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Self-Consistent Synthesis of the Squalene Synthase Inhibitor Zaragozic Acid C via Controlled Oligomerization

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In the realm of materials chemistry, selective repetitive incorporation of prochiral monomers is used to prepare production-scale quantities of stereochemically defined polymers. Chiral natural products such as polyketides, oligosaccharides, and peptides feature repeating subunits, but the application of controlled oligomerization for the concurrent creation of carbon skeletal frameworks and tetrahedral stereochemistry is an undeveloped tactic in total synthesis (Fig. 1).[1] The zaragozic acids – picomolar inhibitors of the enzyme catalyzing the first committed step in the production of cholesterol[2,3] and compounds that potentiate radiochemotherapy in the destruction of acute myeloid leukemia (AML) cell lines[4] – provide the context for the development and implementation of a new synthetic strategy that reduces this idea to practice. This report discloses the conceptual framework and experimental details for a short synthesis of zaragozic acid C (**1**). The brevity of the sequence described herein is the consequence of a heretofore unprecedented stereoselective oligomerization reaction and adherence to a synthetic plan predicated on the minimization of oxidation state variance and protecting group manipulation.

The highly oxygenated 2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core of zaragozic acid C features six contiguous asymmetric centers that comprise the principal obstacle to synthesis. The two fully substituted hydroxy acids at C4 and C5 in the hydrated acyclic precursor **2** have been particularly nettlesome in extant syntheses[5,6] and commonly require multistep oxidation state, functional group, and/or protecting group adjustment. What we found striking about zaragozic acid C was that the global complexity masks a rather elementary composition of simple building blocks. A retrosynthetic analysis of zaragozic acid C through bond disconnection into its constituent synthons (Fig. 2, blue arrows) reveals a repeating series of glycolic acid fragments.

In contemplating efficient connections that would enable the rapid construction of **2** or its equivalent, we were compelled to consider a “self-consistent sequence,” one that concurrently merges carbon skeletal buildup with the introduction of stereochemistry, as a method that would be uniquely efficient.[7,8] Thus, a self-consistent synthesis of the zaragozic acid core would be one with connection of the glycolic acid subunits in the correct relative configuration (red arrows). The successful implementation of this strategy requires a synthetic equivalent to the unusual geminal dipolar glycolic acid synthon **3**. We recently developed the silyl glyoxylate **4** to function as a reagent for the geminal grafting of complementary nucleophilic and electrophilic reagents onto a protected glycolic acid.[9–11] The reactivity pattern exhibited by **4** is summarized in Fig. 3. Nucleophilic attack on the silyl glyoxylate facilitates C→O silicon migration (Brook rearrangement)[12] to form a stabilized carbanion. This nascent enolate reacts with an electrophile giving rise to a product wherein two new bonds have been formed at the same carbon atom.

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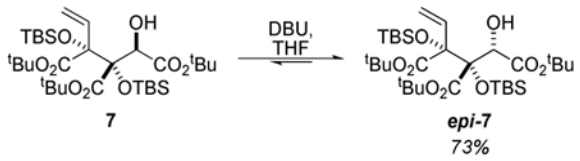
Given the retrosynthetic analysis presented in Fig. 2 and the surrogacy of **4** for **3**, we tested the hypothesis that enchainment of >1 equivalent of **4** could be used to assemble the zaragozic acid backbone in one step. The addition of one equivalent of vinylmagnesium bromide to two equivalents of **4** at −78 °C initiated the oligomerization detailed in Scheme 1. The initial adduct rearranged to provide a new carbon nucleophile that enchained a second equivalent of **4**. A second Brook rearrangement delivered the second magnesium enolate of the cascade. The sequence was terminated via the introduction of *tert*-butyl glyoxylate (**6**). The α-hydroxy ester **7** was obtained in 45–50% yield on a 15 g scale as one diastereomer, the structure of which was determined from an X-ray diffraction study.[13,14] Three contiguous stereogenic centers of the carbon skeleton were assembled in the correct oxidation state. The direct delivery of the needed functional array meant that no oxidation state adjustment was required in this domain for the remainder of the synthesis. Beyond the native efficiency issues, *this attribute was unexpectedly critical for the successful completion of the synthesis (vide infra).* Moreover, the reaction achieved its secondary design purpose of providing an ideal protecting group scheme that masked every functional group except the secondary alcohol that would participate in the subsequent reaction. The product obtained possessed the correct relative stereochemistry for the challenging C4 and C5 tertiary alcohols, while the stereocenter that would eventually become C3 of the core required inversion. Epimerization of **7** with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) was possible at this stage (eq 1), but multiple downstream operations were unsuccessful with *epi*-**7**. For this reason, compound **7** bearing the incorrect C3 configuration was advanced with the expectation that it could be rectified later in the synthesis.



