A Symmetry-Based Formal Synthesis of Zaragozic Acid A

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A symmetry-based strategy for the synthesis of the zaragozic acids is reported. Two enantioselective dihydroxylations were used to establish the absolute configuration of a C_2 symmetric intermediate. Noteworthy transformations include a group-selective lactonization, which accomplished an end-differentiation of a pseudo-C_2 symmetric intermediate. Late stage protecting group adjustments and oxidations accomplished a formal synthesis of zaragozic acid A.

In 1992, workers at Merck described the first member of a new class of natural products.[1] This compound was produced by a fungus found in filtrates of the Jalon river in the Zaragoza province of Spain. Nearly simultaneously with this discovery, a group at Glaxo reported the isolation of the same substance from a different fungus found in a soil sample from Portugal.[2] This compound, named zaragozic acid A (**1**, Figure 1) by the Merck group and squalestatin S1 by the Glaxo researchers, was the first example of what would turn out to be an extensive family of natural products. New members of this family have subsequently been isolated from fungal sources all over the world.[3] Throughout the past decade, compounds in this class have received a significant amount of attention from the scientific community, both because of their unusual, highly functionalized structures and their important biological activities.

One such activity is their ability to inhibit squalene synthase, a key enzyme in the cholesterol biosynthesis pathway[4] and a desirable target for therapeutic intervention for the reduction of serum cholesterol levels. In addition, these compounds inhibit ras farnesyl protein transferase.[1c] Ras is a protein that regulates cell proliferation and differentiation. It has been estimated that the *ras* oncogene is mutated in approximately 20% of all human cancers and in more than 50% of colon and pancreatic cancers.[5] Therefore, these compounds show promise as leads for the development of anticancer substances as well as cholesterol-lowering agents. Zaragozic acid has been a template for the development of novel synthesis methods and strategies in a number of laboratories,[6,7] including ours.[8] Described here is a formal synthesis of zaragozic acid A.

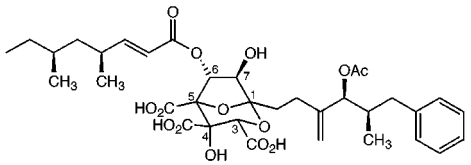

Figure 1. Zaragozic acid A.

(1) (a) Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151. (b) Dufresne, C.; Wilson, K. E.; Zink, D. L.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L. Y.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221. (c) Dufresne, C.; Wilson, K. E.; Singh, S. B.; Zink, D. L.; Bergstrom, J. D.; Rew, D.; Polishook, J. D.; Meinz, M.; Huang, L. Y.; Silverman, K. C.; Lingham, R. B.; Mojena, M.; Cascales, C.; Pelaez, F.; Gibbs, J. B. *J. Nat. Prod.* **1993**, *56*, 1923. (d) Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. *Tetrahedron Lett.* **1993**, *34*, 399. (e) 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.

(2) (a) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. *J. Antibiot.* **1992**, *45*, 639. (b) Sidebottom, P. J.; Highcock, R. M.; Lane, S. J.; Procopiou, P. A.; Watson, N. S. *J. Antibiot.* **1992**, *45*, 648. (c) Baxter, A.; Fitzgerald, B. J.; Hutson, J. L.; McCarthy, A. D.; Motteram, J. M.; Ross, B. C.; Sapra, M.; Snowden, M. A.; Watson, N. S.; Williams, R. J.; Wright, C. *J. Biol. Chem.* **1992**, *267*, 11705.

(3) Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1623.

(4) Lindsey, S.; Harwood: H. J. *J. Biol. Chem.* **1995**, *270*, 9083.

(5) Gibbs, J. B. *Cell* **1991**, *65*, 1.

(6) Syntheses of zaragozic acid: (a) Nicolaou, K. C.; Yue, E. W.; Lagreca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; Dericcardis, F. *Chem.-Eur. J.* **1995**, *1*, 467. (b) Carreira, E. M.; Dubois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106. (c) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111. (d) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126. (e) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115. (f) Sato, H.; Nakamura, S.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 451. (g) Armstrong, A.; Jones, L. H.; Barsanti, P. A. *Tetrahedron Lett.* **1998**, *39*, 3337.

(7) Selected other approaches to zaragozic acid: (a) Martin, S. F.; Naito, S. *J. Org. Chem.* **1998**, *63*, 7592. (b) Koshimizu, H.; Baba, T.; Yoshimitsu, T.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 2777. (c) Maezaki, N.; Gijsen, H. J. M.; Sun, L. Q.; Paquette, L. A. *J. Org. Chem.* **1996**, *61*, 6685. (d) Xu, Y. P.; Johnson, C. R. *Tetrahedron Lett.* **1997**, *38*, 1117. (e) Paterson, I.; Fessner, K.; Finlay, M. R. V. *Tetrahedron Lett.* **1997**, *38*, 4301. (f) Kataoka, O.; Kitagaki, S.; Watanabe, N.; Kobayashi, J.; Nakamura, S.; Shiro, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 2371. (g) Hodgson, D. M.; Bailey, J. M.; Harrison, T. *Tetrahedron Lett.* **1996**, *37*, 4623. (h) Brogan, J. B.; Zercher, C. K. *Tetrahedron Lett.* **1998**, *39*, 1691. (i) Calter, M. A.; Sugathapala, P. M. *Tetrahedron Lett.* **1998**, *39*, 8813. (j) Walker, L. F.; Connolly, S.; Wills, M. *Tetrahedron Lett.* **1998**, *39*, 5273. (k) Kraus, G. A.; Maeda, H. *J. Org. Chem.* **1995**, *60*, 2. (l) Mann, R. K.; Parsons, J. G.; Rizzacasa, M. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1283. (m) Hegde, S. G.; Myles, D. C. *Tetrahedron* **1997**, *53*, 11179. (n) Tsubuki, M.; Okita, H.; Honda, T. *Synlett* **1998**, 1417. (o) Ito, H.; Matsumoto, M.; Yoshizawa, T.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1997**, *38*, 9009. (p) Fraisse, P.; Hanna, I.; Lallemand, J. Y. *Tetrahedron Lett.* **1998**, *39*, 7853. (q) Tomooka, K.; Kikuchi, M.; Igawa, K.; Keong, P. H.; Nakai, T. *Tetrahedron Lett.* **1999**, *40*, 1917. (r) Reid, A. M.; Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2795.

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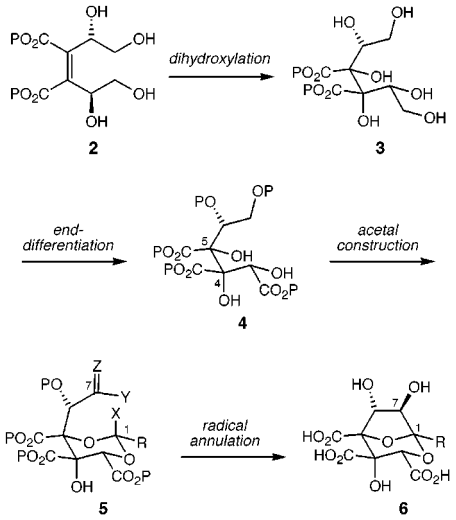
Scheme 1



The route developed in this lab was intended to exploit both the reactivity and the synthetic potential of oxygen-substituted radicals. It relies on the cyclization of a radical derived from homolytic cleavage of C1-X of **5** (Scheme 1) onto a radical acceptor to construct the unique 2,8-dioxabicyclo[3.2.1]octane ring system **6**. Such a strategy would allow the exploitation of symmetry within the system. Beyond this, it was anticipated that this route for constructing the zaragozic acids would be novel and could perhaps be broadly applicable to the construction of a variety of bicyclic ketals.

