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Synthesis of (−)-6,7-Dideoxysqualestatin H5 by Carbonyl Ylide Cycloaddition−Rearrangement and Cross-electrophile Coupling

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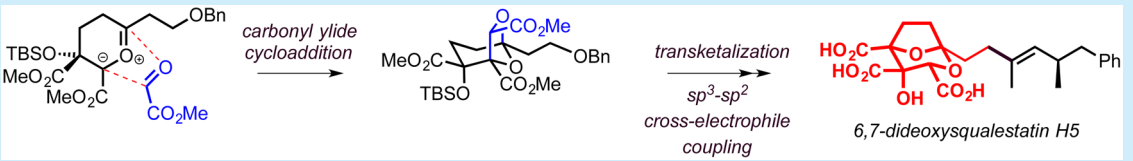
Supporting Information



ABSTRACT: An asymmetric synthesis of (−)-6,7-dideoxysqualestatin H5 is reported. Key features of the synthesis include the following: (1) highly diastereoselective *n*-alkylation of a tartrate acetonide enolate and subsequent oxidation−hydrolysis to provide an asymmetric entry to a *β*-hydroxy-*α*-ketoester motif; (2) facilitation of Rh(II)-catalyzed cyclic carbonyl ylide formation−cycloaddition by co-generation of keto and diazo functionality through ozonolysis of an unsaturated hydrazone; and (3) stereoretentive Ni-catalyzed Csp^3−Csp^2 cross-electrophile coupling between tricarboxylate core and unsaturated side chain to complete the natural product.

Characterized by a 2,8-dioxabicyclo[3.2.1]octane core adorned with hydroxyl and carboxylic acid functionality (**1**, Scheme 1), the zaragozic acids/squalestatins have been the focus of considerable interest ever since reports of their isolation appeared in the early 1990s.[1] Potent mammalian squalene synthase inhibition originally propelled these natural products into the limelight as lead structures for cholesterol-lowering therapeutics.[2] More recent studies include potential application for retinal degenerative disorders,[3] new antimalarials,[4] activity against hepatitis C,[5] and antitumor agents.[6] The biological activity combined with their structural challenges and novelty have made them compelling targets for synthetic studies, and many inventive strategies have been investigated resulting in several full, partial, and model syntheses of members of the zaragozic acid/squalestatin family.[7] Our approach has focused on construction of the core **3** of 6,7-dideoxysqualestatin H5 (**2**)[8] from a diazoketone **8** using Rh(II)-catalyzed tandem carbon ylide formation and cycloaddition with a glyoxylate (**8** → **7** → **5**), followed by acid-catalyzed transketalization (Scheme 1). While so far only demonstrated on a racemic model system bearing a methyl group at C-1 (CH_2X = H),[9] we considered the complexity-inducing pericyclic transformation[10] attractive for further development as it delivers the correct stereochemistry at the desired triacid oxidation level. In the present work, we report the advancement of this chemistry to a synthesis of (−)-6,7-dideoxysqualestatin H5 (**2**).[11]

Successful translation of our earlier observations to a synthesis of (−)-6,7-dideoxysqualestatin H5 (**2**) first required asymmetric access to a carbonyl ylide precursor **8**, containing functionality (X) to subsequently install the full side-chain at the C-1 position of the 2,8-dioxabicyclo[3.2.1]octane core **3**. Following cycloaddition and rearrangement, it was anticipated this strategy would then allow convergent and flexible side-chain introduction through Csp^3−Csp^2 cross-coupling[12] with a suitable alkene partner **4**. The carbonyl ylide precursor, diazoketone **8**, could, in principle, be accessed following our earlier racemic approach involving aldol reaction between a diazoacetate and an *α*-ketoester; however, the only known asymmetric variant is not viable with enolizable *α*−ketoesters.[13]