(1)

The racemic α-hydroxy ester (±)-**7** was subjected to a vanadium-catalyzed oxidative kinetic resolution using O_2 as the stoichiometric oxidant (Scheme 2).[15] The resolution yielded 48% (of a maximum 50%) of (−)-**7** with an enantiomer ratio (er) of 90:10. In anticipation of a projected intramolecular aldol reaction to introduce the C6/C7 diol, the C3 hydroxyl group was converted to its derived ester **9** with α-benzyloxyacetyl chloride. Neither the resolution nor the acylation was successful with *epi*-**7**. The requisite C6 electrophile was then revealed through ozonolysis of the vinyl group to provide aldehyde **10**.

A completely diastereoselective intramolecular aldol reaction under carefully prescribed conditions fashioned the C6–C7 bond and led to ε-lactone **11**. Aldolization to form ε-lactones is unusual[16,17] and this case may be assisted by the high level of substitution in the connecting carbon atoms.[18] The ring closure is proposed to proceed via the illustrated transition structure (based on the X-ray diffraction study of **11**) and gives the correct stereochemistry at C7 but the incorrect configuration at C6. Epimerization of **11** was possible to correct the C3 stereochemistry at this stage, but once again the correct C3 epimer was found to be unsuitable in subsequent manipulations.

The C1 side chain was appended by means of a nucleophilic addition of the organolithium **12**[19] to the ε-lactone **11**. The resulting lactol/ketol mixture (**13**) was treated with *p*-toluenesulfonic acid in methanol, affording three products that were easily converged to the desired tricyclic ketal **14**. In addition to **14** (~10–15%), the acid-catalyzed ketalization yielded a tricyclic lactone lacking the C4 silyl protecting group (~45–55%) and an unidentified

isomeric ketal (~15–20%). Resubmission of the isomeric ketal to the TsOH/MeOH conditions, combination with the unprotected tricyclic lactone, and silylation of the C4 hydroxyl group provided an acceptable combined yield of **14**.

The presence of the δ-lactone in **14** highlights the remaining stereochemical problem: the incorrect configurations at C6 and C3. The lactone was opened under unusual but uniquely effective conditions (potassium *tert*-butoxide in *tert*-amyl alcohol) and surprisingly occurred with concomitant inversion of the C6 stereocenter.[20] A retro-aldol/aldol sequence is the probable mechanism accounting for this fortuitous stereochemical correction,[21] *the occurrence of which would have been impossible in the absence of functional groups in the correct oxidation state*. The reaction conditions resulted in partial saponification of the methyl esters necessitating re-esterification with isourea **15**.[22] Epimerization of the inconsequential mixture of esters (**16**) with NaOMe in MeOH achieved the desired configuration of the C3 stereocenter. All of the ester groups were unexpectedly cleaved in this reaction; re-esterification of the resulting triacid using **15** gave the fully functionalized zaragozic acid core **17** with the required stereochemistry.

Our synthesis differentiates the C6 and C7 alcohols in the key intermediate **17**, but installation of the C6 acyl side chain rendered subsequent debenzylation impracticable in our hands. Instead, debenzylation and acetylation were achieved under standard conditions to give the triacetate **18**, a compound utilized by Carreira in the total synthesis of zaragozic acid C.[5a,b] The analytical data were in full accord with those reported (^{1}H NMR in $CDCl_3$ and ^{13}C NMR in both CD_3OD[5b] and $CDCl_3$,[5r] IR, TLC, sign of rotation). The preparation of **18** thus constitutes a formal synthesis of zaragozic acid C. As illustrated in Scheme 2, we applied the Carreira protocol to complete the synthesis of zaragozic acid C (1) in four steps from triacetate **18**. The synthetic material was identical to a sample of natural material.