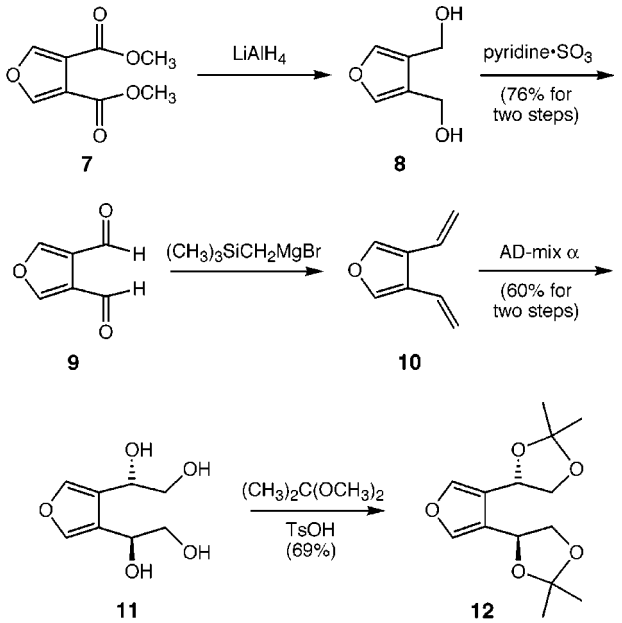
The synthesis plan (Scheme 1) would primarily be guided by a desire to utilize hidden symmetry within the core structure. One benefit of the C1−C7 bond connection (**5** → **6**) is that it allows an intermolecular acetal construction. Therefore, acetal **5** (X = H) could, in principle, be prepared from triol **4**. Examination of **4** reveals the symmetry element of interest. The central carbons (C4 and C5) each bear a carboxylic acid and a tertiary alcohol. Each of these carbons is flanked by a carbon bearing a secondary alcohol, then by a group which could be derived from a primary alcohol (CH_2OP and CO_2P).

Compound **4** could potentially be derived from an intermediate such as **3**. The plan for the synthesis of intermediates corresponding to **4** was to utilize a series of reactions that would accomplish, among other things, differentiation of the two primary as well as the two secondary alcohols of **3**. Since compound **3** is not truly symmetric because the stereocenters bearing the tertiary alcohols have different configurations, it was hypothesized that a transformation such as a diastereotopic group-selective lactonization could be employed to differentiate the various hydroxyls. This would accomplish the selective protection of one (or possibly two) of the alcohols, while minimizing the use of extraneous protecting groups.

The synthesis of the pseudosymmetric intermediate **3** was envisioned to proceed via the tetrasubstituted olefin **2**. The installation of the tertiary hydroxyls (**2** → **3**) would break the C_2 symmetry and provide the basis for the subsequent discrimination of the primary and secondary

(8) (a) Freeman-Cook, K. D.; Halcomb, R. L. *Tetrahedron Lett.* **1996**, *37*, 4883. (b) Freeman-Cook, K. D.; Halcomb, R. L. *Tetrahedron Lett.* **1998**, *39*, 8567.

Scheme 2



hydroxyls in more advanced intermediates. Since **2** is C_2 symmetric, it was anticipated that a relatively short and efficient sequence could be used to prepare it. Furthermore, the symmetry of **2** assured that the installation of the tertiary alcohols could be accomplished without necessitating a face-selective reaction.

Commercially available furan diester **7** (Scheme 2) was chosen as a starting material. The furan ring serves as both a symmetric scaffold and as a protecting group for the carboxylic acids and the tetrasubstituted olefin of **2**. Reduction of **7** gave diol **8**, and subsequent reoxidation by an adaptation of a published procedure[9] provided furan dialdehyde **9** in 76% yield for two steps. A Peterson olefination produced compound **10**,[10] which was treated directly with AD-mix α to afford **11** (60% yield for two steps). The enantioselective dihydroxylation installed four hydroxyl groups and established each of the secondary alcohol stereocenters in the appropriate (*S*) configuration.[11−13] Since each dihydroxylation was enantioselective (approximately 80% enantiomeric excess, assuming the outcome of the first reaction does not influence the second) and two sequential dihydroxylations were performed in the same synthesis operation, the tetraol **11**

(9) Cook, M. J.; Forbes, E. J. *Tetrahedron* **1968**, *24*, 4501.

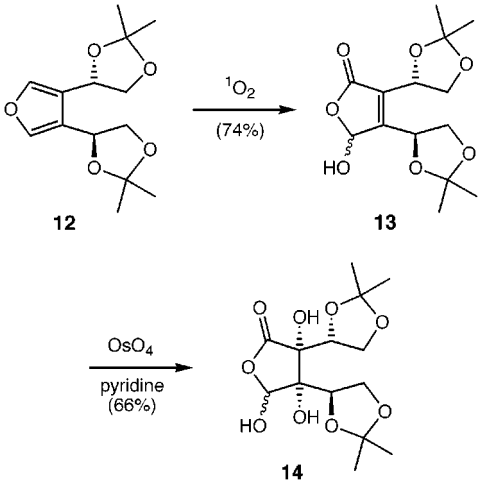
(10) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Ager, D. J. *Synthesis* **1984**, 384. (b) For a similar application to a vinyl furan, see: Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982 and references therein.

(11) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(12) Sharpless, K. B.; Amberg, W.; Bennani, Y.; Crispino, G.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768. This ee was measured as follows. Treatment of the tetraol **13** with 2 equiv of TBDPS-Cl to protect the primary alcohols was followed by formation of the bis-Mosher ester of the resulting bis-secondary alcohol. The bis-Mosher ester itself was prepared using both (*R*)-(+)-MPTA, and (*S*)-(−)-MPTA. 500 MHz ^{1}H NMR spectroscopy was used to measure the diastereomeric ratio of the bis-Mosher esters (see ref 13). The >100:1 ratio of diastereomers (corresponding to >98% ee) probably is a minimum value and beyond the limit of accuracy that can be expected by this method. Additional support for this determination was provided by measuring the ratio of diastereomers produced in the dihydroxylation. An ee of 97.6% was calculated by this method. For a mathematical description of related ee enhancements, see ref 14.

(13) (a) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1972**, *95*, 512.

Scheme 3

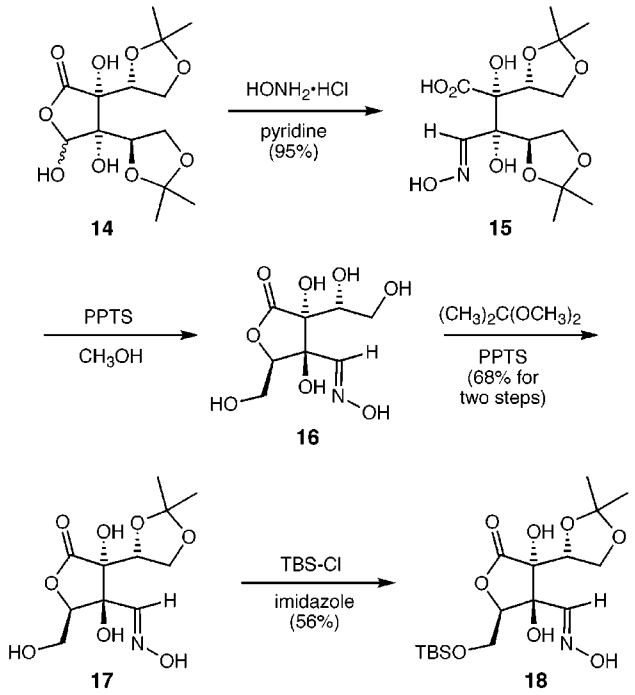


was produced in high enantiomeric excess (>98%).[14] The tetraol **11** was then protected in a straightforward manner as the bisacetonide **12** in 69% yield.

