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Total Synthesis of Zaragozic Acid C: Implementation of Photochemical C(sp^3)−H Acylation

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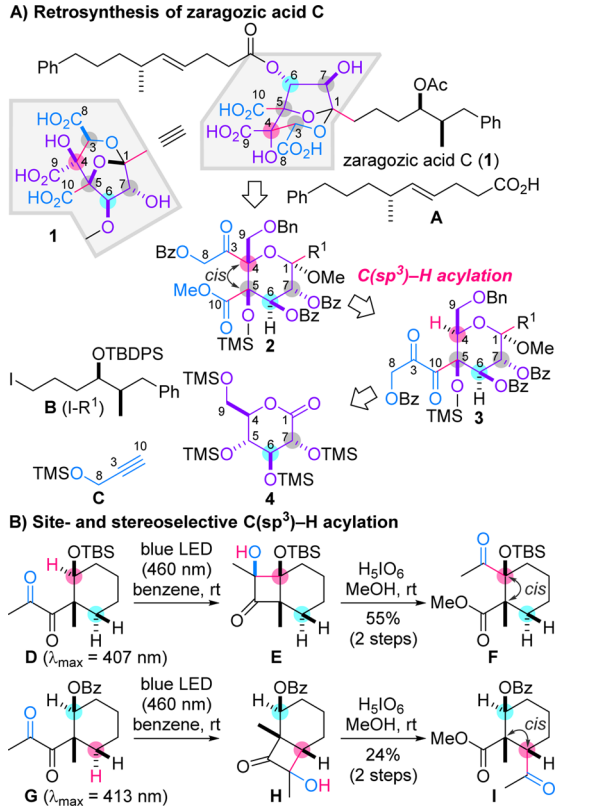
Supporting Information

ABSTRACT: Zaragozic acid C (**1**) was isolated as a potent squalene synthase inhibitor. The 2,8-dioxabicyclo[3.2.1]octane core of **1** is decorated with the three hydroxycarbonyl (C3,4,5), two hydroxy (C4,7), one acyloxy (C6), and one alkyl (C1) groups. Installation of the contiguous C4- and C5-fully substituted carbons presents a formidable synthetic challenge. Our approach to address this problem used a two-step photochemical C(sp^3)−H acylation. Persilylated D-gluconolactone **4** was derivatized into **3** with the 1,2-diketone moiety at the C5-tetrasubstituted center. Norrish−Yang cyclization of **3** under violet LED irradiation followed by oxidative opening of the resultant α-hydroxycyclobutanone regio- and stereoselectively transformed the electron-rich tertiary C(sp^3)−H bond at C4 into a C(sp^3)−C bond to produce densely functionalized **2**. A subsequent series of judicious functional group transformations gave rise to **1**.

Zaragozic acid C (**1**) (Scheme 1A) is a representative example of a family of natural products, zaragozic acids[1] and squalestatins,[2] which constitute a class of potent inhibitors of mammalian squalene synthase (K_i = 29−78 pM).[3] Squalene synthase plays a key role in catalyzing the conversion of presqualene pyrophosphate into squalene at the last branching point of cholesterol biosynthesis, and thus, zaragozic acids/squalestatins are promising lead structures for the development of cholesterol-lowering drugs. Recent findings of other pharmacologically important activities have spurred renewed interest in these molecules. Several act as nanomolar inhibitors of ras farnesyl protein transferase, which is a useful property for antitumor agents.[4] Moreover, these compounds protect neurons against the toxic effects of prions and amyloid-β peptides[5] and inhibit dengue virus replication and hepatitis C virus production.[6]

Zaragozic acid C (**1**) is characterized by a hydrophilic 2,8-dioxabicyclo[3.2.1]octane-4,6,7-trihydroxy-3,4,5-tricarboxylic acid core with an array of six stereogenic centers and hydrophobic C6-acyloxy and C1-alkyl side chains. The two adjacent fully substituted carbons at C4 and C5 within the densely oxygenated core represent a further challenge for its chemical synthesis. Inspired by the complex architecture and potential benefits for human medicine, various creative strategies and tactics have been tested, ultimately resulting in 10 total[7] and three formal syntheses[8] of **1** and congeners.[9] These syntheses constructed the unusually hindered oxygen-based tetrasubstituted C4- and C5-centers by osmylation of a tri- or tetrasubstituted C=C bond,[7c,g,j,8a] the addition of a carbon nucleophile to the C=O bond,[7a,b,d−f,h] alkylation of a trisubstituted α-alkoxy anion,[7b,d,f,i] or pericyclic reaction.[7e,8b] Here we disclose the design and execution of a novel strategy for the total synthesis of **1**. Specifically, photochemical C(sp^3)−H functionalization was devised as the key transformation for securing the cumbersome C4,5-stereochemical relationship.