The zaragozic acid C synthesis was achieved with concurrent creation of the carbon skeleton and tetrahedral stereochemistry with only one oxidation state change (alkene ozonolysis) and no functional group repair in the core synthesis. This study further highlights the utility of silyl glyoxylates as geminal dipolar glycolic acid synthons. Considering the ubiquity of this functional group in organic chemistry, the applicability of reagents like **4** for a range of efficient molecular constructions appears promising. More broadly, given the common occurrence of natural products that contain repeating subunits, the concept of controlled oligomerization could have significant ramifications in small molecule synthesis. The development of new reagents and attendant synthetic strategy will be required for the full realization of this potential, but the chemistry described herein provides a working blueprint for such tactics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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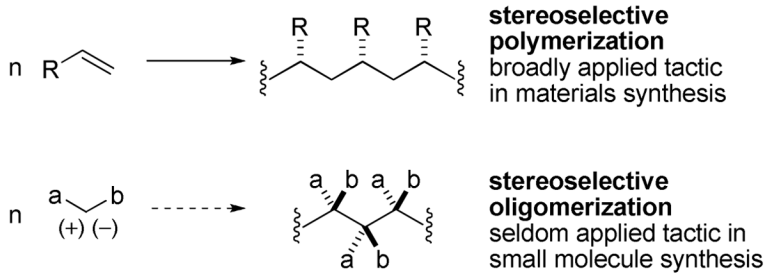


Figure 1.

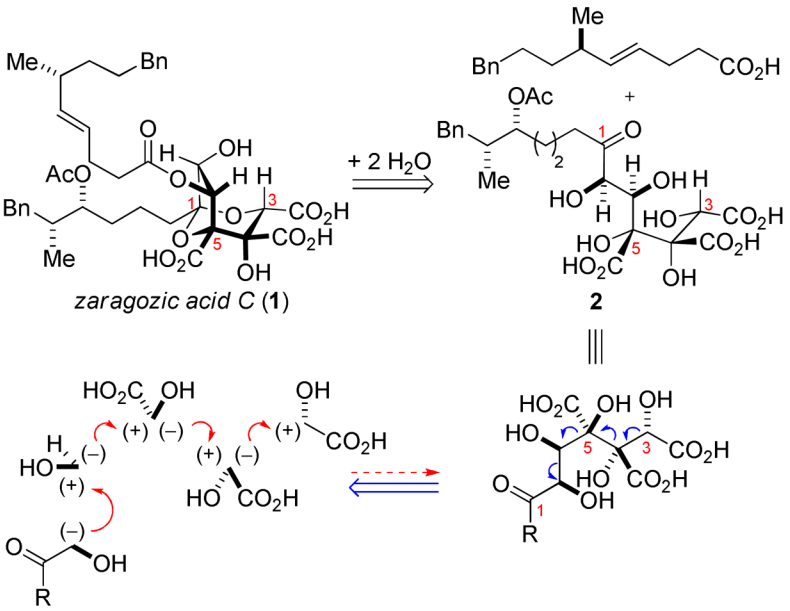


Figure 2.
Retrosynthetic analysis.