The furan ring of **12** was oxidized using singlet oxygen at −20 °C (Scheme 3).[15] This oxidation not only provided one of the three carboxylic acids of zaragozic acid but also unveiled another carboxylic acid precursor as an aldehyde engaged in a hemiacetal and produced the desired (*Z*) tetrasubstituted olefin **13** in 74% yield (5:1 mixture of epimers at the hemiacetal). Dihydroxylation of **13** with OsO_4 installed the two tertiary alcohol stereocenters and provided the key intermediate **14** in 66% yield. Other catalytic dihydroxylation conditions were examined but were not successful. A variety of solvents, additives, and reagent combinations too numerous to list were evaluated, as were other oxidation reagents such as $RuCl_3$. The intermediate osmate ester appears to be resistant to hydrolysis, so turnover is inhibited. The structure of triol **14** was confirmed by X-ray crystallography (see Supporting Information). Compound **14** appeared to be a 5:1 mixture of inseparable hemiacetal isomers in solution, as measured by NMR, but a single isomer appeared to crystallize from solution. Although the precursor **13** also existed as a mixture of diastereomers at the hemiacetal carbon (2:1), the dihydroxylation appeared to be quite face-selective. Spectroscopic evidence suggests that the product that resulted from dihydroxylation of the opposite face may have been produced in small quantity (<5%). Purification of this and other minor byproducts was difficult, however, and since these byproducts would not be useful in the synthesis sequence, their structures were not rigorously established. One possible interpretation of these observations is that the chirality on the side chains, namely, the acetonide-protected secondary alcohols, are primarily responsible for controlling the face selectivity of the dihydroxylation.

Early attempts to remove the acetonide protecting groups of **14** resulted in the formation of a product containing a cyclic acetal. Because this compound was too inert for chemical manipulation, a protection of the aldehyde group of **14** was undertaken to prevent the formation of such offending acetals. After investigation of a variety of aldehyde protecting groups, an oxime was

Scheme 4



chosen because it could be installed under mildly basic conditions and was expected to be resistant to acetal formation. Treatment of **14** with hydroxylamine hydrochloride and pyridine smoothly produced the oxime **15** in 95% yield and liberated the carboxylic acid functional group (Scheme 4). The carboxylic acid was then used for the discrimination of the two secondary alcohols in a group-selective lactonization. Removal of the acetonides from compound **15** with PPTS in methanol produced a polar intermediate, presumably a hexaol, which was not isolated but was allowed to lactonize upon prolonged exposure to the reaction conditions to provide compound **16** as the sole product. This accomplished the necessary end differentiation in a short, efficient sequence of reactions. The high regioselectivity and high yield of this lactonization was not entirely expected, but a similar lactonization exists as a precedent.[6a]

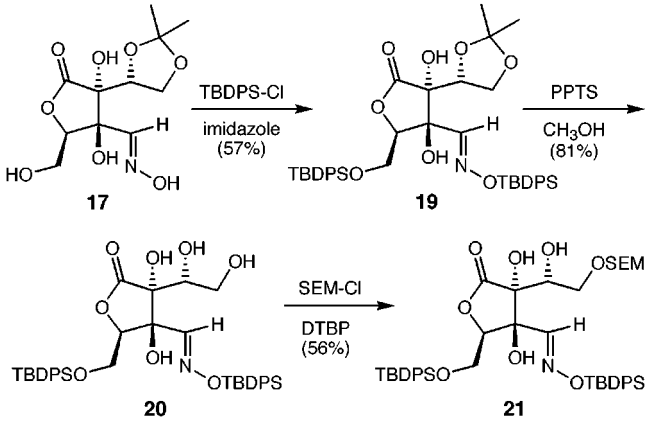
Reprotection of the vicinal diol as an acetonide yielded compound **17** (68% for two steps). Subsequent protection of the remaining primary hydroxyl as a TBS ether afforded **18** (56% yield). All four nontertiary alcohols in compound **18** are differentiated from each other. X-ray crystallographic analysis of **18** confirmed the structural assignments (see Supporting Information).

After the end differentiation was solved, attention was focused on the completion of a formal synthesis of zaragozic acid A. It was observed that compound **17** was structurally similar to an intermediate in the Nicolaou synthesis of zaragozic acid A.[6a] A formal synthesis was indeed accomplished in a straightforward manner from **17** by matching the Nicolaou intermediate. This involved simply installing the same array of protecting groups that was employed in the Nicolaou route, removing the oxime, and oxidizing the resulting aldehyde to the carboxylic acid oxidation state.

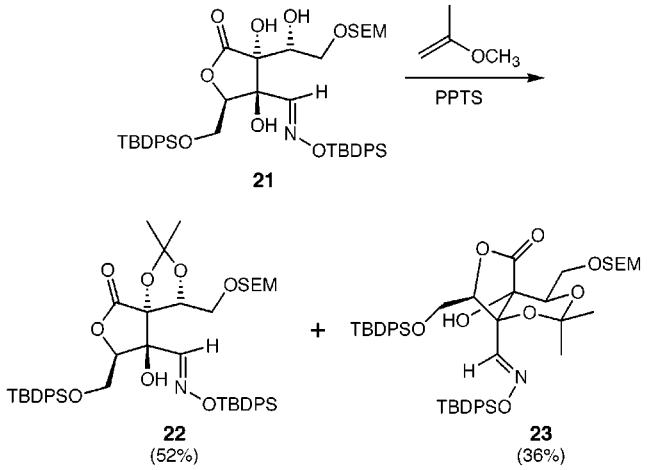
Protection of **17** as a bis(*tert*-butyldiphenylsilyl) ether using TBDPS-Cl and imidazole provided **19** in 57% yield (Scheme 5). The acetonide within **19** was cleanly removed using PPTS in methanol to generate **20** in 81% yield.

(14) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.
(15) Ickikawa, Y.; Tsuboi, K.; Naganawa, A.; Isobe, M. *Synlett* **1993**, *12*, 907.

Scheme 5



Scheme 6

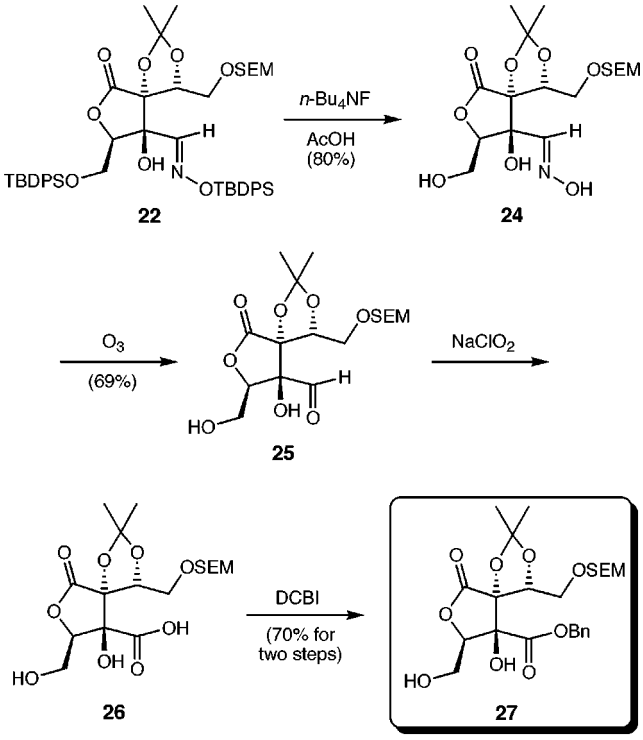


Selective protection of the primary alcohol as a SEM ether was not straightforward, and significant optimization was needed to produce substantial quantities of **21**. After a variety of conditions and methods were examined, it was found that this protection proceeded best when compound **20** was stirred with SEM-Cl in the presence of the base 2,6-di-*tert*-butylpyridine for 48 h at room temperature. Compound **21** was obtained from this transformation in 56% yield. This product was accompanied by a small amount of the secondary SEM ether (11%) and the bis-SEM ether (24%). These were easily separated by flash column chromatography. The use of this particular base was crucial to obtaining optimal yields and regioselectivities. Other bases such as pyridine or tertiary amines resulted in lower regioselectivities and greater quantities of the bis-SEM ether.