On consideration of alternatives, we conceived a new strategy that would simultaneously generate the ylidic carbonyl progenitor and diazo functionality, involving chemoselective ozonolysis of an unsaturated hydrazone **9**. We viewed the corresponding unsaturated ketone precursor **10** as potentially being available, as a single enantiomer, through a novel use of *R,R*-tartrate **11** "contra-steric"[14] alkylation chemistry originally described by Seebach.[15] Although Seebach reported that the limited stability of the lithium enolate of tartrate acetonide **11** restricted feasible alkylation to reactive (methyl, allylic, benzylic) halides (~85:15 drs),[15] we have found that *n*-alkyl iodides can be successfully induced to react under prolonged reaction times at low temperature and with improved (essentially complete) diastereoselectivity (eg, *n*-PrI, 66% yield). For the current synthesis (Scheme 2), homoallylic iodide **15** was prepared in three steps from isoprenol (**12**) by addition of paraformaldehyde to the corresponding dianion,[16] monobenzylation[17] of the resulting symmetrical diol **13**, and iodination of benzyl ether **14**. Reaction of iodide **15** with

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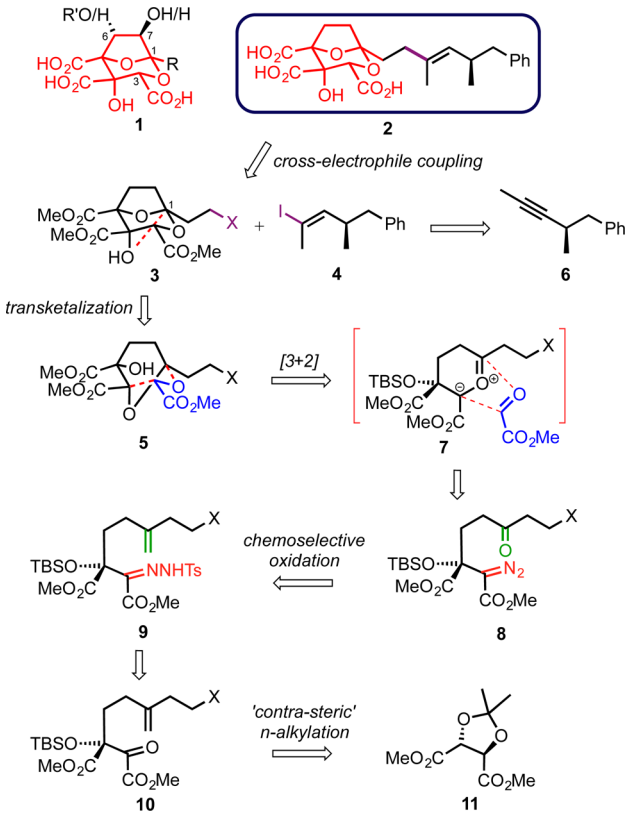
Scheme 1. Retrosynthetic Analysis of 2