Scheme 1. Synthetic Plan for Zaragozic Acid C and Site- and Stereoselective C(sp^3)−H Acylation



The direct transformation of C(sp^3)−H bonds into C(sp^3)−C bonds enables new strategic disconnections during the planning of a synthetic route.[10] Our retrosynthesis of **1** was based on photochemically induced C(sp^3)−H acylation, which we previously reported (Scheme 1A).[11] Photoinduced Norrish−Yang cyclization of 1,2-diketone **3**[12,13] followed by oxidative ring opening would substitute the tertiary C4-H with the α-

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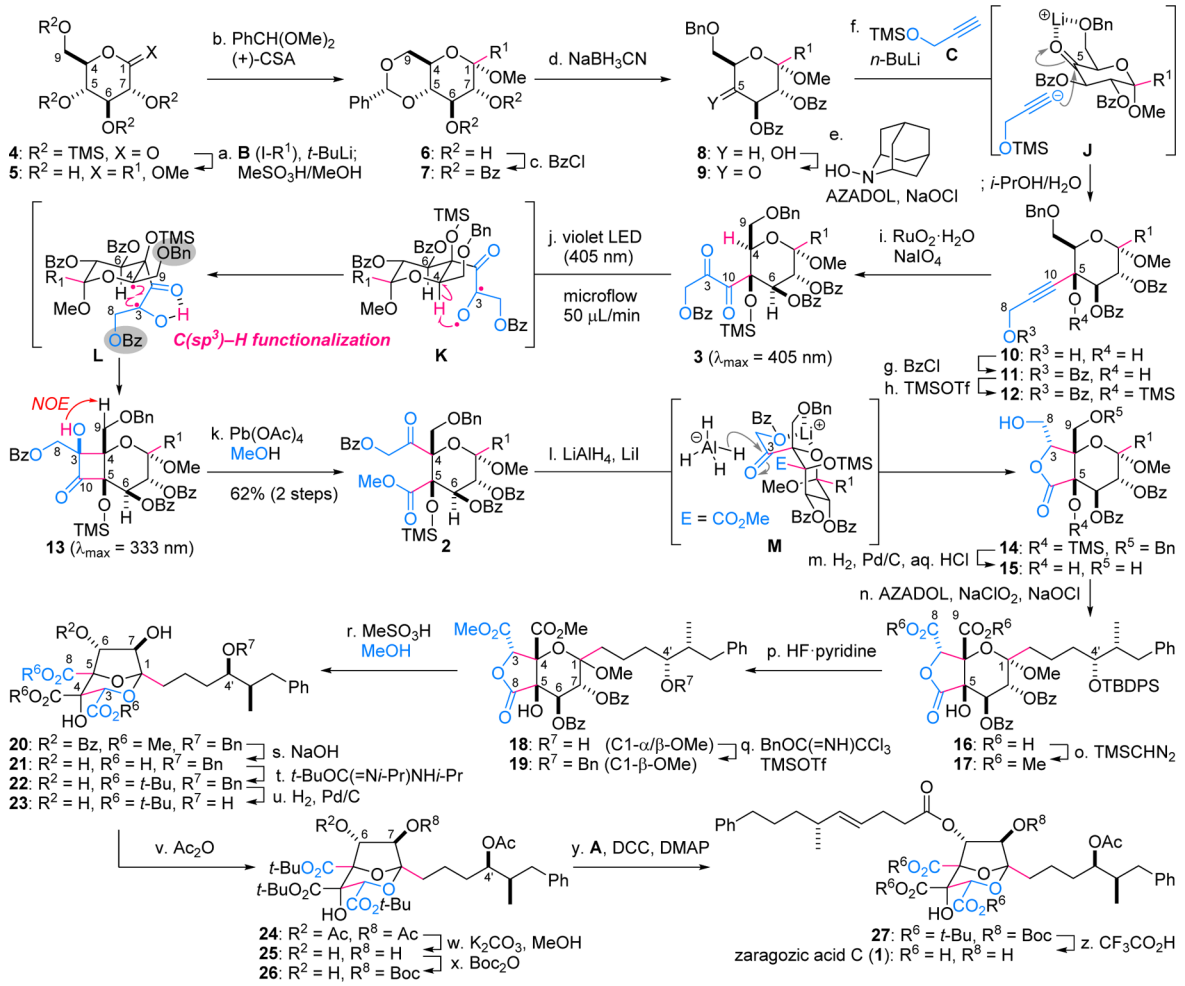
Scheme 2. Total Synthesis of Zaragozic Acid C[a]