Protection of the secondary and tertiary hydroxyls of **21** as an acetonide was accomplished with 2-methoxypropene and PPTS (Scheme 6). This produced not only the desired acetonide **22** but also the regioisomer **23**, in a 1.4:1 ratio (88% yield overall). Attempts to convert the minor compound (**23**) to the major (**22**) were unsuccessful.

The conversion of **22** to the desired zaragozic acid intermediate was accomplished in a straightforward way (Scheme 7). Removal of the TBDPS protecting groups with *n*-Bu_4NF and acetic acid provided **24** in 80% yield. The oxime was removed by ozonolysis to produce aldehyde **25** (69% yield, quantitative based on recovered **24**). $NaClO_2$ oxidation produced the carboxylic acid **26**.[16] Without purification, the carboxylic acid was esterified

Scheme 7



with DCBI to afford **27** (70% yield, for two steps).[17] The spectral and chromatographic properties of **27** (^1H and ^{13}C NMR, IR, HRMS, TLC) were identical to the published data for this compound in all respects.[6a] Since this intermediate has been converted into zaragozic acid A,[6a] this synthesis of **27** constitutes a formal synthesis of zaragozic acid A.

Described here is a symmetry-based approach to the synthesis of advanced zaragozic acid intermediates and the subsequent end-differentiation of these compounds. This plan has culminated in a formal synthesis of zaragozic acid A. In addition to providing a novel entry into the zaragozic acids, it provides the basis for a continued exploration of a radical-based approach to the zaragozic acid core. These pursuits are the subject of a continuing effort in this laboratory.

Experimental Section

3,4-Divinylfuran (10). Dialdehyde **9** (2.95 g, 0.023 mol) was dissolved in Et_2O (65 mL) and stirred under N_2 at 0 °C for 15 min. A solution of (trimethylsilyl)methylmagnesium chloride (50 mL, 1 M in Et_2O, 0.05 mol) was added dropwise, and the reaction mixture allowed to warm to room temperature. After 1.5 h, AcOH (50 mL) and H_2O (33 mL) were added, and the Et_2O was removed by distillation. The mixture was extracted with pentane and washed with saturated $NaHCO_3$ and H_2O. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum (bath temperature = 0 °C). This gave 4.4 g of a solution of **10** in Et_2O (^1H NMR estimate, 0.018 mol, 80%). This solution was used directly without further purification in the next reaction: ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.57 (dd, J = 10.98, 17.67 Hz, 1H), 5.50 (dd, J = 1.61, 17.67 Hz, 1H), 5.22 (dd, J = 1.61, 10.98 Hz, 1H).

(1′*S*, 1″*S*)-3,4-Bis(1,2-dihydroxyethyl)furan (11). AD-mix α (5.6 g), *tert*-butyl alcohol (35 mL), and H_2O (35 mL) were mixed at room temperature, and the mixture was stirred for

(16) Balkrishna, S. B.; Childers, W. E.; Pinnick, H. W. *Tetrahedron Lett.* **1981**, *37*, 2091.
(17) Mathias, L. J. *Synthesis* **1979**, *8*, 561.

10 min at 0 °C. A solution of compound **10** (508 mg, 4.0 mmol) in THF (2 mL) was added. $K_3Fe(CN)_6$ (4 g, 12.09 mmol) and K_2CO_3 (1.67 g, 12.09 mmol) were added, and stirring was continued at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by the addition of Na_2SO_3 (s) (17.9 g, 0.14 mol) and stirred for an additional 14 h. The aqueous layer was saturated with NaCl (s), and the mixture was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 444.9 mg (59%) of compound **11** as a white powder. This was pure enough for direct use in the following reaction. A small sample was further purified for characterization by flash chromatography (SiO_2, 1:6:1 hexanes/EtOAc/MeOH, $R_f = 0.3$): $[\alpha]^{20}_D$ +33.6° (*c* 1.1, CH_3OH); IR (KBr) 3400 (br), 1625 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.44 (s, 1H), 4.71 (dd, $J = 4.66$, 7.15 Hz, 1H), 3.75 (dd, $J = 4.66$, 11.22 Hz, 1H), 3.68 (dd, $J = 7.25$, 11.22 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 141.7, 126.2, 68.2, 67.2; MS *m*/*z* EI^+ 188 (M^+), CI^- 187 ($M - H)^-$; HRMS (EI^+) calcd for $C_8H_{12}O_5$ (M^+) 188.0685, found 188.0724.

(1′*S*, 1″*S*)-3,4-Bis(2,2-dimethyl-(1,3)dioxolan-4-yl)furan (12). Tetraol **11** (843.8 mg, 4.5 mmol) was dissolved in anhydrous DMF (30 mL) and 2,2-dimethoxypropane (10 mL). TsOH (85.4 mg, 0.45 mmol) was added, and the mixture was stirred at room temperature for 21 h. The reaction was diluted with EtOAc and washed with saturated $NaHCO_3$, H_2O, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a yellow syrup. Flash chromatography (SiO_2, 8:2 hexanes/EtOAc) gave **12** (827 mg, 69%) as a yellow oil: $R_f = 0.3$ (SiO_2, 8:2 hexanes/EtOAc); $[\alpha]^{20}_D$ +30.5° (*c* 1.2, $CHCl_3$); IR (film) 2986, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 5.08 (dd, $J = 6.15$, 7.64 Hz, 1H), 4.31 (dd, $J = 6.15$, 8.04 Hz, 1H), 3.78 (t, $J = 7.8$ Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 123.1, 109.3, 70.4, 69.9, 26.5, 25.7; MS *m*/*z* EI^+ 268 (M^+), CI^+ 269 ($M + H)^+$, CI^- 267 ($M - H)^-$; HRMS (EI^+) calcd for $C_{14}H_{20}O_5$ (M^+) 268.1311, found 268.1327.

