −78 °C) in 1:1 hexane/ether followed by addition of **12** cleanly provided **14** as a mixture of lactol diastereomers. Solvent selection is critical in this step, as this alkyllithium reagent is unstable in THF.[17]

Oxidative cleavage of the *p*-methoxybenzyl ether (DDQ, CH_2Cl_2/H_2O) followed by immediate acetylation (Ac_2O, DMAP, pyridine) of the $C_{4'}$ hydroxyl completed the assemblage of lactol **15**, the synthon equivalent to intermediate **C** and direct precursor to the bicyclic core and associated C_1 side chain. In the critical ketalization/hydrolysis step, acid-catalyzed transformation of lactol **15** (20:10:1 CH_2Cl_2/TFA/H_2O, 14 h, 23 °C) afforded the triacid, which was esterified with *N,N'*-diisopropyl-*O*-*tert*-butylisourea[18] to provide **16a** along with small quantities of the derived C_7 desilylated analog **16b**, which was resilylated. Hydrogenolysis of the C_6 benzyloxy substituent then afforded alcohol **17** in preparation for coupling to the C_6 acyl residue. Acylation of **17** with (4*E*,6*R*)-6-methyl-9-phenylnon-4-enoic acid[3e] (DCC, DMAP, CH_2Cl_2, 23 °C) afforded the zaragozic acid C derivative **18a** in protected form. Successive fluoride-mediated desilylation and hydrolysis provided (+)-zaragozic acid C, whose spectral and chromatographic properties are identical with those of a comparison sample of the natural product.

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Supplementary Material Available: Spectral data for all compounds are provided (6 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.

(16) This iodide was readily prepared from intermediates previously reported by us, ref 3d.

(17) Bailey, W. F.; Punzalen, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

(18) Mathias, L. J. *Synthesis* **1979**, 561−576.