[a]Reagents and conditions: (a) **B**, *t*-BuLi, hexane/Et_2O, −78 °C; $MeSO_3H$, MeOH, −78 to 0 °C; (b) $PhCH(OMe)_2$, (+)-10-camphorsulfonic acid (CSA), MeCN, 0 °C, 64% (two steps); (c) benzoyl chloride (BzCl), 4-dimethylaminopyridine (DMAP) (5 mol %), pyridine, rt, 93%; (d) $NaBH_3CN$, 4 M HCl in dioxane, 4 Å MS, THF, 0 °C, 84%; (e) AZADOL (5 mol %), KBr (10 mol %), 1.2 M aq. NaOCl, saturated aq. $NaHCO_3$/CH_2Cl_2, rt; (f) **C**, *n*-BuLi, hexane/Et_2O, −78 to 0 °C; *i*-PrOH/H_2O, rt; (g) BzCl, pyridine, rt, 76% (three steps); (h) TMSOTf, pyridine, CH_2Cl_2, rt, 86%; (i) $RuO_2·H_2O$ (30 mol %), $NaIO_4$, MeCN/CCl_4/H_2O, rt, 72%; (j) violet (405 nm) LED, benzene, 25 °C, 50 μL/min, 85% (NMR yield); (k) $Pb(OAc)_4$, MeOH/benzene, rt, 62% (two steps); (l) $LiAlH_4$, LiI, Et_2O, −78 °C, 65%; (m) H_2, Pd/C, 1 M aq. HCl, MeOH, rt; (n) AZADOL (20 mol %), $NaClO_2$, NaOCl, MeCN/pH 7 buffer, rt; (o) trimethylsilyldiazomethane ($TMSCHN_2$), MeOH/benzene, rt, 75% (three steps); (p) HF·pyridine, MeCN, rt, 95%; (q) $BnC(=NH)CCl_3$, TMSOTf, CH_2Cl_2, 0 °C, 85%; (r) 0.2 M $MeSO_3H$ in MeOH, 100 °C, 40%; (s) 1 M aq. NaOH/1,4-dioxane, 80 °C; (t) *t*-BuOC(=N*i*-Pr)NH*i*-Pr, CH_2Cl_2, rt, 39% (two steps); (u) H_2, Pd/C, MeOH, rt, 84%; (v) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 87%; (w) 0.2% K_2CO_3 in MeOH, 0 °C, 88%; (x) di-*tert*-butyl dicarbonate (Boc_2O), 4-pyrrolidinopyridine, Et_3N, CH_2Cl_2, 0 °C, 100%; (y) **A**, *N*,*N*′-dicyclohexylcarbodiimide (DCC), DMAP, CH_2Cl_2, rt, 70%; (z) CF_3CO_2H, CH_2Cl_2, rt, 100%.

hydroxyacyl group of **2**. As **2** possesses the C4,5,6,7-stereocenters of **1**, C3-reduction, C8,9-oxidation, C1-acetal reorganization, and C6-OH acylation would transform **2** into **1**. Retrosynthetically, the key precursor **3** can be traced back to commercially available persilylated D-gluconolactone **4**, which shares the C6,7-stereochemistry with **3**. Thus, **1** was to be assembled from four structurally simple components: carboxylic acid **A**, C1-lipid tail **B**,[14] C5-side chain **C**, and pyranose **4**.

The presumed Norrish−Yang cyclization of **3** involves γ-hydrogen abstraction by a photogenerated C3-oxyl radical, and thus, the reaction at C6-H could compete with that at C4-H. We envisioned controlling the regioselectivity between C4-H and C6-H by lowering the electron-donating hyperconjugative effect of the C6-oxygen atom with its protective group.[10a,11] To explore this possibility, a proof-of-concept study was performed prior to the total synthesis (Scheme 1B). Differentially protected diketones **D** and **G**[14] were prepared and separately irradiated with a blue (460 nm) light-emitting diode (LED) in benzene. As a result, cyclobutanone formation occurred to furnish **E** and **H**, which were in turn subjected to oxidative cleavage, leading to **F** and **I**, respectively. While the same cis stereoselectivity for **E** and **H** would originate from the lower strain energy of the 6/4-cis-fused system compared with that of the trans counterpart, the protective groups would influence the site selectivity. The electrophilic oxyl radical reacted with the electron-rich ethereal methine C(sp^3)−H bond of **D**, and the electron-withdrawing Bz group of **G** switched the site selectivity, resulting in functionalization at the methylene (reactivity order: C*H*OTBS > CH_2 > C*H*OBz). According to these model studies, the key precursor **3** was designed to have the reactive ethereal C4−H bond and the less reactive BzO-substituted C6−H bond.