(1′*S*,1″*S*)-3,4-Bis(2,2-dimethyl-[1,3]dioxolan-4-yl)-5-hydroxy-5*H*-furan-2-one (13). Acetonide **12** (1.25 g, 4.7 mmol) was dissolved in CH_2Cl_2 (120 mL). $EtN(i\text{-}Pr)_2$ (1.62 mL, 9.3 mmol) and rose bengal (50 mg, 0.047 mmol) were added, and the mixture was cooled to −20 °C. O_2 (g) was bubbled through the solution, and the mixture was irradiated with a 500 W quartz-halogen lamp for 11 h, after which TLC indicated that the reaction was complete. The mixture was concentrated under vacuum. Flash chromatography (SiO_2, 1:1 hexanes/EtOAc) gave **13** (1.04 g, 74%) as a yellow oil. The product was an inseparable mixture of diastereomers (5:1 at the hemiacetal carbon): $R_f = 0.6$ (SiO_2, 1:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +63.2° (*c* 0.95, $CHCl_3$); IR (film) 3372 (br), 1766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) **Major** δ 6.3 (dd, $J = 1.69$, 5.95 Hz, 1H), 5.53 (t, $J = 7.64$ Hz, 1H), 4.91 (m, 1H), 4.46 (dd, $J = 6.6$, 8.48 Hz, 1H), 4.23 (t, $J = 7.54$ Hz, 1H), 4.02 (t, $J = 7.84$, 1H), 3.73 (t, $J = 8.44$, 1H), 3.54 (d, $J = 5.86$, 1H), 1.56 (s, 3H), 1.51 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H); **Minor** δ 6.13 (d, $J = 3.67$, 1H), 5.53 (m, 1H), 4.96 (m, 1H), 4.38 (dd, $J = 7.07$, 8.52 Hz, 1H), 3.95 (d, $J = 3.77$ Hz, 1H), 3.83 (dd, $J = 7.05$, 8.63 Hz, 1H), 3.72 (t, $J = 8.49$, 1H), 1.54 (s, 3H),1.47 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) **Major** δ 169.6, 157.1, 129.0, 110.7, 110.1, 97.0, 71.1, 71.0, 68.7, 68.3, 26.1, 25.9, 25.4, 25.4; MS *m*/*z* EI^+ 285 ($M - CH_3)^+$; HRMS (EI^+) calcd for $C_{13}H_{17}O_7$ ($M - CH_3)^+$ 285.0974, found 285.0948.

(3*R*,4*S*,1′*R*,1″*R*)-3,4-Bis(2,2-dimethyl-[1,3]dioxolan-4-yl)-3,4,5-trihydroxy-4,5-dihydrofuran-2-one (14). Olefin **13** (506.9 mg, 1.69 mmol) was dissolved in pyridine (21 mL), and the mixture was cooled to 0 °C. A solution of OsO_4 in *tert*-butyl alcohol (11 mL, 0.16 M, 1.69 mmol) was added, and the mixture was allowed to warm to room temperature and was stirred for 24 h. The solution was cooled to 0 °C, and $NaHSO_3$ (4.6 g, 44 mmol), pyridine (60 mL), and H_2O (69 mL) were added. This mixture was stirred for an additional 30 min at 0 °C, and for 1 h at room temperature. The solution was extracted with $CHCl_3$. The organic extracts were combined, dried over $MgSO_4$, filtered, concentrated, and azeotroped with toluene to remove traces of pyridine. This gave 622 mg of a sticky, brown solid, which was purified by flash chromatography (SiO_2, 1:2 hexanes/EtOAc). This provided **14** (370 mg, 66%) as an inseparable 2:1 mixture of diastereomers at the hemiacetal carbon: $R_f = 0.68$ (SiO_2, 1:2 hexanes/EtOAc); $[\alpha]^{20}_D$ −49.3° (*c* 0.67, $CHCl_3$); IR (film) 3430 (br), 1782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.63 (m, 1.5H), 5.35 (m, 0.6H), 4.62 (t, $J = 6.75$ Hz, 1H), 4.57 (t, $J = 6.80$ Hz, 1H), 4.52 (m, 2H), 4.39 (dd, $J = 4.57$, 9.43 Hz, 1H), 4.37 (s, 0.5H), 4.34 (s, 0.5H), 4.27 (dd, $J = 6.05$, 8.73 Hz, 0.6H), 4.21 (dd, $J = 6.55$, 8.34 Hz, 0.6H), 4.17 (dd, $J = 6.75$, 9.43 Hz, 1H), 4.08 (m, 3H), 3.60 (s, 1H), 3.27 (s, 0.6H), 3.22 (s, 1H), 3.15 (s, 0.6H), 1.48 (s, 1.7H), 1.47 (s, 1.7H), 1.46 (s, 3H), 1.44 (s, 1.7H), 1.44 (s, 1.7H), 1.43 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) **Major** δ 173.3, 111.0, 109.7, 97.4, 80.7, 77.2, 76.2, 74.3, 65.0, 64.1, 26.0, 25.7, 25.4, 24.6; **Minor** δ 112.1, 110.1, 101.4, 81.4, 77.8, 75.3, 74.0, 65.4, 64.3, 26.0, 25.8, 25.1, 24.9; MS *m*/*z* EI^+ 319 ($M - CH_3)^+$, CI^+ 319 ($M - CH_3)^+$; HRMS (EI^+) calcd for $C_{13}H_{19}O_9$ ($M - CH_3)^+$ 319.1029, found 319.1045.

(2*R*,3*S*,1′*R*,1″*R*)-2,3-Bis(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,3-dihydroxy-4-(carbaldehyde oxime)butyric Acid (15). Hydroxylamine hydrochloride (75.5 mg, 1.08 mmol) was added to a flask containing triol **14** (181.5 mg, 0.54 mmol). The mixture was dissolved in THF (5 mL) and methanol (5 mL). Pyridine (220 μL, 2.7 mmol) was added, and the mixture was then heated to 70 °C for 5.5 h. The solution was concentrated under vacuum and azeotroped with toluene to remove traces of pyridine. Flash chromatography (SiO_2, 7:3 EtOAc/MeOH) provided **15** (178.5 mg, 94%): $R_f = 0.5$ (SiO_2, 7:3 EtOAc/MeOH); $[\alpha]^{20}_D$ −1.8° (*c* 1.1, CH_3OH); IR (film) 3394 (br), 1728 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.24 (s, 1H, C*H*═N), 4.70 (t, $J = 7.23$ Hz, 1H), 4.56 (t, $J = 6.96$, 1H), 3.88 (m, 2H), 3.82 (m, 2H), 1.35 (s, 3H, CH_3), 1.32 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 150.0, 110.7, 109.1, 79.0, 77.9, 77.8, 66.3, 66.0, 26.3, 26.1, 25.8; MS *m*/*z* ESI^+ 350 ($M + H)^+$, FAB^+ 372 ($M + Na)^+$, FAB^- 348 ($M - H)^-$; HRMS (FAB^-) calcd for $C_{14}H_{22}NO_9$ ($M - H)^-$ 348.1295, found 348.1271.

(2*R*,3*S*,4*R*,1′*R*)-4-(1,2-Dihydroxyethyl)-3,4-dihydroxy-2-hydroxymethyl-5-oxotetrahydrofuran-3-carbaldehyde Oxime (16). PPTS (129 mg, 0.51 mmol) and methanol (15 mL) were added to a flask containing acid **15** (178.5 mg, 0.51 mmol). This solution was stirred under N_2 at 65 °C for 15 h. The solution was concentrated, and the product was used without purification in the subsequent reaction. A small sample of **16** was purified by flash chromatography (SiO_2, 1:6:1 hexanes/EtOAc/MeOH, $R_f = 0.3$) for characterization: $[\alpha]^{20}_D$ +100.1° (*c* 0.7, CH_3OH); IR (film) 3280 (br), 1770 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.58 (s, 1H), 4.83 (dd, $J = 2.68$, 7.64 Hz, 1H), 4.08 (dd, $J = 3.87$, 6.75 Hz, 1H), 3.90 (dd, $J = 2.68$, 12.70 Hz, 1H), 3.82 (dd, $J = 7.64$, 12.70 Hz, 1H), 3.81 (dd, $J = 3.87$, 11.41 Hz, 1H), 3.74 (dd, $J = 6.75$, 11.41, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 148.1, 85.0, 80.9, 80.3, 73.4, 62.6, 61.0; MS *m*/*z* ESI^+ 252 ($M + H)^+$, FAB^+ 252 ($M + H)^+$, HRMS (FAB^-) calcd for $C_8H_{12}NO_8$ ($M - H)^-$ 250.0563, found 250.0603.