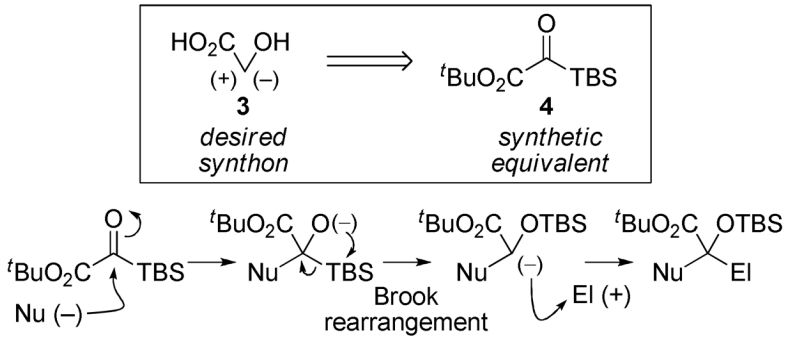
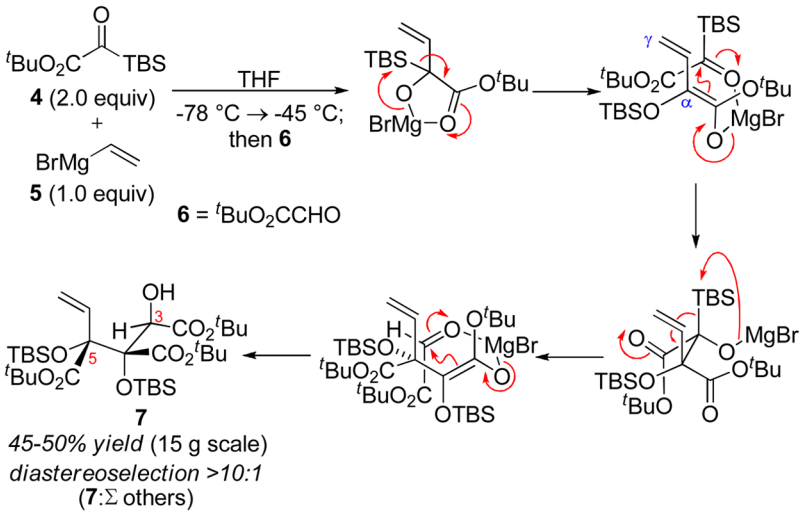
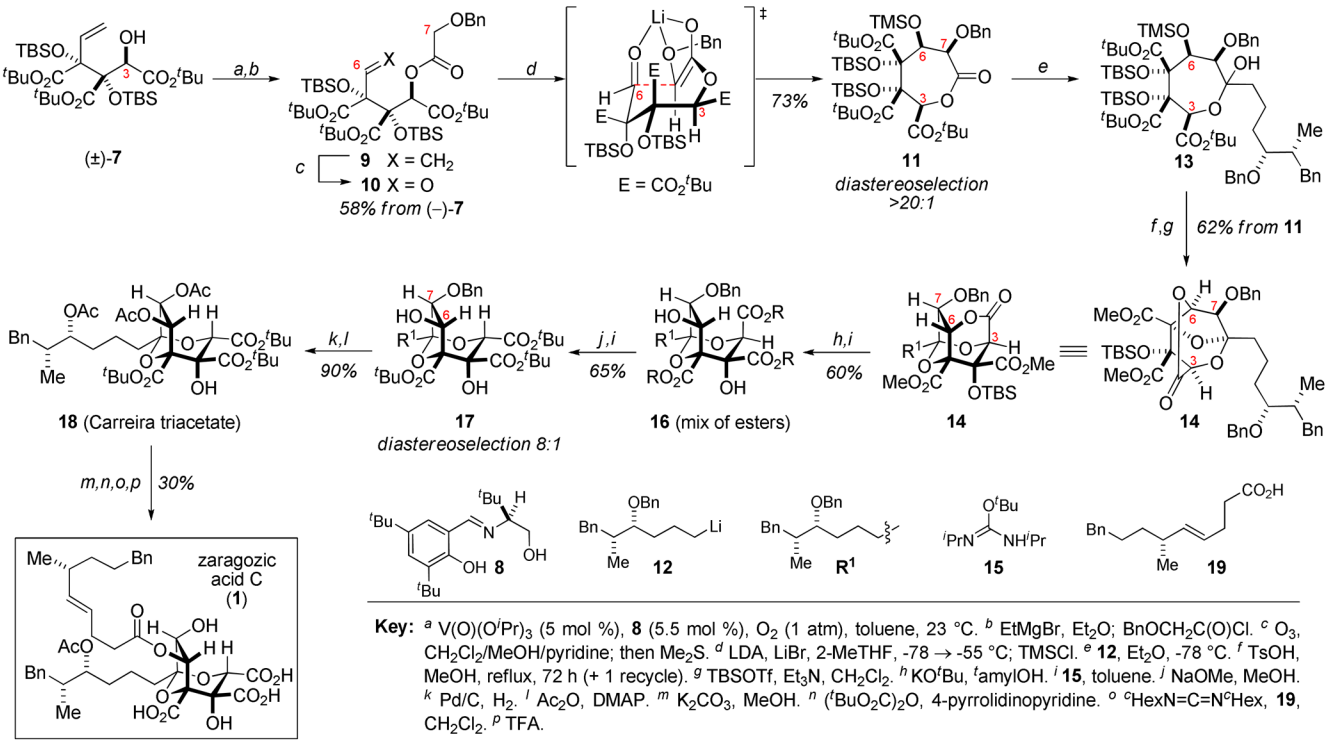


Figure 3.
Silyl glyoxylate as a glycolic acid synthon.



Scheme 1.



Key: [a] V(O)(O^{i}Pr)$_3$ (5 mol %), **8** (5.5 mol %), O_2 (1 atm), toluene, 23 °C. [b] EtMgBr, Et_2O; $BnOCH_2C(O)Cl$. [c] O_3, CH_2Cl_2/MeOH/pyridine; then Me_2S. [d] LDA, LiBr, 2-MeTHF, -78 → -55 °C; TMSCl. [e] **12**, Et_2O, -78 °C. [f] TsOH, MeOH, reflux, 72 h (+ 1 recycle). [g] TBSOTf, Et_3N, CH_2Cl_2. [h] KO^{t}Bu, ^{t}amylOH. [i] **15**, toluene. [j] NaOMe, MeOH. [k] Pd/C, H_2. [l] Ac_2O, DMAP. [m] K_2CO_3, MeOH. [n] (^{t}BuO$_2$C)$_2$O, 4-pyrrolidinopyridine. [o] ^{c}HexN=C=N^{c}Hex, **19**, CH_2Cl_2. [p] TFA.

Scheme 2.