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The synthesis of **3** from gluconolactone derivative **4** required the introduction of the C1-alkyl and C5-alkynyl chains, placement of the appropriate protective groups, and oxidation of the alkyne to the 1,2-diketone (Scheme 2). First, the alkyllithium that was prepared from iodide **B** and *t*-BuLi attacked on the C1-lactone of **4**. The adduct was subsequently treated with $MeSO_3H$ in MeOH to form the C1-methyl acetal and to remove all of the TMS groups, leading to tetraol **5**. Cyclic acetal formation between the C5- and C9-OHs of **5** and benzoylation of the C6- and C7-OHs of **6** provided differentially protected **7**. $NaBH_3CN$[15] and HCl then regioselectively converted the benzylidene acetal of **7** to the C9-benzyl ether of **8**. The liberated C5-hydroxy group of **8** was in turn oxidized with catalytic AZADOL[16] in the presence of NaOCl to afford the C5-ketone of **9**. The lithium acetylide generated via deprotonation of three-carbon unit **C** was selectively added from the α-face to install the correct tetrasubstituted C5-stereocenter of **10**, as lithium-chelated intermediate **J** would block the β-face approach of the nucleophile. The desilylated primary C8-OH of **10** and the tertiary C5-OH of **11** were capped with Bz and TMS groups, respectively, forming **12**. The preparation of 1,2-diketone **3** was completed by oxidation of internal alkyne **12** by the action of a catalytic amount of RuO_2 and stoichiometric $NaIO_4$.[17]

We next investigated the pivotal photochemical C(sp^3)–H functionalization using the highly oxygenated substrate **3**. In doing so, a microflow reactor was selected over a batch reactor because light penetration can be achieved more effectively in a fixed microreaction space and continuous microflow conditions are easily applied to a large-scale reaction.[18] Similar to the conversion of **D** and **G** in Scheme 1B, **3** was irradiated with blue LED light. Although the Norrish–Yang cyclization occurred regio- and stereoselectively at C4, the desired C4,5-cis-fused cyclobutanone **13** was obtained in only 26% yield with 36% of **3** remaining. The use of a UV (365 nm) LED as an alternative higher-energy light resulted in a complex mixture of products, and the UV light was assumed to cause the degradation of the nonconjugated ketone of **13** (λ_{max} = 333 nm; Figure S2).[19] UV–vis analyses of the substrates revealed that the λ_{max} values of **D** (407 nm), **G** (413 nm), and **3** (405 nm) were comparable but that **3** had a significantly narrower UV–vis spectral bandwidth, presumably because of the fixed conformation of the 1,2-diketone moiety of the more substituted **3**. Accordingly, the inefficient Norrish–Yang cyclization of **3** can be attributed to its lower absorptivity in the blue-light region (460 nm). On the basis of these data and considerations, we decided to use a violet (405 nm) LED that matched the λ_{max} of **3** to attain this crucial transformation. After optimization of the flow rate (50 μL/min), the cis-fused bicycle **13** was produced as the sole isomer in 85% ^{1}H NMR yield. Because of its instability, **13** was treated with $Pb(OAc)_4$ in MeOH without purification, giving rise to keto ester **2** in 62% yield over two steps. Hence, the tertiary C4-H of **3** was effectively converted to the α-hydroxyacyl group of **2** by linking the hindered bond within the highly complex environment.

The regio- and stereoselective conversion from **3** to **13** under mild and neutral conditions exemplifies the power and reliability of the Norrish–Yang cyclization. In this reaction, the input of 405 nm light enables selective excitation of the 1,2-diketone structure of **3**. The thus-generated 1,2-biradical **K** abstracts the proximal ethereal C4–H bond selectively over not only the BzO-substituted C6–H bond but also the potentially reactive ethereal C9–H bond.[20] The resultant 1,4-biradical **L** undergoes facile C–C bond formation by avoiding the steric repulsion between the bulky C8- and C9-substituents to afford **13** with complete control of the C3,4-stereocenters. The stereochemistry of the C3-OH of **13** was confirmed by the NOE experiment.