(2*R*,3*S*,4*R*,1′*R*)-4-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3,4-dihydroxy-2-hydroxymethyl-5-oxotetrahydrofuran-3-carbaldehyde Oxime (17). A mixture of **16** (ca. 128 mg, 0.51 mmol) and PPTS (129 mg, 0.51 mmol) was dissolved in 2,2-dimethoxypropane (75.5 mL, 0.61 mmol) and DMF (6 mL). The mixture was stirred under N_2 for 5.5 h at room temperature, concentrated under vacuum, and azeotroped with toluene to remove traces of DMF. The product was purified by flash chromatography (SiO_2, 1:2 hexanes/EtOAc, $R_f = 0.3$). This provided **17** (101.8 mg, 68% for two steps) as well as recovered **16** (24 mg, 19%): $[\alpha]^{20}_D$ +73.4° (*c* 1.6, CH_3OH); IR (film) 3382 (br), 1770 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.50 (s, 1H), 4.83 (dd, $J = 3.48$, 6.96 Hz, 1H), 4.41 (dd, $J = 6.42$, 8.30 Hz, 1H), 4.01 (dd, $J = 6.43$, 8.03 Hz, 1H), 3.90 (t, $J = 8.30$ Hz, 1H), 3.82 (m, 2H), 1.40 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.6, 147.5, 110.8, 84.8, 81.1, 79.4, 76.5, 65.7, 60.9, 26.2, 25.9; MS *m*/*z* EI^+ 276 ($M - CH_3)^+$, CI^+ 292 ($M + H)^+$, CI^+ 276 ($M - CH_3)^+$; HRMS (EI^+) calcd for $C_{10}H_{14}NO_8$ ($M - CH_3)^+$ 276.0719, found 276.0707.

(2*R*,3*S*,4*R*,1′*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)-4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3,4-dihydroxy-5-oxotet-

rahydrofuran-3-carbaldehyde Oxime (18). Imidazole (64 mg, 0.94 mmol), *tert*-buyldimethylsilyl chloride (73 mg, 0.48 mmol), and DMF (2 mL) were added to a flask containing acetonide **17** (136.2 mg, 0.47 mmol). The reaction mixture was stirred for 12 h under N_2 at room temperature, concentrated under vacuum, and azeotroped with toluene to remove traces of DMF. The product was then purified by flash chromatography (SiO_2, 6:4 hexanes/EtOAc). This provided a small amount of bis-silylated material (22 mg, 9%, $R_f = 0.8$), desired product **18** (105 mg, 56%, $R_f = 0.4$), and unreacted starting material **17** (26 mg, 19%): $[\alpha]^{20}_D$ +78.8° (*c* 1.0, $CHCl_3$); IR (film) 3362 (br), 1782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 5.17 (s, 1H), 4.71 (t, $J = 3.75$ Hz, 1H), 4.52 (dd, $J = 6.16$, 8.57 Hz, 1H), 4.12 (m, 3H), 3.81 (t, $J = 8.57$, 1H), 3.69 (s, 1H), 1.47 (s, 6H), 0.89 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 147.8, 109.9, 80.4, 79.5, 78.2, 74.2, 64.4, 60.4, 25.9, 25.7, 25.6, 18.0, −5.6, −5.7; MS *m*/*z* EI^+ 390 $(M - CH_3)^+$; HRMS (EI^+) calcd for $C_{16}H_{28}NO_8Si$ $(M - CH_3)^+$ 390.1584, found 390.1574.

(2*R*,3*S*,4*R*,1′*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3,4-dihydroxy-5-oxotetrahydrofuran-3-[(*tert*-butyldiphenylsilyloxy)carbaldehyde oxime] (19). Lactone **17** (382.1 mg, 1.313 mmol) and imidazole (357 mg, 5.25 mmol) were dissolved in anhydrous DMF (5 mL). *tert*-Butyldiphenylsilyl chloride (751 μL, 2.88 mmol) was added, and the reaction mixture was stirred under N_2 at room temperature. After 16 h, the solution was concentrated under high vaccuum (bath temperature of 35 °C) and azeotroped with toluene to remove residual DMF. The residue was redissolved in EtOAc and washed sequentially with NH_4Cl, H_2O, and NaCl. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuum to provide 1.41 g crude material. Flash chromatography on silica gel (8:2 hexanes/EtOAc) provided bis-silyl ether **19** (571.6 mg, 57%) as a clear oil: $R_f = 0.2$ (SiO_2, 8:2 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.60 (m, 8H), 7.40 (m, 12H), 4.79 (s, 1H), 4.64 (t, $J = 4.37$ Hz, 1H), 4.34 (t, $J = 7.25$ Hz, 1H), 3.92 (t, $J = 4.92$ Hz, 2H), 3.87 (m, 2H), 3.76 (s, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.10 (s, 9H), 1.04 (s, 9H); MS *m*/*z* ESI^+ 790 $(M + Na)^+$, ESI^- 802 $(M + Cl)^-$.

(2*R*,3*S*,4*R*,1′*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-4-(1,2-dihydroxyethyl)-3,4-dihydroxy-5-oxotetrahydrofuran-3-[(*tert*-butyldiphenylsilyloxy)carbaldehyde oxime] (20). Acetonide **19** (380 mg, 0.50 mmol) and PPTS (186 mg, 0.74 mmol) were dissolved in methanol (25 mL), and the reaction mixture was heated to 55 °C for 4 h. Although some starting material remained at this point on the basis of TLC analysis, loss of the TBDPS groups started to become competitive with acetonide removal. The reaction was then cooled to room temperature and concentrated under vacuum. Flash chromatography on silica gel (1:1 hexanes/EtOAc) gave **20** (290 mg, 81%) as a clear oil: $R_f = 0.48$ (SiO_2, 1:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +42.94° (*c* 0.85, CH_2Cl_2); IR (film) 3400, 1775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.65 (m, 8H), 7.40, (m, 12H), 5.34 (s, 1H), 4.71 (t, $J = 4.77$ Hz, 1H), 4.16 (s, 1H), 4.02 (m, 1H), 4.00 (dd, $J = 4.77$, 11.71 Hz, 1H), 3.93 (dd, $J = 4.77$, 11.71 Hz, 1H), 3.68 (m, 3H), 1.10 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 153.3, 135.6, 135.4, 135.3, 135.3, 132.4, 132.3, 132.1, 131.9, 130.1, 130.0, 130.0, 128.1, 127.9, 127.9, 127.7, 127.7, 82.4, 79.9, 79.7, 69.8, 61.1, 60.9, 26.8, 26.6, 19.0; MS *m*/*z* ESI^+ 750 $(M + Na)^+$, ESI^- 762 $(M + Cl)^-$; HRMS ($MALDI^+$) calcd for $C_{40}H_{49}NO_8Si_2Na$ $(M + Na^+)$ 750.2894, found 750.2873.

(2*R*,3*S*,4*R*,1′*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3,4-dihydroxy-4-[1′-hydroxy-2′-(2-trimethylsilylethoxymethoxy)ethyl]-5-oxo-tetrahydrofuran-3-[(*tert*-butyldiphenylsilyloxy)carbaldehyde oxime] (21). Tetraol **20** (35.1 mg, 0.048 mmol) was dissolved in CH_2Cl_2 (5 mL) and was stirred under N_2. 2,6-Di-*tert*-butylpyridine (163 μL, 0.73 mmol) was added, and the solution was cooled to 0 °C. A solution of anhydrous SEM-Cl (256 μL, 0.94 M in benzene, 0.24 mmol) was added, and the reaction was stirred under N_2 for 48 h. During this time the cooling bath was allowed to warm to room temperature, but the reaction flask was kept in the bath. After 48 h, TLC indicated that the undesired bis-SEM ether was starting to become more prominent, so the reaction was concentrated under vacuum. Flash chromatography on silica gel (gradient, 9:1 → 8:2 hexanes/EtOAc) gave bis-SEM ether (11.5 mg, 24%, $R_f = 0.66$, SiO_2, 6:4 hexanes/EtOAc), as well as **21** (23 mg, 56%, $R_f = 0.5$, SiO_2, 6:4 hexanes/EtOAc) and a small amount of the SEM ether of the secondary alcohol (4.3 mg, 11%, $R_f = 0.45$, SiO_2, 6:4 hexanes/EtOAc): $[\alpha]^{20}_D$ +43.19° (*c* = 0.47, CH_2Cl_2); IR (film) 3390 (br), 1778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.62 (m, 8H), 7.40 (m, 12H), 5.34 (s, 1H), 4.70 (t, $J = 3.97$ Hz, 1H), 4.61 (s, 2H), 4.31 (s, 1H), 4.27 (t, $J = 4.86$ Hz, 1H), 3.98 (dd, $J = 3.97$, 12.11 Hz, 1H), 3.94 (dd, $J = 4.27$, 12.11 Hz, 1H), 3.87 (dd, $J = 4.44$, 11.19 Hz, 1H), 3.74 (m, 1H), 3.63 (m, 2H), 1.09 (s, 9H), 1.04 (s, 9H), 0.95 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 153.3, 135.6, 135.5, 135.4, 132.5, 130.1, 130.0, 129.9, 127.9, 127.9, 127.7, 95.6, 81.5, 80.5, 79.5, 69.2, 68.1, 65.9, 61.3, 26.9, 26.7, 19.2, 19.1, 18.0, −1.3; MS *m*/*z* ESI^+ 880 $(M + Na)^+$, ESI^- 892 $(M + Cl)^-$; HRMS ($MALDI^+$) calcd for $C_{46}H_{63}NO_9Si_3Na$ $(M + Na^+)$ 880.3708, found 880.3688.

(4*R*,5*R*,8*R*,9*S*)-8-(*tert*-Butyldiphenylsilyloxymethyl)-9-hydroxy-2,2-dimethyl-6-oxo-4-(2-trimethylsilylethoxymethoxymethyl)-1,3,7-trioxa-spiro[4.4]nonane-9-[(*tert*-butyldiphenylsilyloxy)carbaldehyde oxime] (22). Triol **21** (12 mg, 0.014 mmol) and PPTS (4 mg, 0.016 mmol) were dissolved in CH_2Cl_2, and the solution was stirred at room temperature under N_2. 2-Methoxypropene (10 μL, 0.10 mmol) was added, and the reaction mixture was sealed and stirred overnight. After 48 h the reaction was mostly complete by TLC, but a small amount of starting material remained. After an additional 48 h, the reaction mixture was concentrated under vacuum. Flash chromatography on silica gel (9:1 hexanes/EtOAc) gave **22** (6.5 mg, 52%, $R_f = 0.32$) and **23** (4.5 mg, 36%, $R_f = 0.26$). Data for **22**: $[\alpha]^{20}_D$ +54.33° (*c* = 1.34, CH_2Cl_2); IR (film) 34000 (br), 1790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.62 (m, 9H), 7.40 (m, 9H), 7.26 (m, 2H), 5.52 (s, 1H), 4.92 (dd, $J = 3.38$, 7.74 Hz, 1H), 4.66 (t, $J = 3.18$ Hz, 1H), 4.64 (AB, $J_{AB} = 6.95$ Hz, $\Delta\nu_{AB} = 37.48$ Hz, 2H), 4.13 (dd, $J = 3.38$, 11.32 Hz, 1H), 3.96 (d, $J = 3.18$ Hz, 2H), 3.78 (dd, $J = 7.74$, 11.32 Hz, 1H), 3.62 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 1.08 (s, 9H), 1.01 (s, 9H), 0.94 (t, $J = 8.34$ Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 152.1, 135.7, 135.5, 135.4, 135.4, 132.9, 132.8, 132.1, 131.6, 130.1, 130.0, 129.8, 129.8, 127.9, 127.9, 127.6, 111.1, 95.0, 84.7, 80.2, 79.5, 77.5, 65.5, 64.9, 62.3, 27.0, 26.9, 26.6, 25.1, 19.2, 19.1, 18.0, −1.4; MS *m*/*z* ESI^+ 920 $(M + Na)^+$, ESI^- 932 $(M + Cl)^-$; HRMS ($MALDI^+$) calcd for $C_{49}H_{67}NO_9Si_3Na$ $(M + Na^+)$ 920.4021, found 920.4062.

(4*R*,4a*R*,7*R*,7a*S*)-7-(*tert*-Butyldiphenylsilyloxymethyl)-4a-hydroxy-2,2-dimethyl-5-oxo-4-(2-trimethylsilylethoxymethoxymethyl)dihydrofuro[3,4-*d*][1,3]dioxine-7a-[(*tert*-butyldiphenylsilyloxy)carbaldehyde oxime] (23). $[\alpha]^{20}_D$ −2.68° (*c* = 0.97, CH_2Cl_2); IR (film) 34000 (br), 1806 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.65 (m, 9H), 7.40 (m, 13H), 4.74 (s, 1H), 4.66 (AB, $J_{AB} = 6.55$ Hz, $\Delta\nu_{AB} = 9.47$ Hz, 2H), 4.57 (dd, $J = 5.06$, 8.64 Hz, 1H), 4.06 (d, $J = 4.96$ Hz, 2H), 4.03 (t, $J = 9.43$ Hz, 1H), 3.94 (t, $J = 5.06$ Hz, 1H), 3.83 (dd, $J = 5.36$, 10.12 Hz, 1H), 3.61 (dd, $J = 7.54$, 8.93 Hz, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 1.14 (s, 9H), 1.10 (s, 9H), 0.95 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 156.8, 135.6, 135.4, 135.3, 135.3, 130.3, 130.3, 130.0, 129.9, 128.0, 127.9, 127.8, 127.6, 100.2, 95.1, 83.2, 78.0, 73.6, 70.6, 65.8, 65.1, 58.8, 29.6, 26.9, 26.8, 22.7, 19.1, 19.1, 18.0, −1.4; MS *m*/*z* ESI^+ 920 $(M + Na)^+$, ESI^- 932 $(M + Cl)^-$; HRMS ($MALDI^+$) calcd for $C_{49}H_{67}NO_9Si_3Na$ $(M + Na^+)$ 920.4021, found 920.3983.