The contiguous tetrasubstituted C4 and C5 centers of **2** were successfully established on the pyranose format. Next, stereoselective reduction of the C3-ketone and oxidation at the C8 and C9 positions from **2** generated **17**, which has the entire stereochemistry and carboskeleton of **1**. To introduce the C3-stereocenter, various reductants and additives were screened, and the reagent combination of $LiAlH_4$ and LiI[21] realized chemo- and stereoselective reduction of the C3-ketone of **2**.[22] The stereoselectivity of the C3-reduction would come from the β-face reaction of $LiAlH_4$ to the lithium-chelated *cis*-decalin-like structure **M**. Under the same reaction conditions, regioselective removal of the Bz group at the primary C8-OH and attack of the C3-oxygen atom on the C10-carbonyl group proceeded to furnish cis-fused lactone **14** with the two intact Bz groups. The Bn and TMS groups were simultaneously detached from **14** by hydrogenolysis (H_2, Pd/C) in the presence of HCl, resulting in the formation of triol **15**. The two primary hydroxy groups at C8 and C9 of **15** were oxidized together by applying AZADOL, $NaClO_2$, and NaOCl to produce dicarboxylic acid **16**,[23] and ensuing treatment with $TMSCHN_2$ gave bis(methyl) ester **17**.

The 5/6-cis-fused ring system of **17** was then altered to the 2,8-dioxabicyclo[3.2.1]octane core of **20** via transacetalization. Before this was done, the TBDPS group on the C4′-hydroxy group of **17** was exchanged with the more robust benzyl group of **19**.[24] Treatment of **17** with HF·pyridine led to desilylated **18**, the resultant C4′-OH of which was benzylated with benzyl trichloroacetimidate and TMSOTf,[25] affording **19** with concomitant acidic C1-epimerization. The following ring reorganization necessitated detachment of C4-OH and MeOH from C1 of **19**, methanolysis of the C8-lactone, and attachment of C3-OH and C5-OH to C1. This complicated cascade reaction was realized in a single step by the use of $MeSO_3H$. When **19** was subjected to 0.2 M $MeSO_3H$/MeOH at 100 °C for 24 h, the core structure **20** was obtained with deprotection of C7-OH in 40% yield. It is noteworthy that Lewis acids and weaker or stronger Brønsted acids (Table S2) were ineffective for the transformation or detrimental to the product.

In the final eight steps from **20**, the surrounding functional groups were adjusted to yield zaragozic acid C (**1**). Basic hydrolysis of the one Bz group and the three methyl esters of **20** gave **21**, the tricarboxylic acids of which were converted to the tris(*tert*-butyl) esters of **22** with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea.[26] Then a reaction sequence established by Hashimoto[7d] and Carreira[7a] was applied to **22** to finish the total synthesis of **1**. Hydrogenolysis of the benzyl group of the side chain of **22** gave triol **23**. Regioselective acetylation of the C4′-OH of **23** to produce **25** was realized by peracetylation of the three hydroxy groups, and methanolysis of the two acetyl groups at the C6- and C7-oxygen atoms of **24**. Lastly, selective Boc protection of the C7-OH of diol **25** with Boc_2O and 4-pyrrolidinopyridine (**25** → **26**), condensation between C7-OH and carboxylic acid **A** using DCC and DMAP (**26** → **27**), and removal of the three *t*-Bu and one Boc groups with CF_3CO_2H (**27** → **1**) delivered the target molecule, zaragozic acid C (**1**). All of the spectral and physical data of **1**, including ^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, and HRMS data, matched those of naturally occurring **1**.[1]

In summary, we accomplished the total synthesis of bioactive zaragozic acid C (**1**) in 26 steps from persilylated D-gluconolactone **4**. Among the variety of selective reactions, a

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special feature of the present synthesis is the Norrish–Yang cyclization of **3** to give **13**. The strategically placed electron-withdrawing Bz group decreased the reactivity of the proximal C6–H bond, permitting selective functionalization of the electron-rich ethereal C4–H bond. Moreover, violet LED irradiation in a microflow system improved the efficiency and scalability of the transformation without any additional reagents. Hence, the present photochemical C(sp^3)–H functionalization allowed access to unique molecular structures that are difficult to obtain by conventional polar reactions, thus simplifying the synthetic scheme leading to **1**. The substrate design principle employed here for site- and stereoselective C(sp^3)–H functionalization should have broad applications in the total syntheses of other structurally complex natural products and pharmaceuticals with multiple oxygen functionalities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13263.

Procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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