(4*R*,5*R*,8*R*,9*S*)-9-Hydroxy-8-hydroxymethyl-2,2-dimethyl-6-oxo-4-(2-trimethylsilylethoxymethoxymethyl)-1,3,7-trioxaspiro[4.4]nonane-9-carbaldehyde Oxime (24). Silyl ether **22** (33 mg, 0.037 mmol) was dissolved in anhydrous THF (10 mL). AcOH (10.5 μL, 0.18 mmol) was added, and the mixture was stirred at room temperature. A solution of TBAF (75.4 μL, 1 M in THF, 0.075 mmol) was added, and the reaction mixture stirred for 30 min at room temperature. The reaction mixture was then concentrated under vacuum, and flash chromatography on silica gel (1:1 hexanes/EtOAc) gave **24** (12.2 mg, 80%) as a clear oil: $R_f = 0.18$ (SiO_2, 6:4 hexanes/

EtOAc); IR (film) 3400 (br), 1791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 5.24 (s, 1H), 4.85 (t, J = 4.37 Hz, 1H), 4.77 (m, 3H), 4.15 (m, 2H), 4.07 (dd, J = 4.37, 11.91 Hz, 1H), 3.93 (dd, J = 4.37, 11.91 Hz, 1H), 3.65 (m, 2H), 1.47 (s, 3H), 1.45 (s, 3H), 0.96 (m, 2H), 0.03 (s, 9H,); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 148.0, 111.2, 95.2, 84.8, 81.5, 78.5, 66.1, 64.1, 59.8, 27.0, 25.2, 18.0, −1.4; MS m/z ESI$^+$ 444 $(M + Na)^+$, ESI$^-$ 456 $(M + Cl)^-$; HRMS (MALDI$^+$) calcd for $C_{17}H_{31}NO_9SiNa$ ($M + Na^+$) 444.1666, found 444.1652.

(4*R*,5*R*,8*R*,9*S*)-9-Hydroxy-8-hydroxymethyl-2,2-dimethyl-6-oxo-4-(2-trimethylsilylethoxymethoxymethyl)-1,3,7-trioxaspiro[4.4]nonane-9-carbaldehyde (25). Oxime **24** (7.3 mg, 0.017 mmol) was dissolved in CH_2Cl_2 (8 mL) and methanol (0.4 mL). $NaHCO_3$ (15 mg) was added, and the mixture was cooled to −78 °C and stirred for 20 min. O_3 was bubbled through the solution for 2 min (until a blue color persisted). The solution was then kept at −78 °C for 1 h (without stirring) and then at −70 °C overnight. After 16 h, dimethyl sulfide (2 mL) was added, and the reaction was warmed to room temperature. After 10 min, the mixture was concentrated under vacuum, and flash chromatography (gradient, 6:4 → 1:2 hexanes/EtOAc) gave aldehyde **25** (5 mg, 69%, R_f = 0.47, SiO_2, 1:1 hexanes/EtOAc) and unreacted starting material **24** (2.2 mg, 30%): IR (film) 3434 (br), 1792, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 5.19 (s, 1H), 5.01 (t, J = 5.56 Hz, 1H), 4.84 (t, J = 3.38 Hz, 1H), 4.69 (AB, J_{AB} = 6.55 Hz, $\Delta\nu_{AB}$ = 6.36 Hz, 2H), 3.98 (dd, J = 3.77, 11.91 Hz, 1H), 3.95 (m, 2H), 3.90 (dd, J = 3.38, 11.91 Hz, 1H), 3.64 (m, 2H), 1.48 (s, 3H), 1.46 (s, 3H), 0.96 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 172.2, 111.4, 94.9, 85.6, 82.0, 79.4, 79.3, 66.1, 63.6, 59.3, 26.7, 25.1, 18.0, −1.4; MS m/z ESI$^-$ 405 $(M - H)^-$; HRMS (MALDI$^+$) calcd for $C_{17}H_{31}O_9Si$ ($M + H^+$) 407.1737, found 407.1743.

(4*R*,5*R*,8*R*,9*S*)-9-Hydroxy-8-hydroxymethyl-2,2-dimethyl-6-oxo-4-(2-trimethylsilylethoxymethoxymethyl)-1,3,7-trioxaspiro[4.4]nonane-9-carboxylic Acid (26). Aldehyde **25** (8 mg, 0.020 mmol) was dissolved in *tert*-butyl alcohol (1.2 mL) and H_2O (0.3 mL). NaH_2PO_4 (12 mg, 0.087 mmol) and a solution of 2-methyl-2-butene (83 μL, 2 M in THF, 0.17 mmol) were added, and the reaction mixture was stirred for 5 min at room temperature. $NaClO_2$ (12 mg, 0.13 mmol) was added, and the reaction mixture was stirred at room temperature. After 3 h, the reaction was quenched with H_2O (2 mL), and 5 drops of 5% HCl were added (to adjust the pH to ca. 1.5). The aqueous layer was extracted with $CHCl_3$, dried over $MgSO_4$, filtered, and concentrated under vacuum to provide **26** (12.3 mg), which was used without purification: ^1H NMR (500 MHz, $CDCl_3$) δ 4.99 (t, J = 3.08 Hz, 1H), 4.91 (t, J = 2.98 Hz, 1H), 4.83 (s, 2H), 4.33 (m, 2H), 4.17 (m, 2H), 3.70 (m, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 0.96 (m, 2H), 0.03 (s, 9H).

(4*R*,5*R*,8*R*,9*S*)-9-Hydroxy-8-hydroxymethyl-2,2-dimethyl-6-oxo-4-(2-trimethylsilylethoxymethoxymethyl)-1,3,7-trioxaspiro[4.4]nonane-9-carboxylic Acid Benzyl Ester (27). Crude acid **26** (7.5 mg) was dissolved in anhydrous THF (3 mL) and stirred under N_2 at room temperature. A solution of DCBI (100 μL, 0.636 M in toluene, 0.064 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. The reaction was then concentrated under vacuum. Flash chromatography on silica gel (6:4 hexanes/EtOAc) provided **27** (3.7 mg, 70% for 2 steps): R_f = 0.4 (SiO_2, 6:4 hexanes/EtOAc); $[\alpha]^{20}_D$ +36.47° (c 0.26, CH_2Cl_2); IR (film) 3400 (br), 1793, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39, (m, 5H), 5.84, (s, 1H), 5.26, (AB, J_{AB} = 12.11 Hz, $\Delta\nu_{AB}$ = 9.33 Hz, 2H), 5.09, (t, J = 4.86 Hz, 1H), 4.89, (dd, J = 4.96, 6.35, 1H), 4.70, (AB, J_{AB} = 6.75 Hz, $\Delta\nu_{AB}$ = 21.19 Hz, 2H), 4.11, (dd, J = 6.35, 11.32 Hz, 1H), 4.07, (m, 1H), 4.02 (m, 1H), 3.93, (dd, J = 4.96, 11.51 Hz, 1H), 3.61, (m, 2H), 1.42, (s, 3H), 1.27, (s, 3H), 0.94, (m, 2H), 0.03, (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 168.9, 134.7, 129.1, 129.0, 128.9, 112.0, 95.4, 85.9, 81.4, 81.3, 77.5, 68.4, 66.3, 64.5, 60.3, 27.5, 25.8, 18.3, −1.1; MS m/z ESI$^+$ 535 $(M + Na)^+$, ESI$^-$ 547 $(M + Cl)^-$, ESI$^-$ 511 $(M - H)^-$; HRMS (MALDI$^+$) calcd for $C_{24}H_{36}O_{10}SiNa$ ($M + Na^+$) 535.1975, found 535.1978.

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Supporting Information Available: Complete X-ray crystallography data for compounds **14** and **18**, and photocopies of selected ^1H and ^{13}C NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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