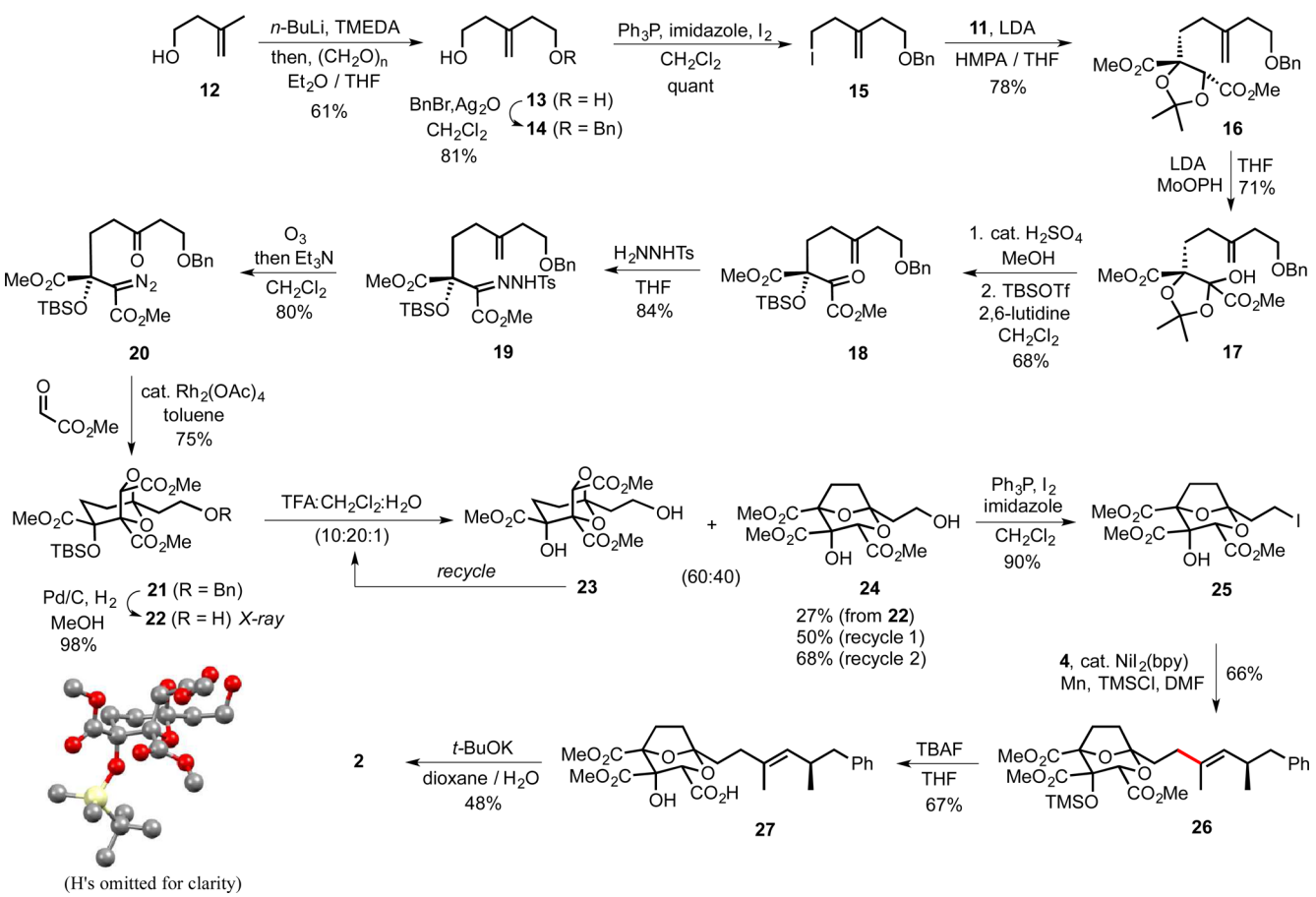


lithiated tartrate acetonide resulted in the isolation of diastereomerically pure alkylated tartrate **16** in 78% yield. Conversion of the alkylated tartrate **16** to the unsaturated ketone **18** was achieved by oxidation of the lithium enolate of the alkylated tartrate **16** using MoOPH[18] followed by acid-catalyzed elimination of acetone from the resulting hydroxyacetonide **17** and tertiary alcohol silylation.

With a new and asymmetric route to the β-oxy-α-ketoester motif established, conversion of the hydrazone **19**, derived from unsaturated ketone **18**, to the carbon ylide precursor, diazoketone **20**, could be studied. Revealing the diazo functionality prior to double-bond manipulation was anticipated to be problematic since a structurally related (but simpler) unsaturated α-diazoester has been observed to undergo spontaneous intramolecular dipolar cycloaddition to give a 1-pyrazoline.[19] Also, under ozonolysis conditions, hydrazones are known to transform to ketones,[20] but the rate of this currently undesired process is expected to be reduced by proximal electron deficiency[20a] (in the present case by the presence of the ester and Ts groups). In the event, ozonolysis of unsaturated hydrazone **19** in the presence of Sudan red 7B as an end-point indicator[21] followed by addition of Et_3N cleanly produced diazoketone **20** (80% yield);[22] here, the Et_3N functions as a base in two processes: facilitating anionic cycloreversion of the intermediate ozonide to the ketone (and triethylammonium formate)[23] and in the Bamford–Stevens reaction.[24]

$Rh_2(OAc)_4$-catalyzed tandem carbon ylide formation cycloaddition of diazoketone **20** with methyl glyoxylate followed the

Scheme 2. Synthesis of (−)-6,7-Dideoxysqualestatin H5 (2)



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desired regio- and stereochemical induction for squalestatin synthesis, as anticipated from our previous model study.[9] Cycloadduct **21** was isolated in 75% yield; minor isomeric cycloadducts may have also formed in the reaction but could not be isolated. The structure of cycloadduct **21** was confirmed following debenzylation by X-ray crystallographic analysis of the resulting primary alcohol **22**.[25] The stereochemical outcome of the cycloaddition can be rationalized by the glyoxylate preferentially undergoing reaction on the less-hindered face (opposite the silyloxy group) of the carbonyl ylide **7** (Scheme 1) and orientating *exo* (with respect to the ylide-containing ring) to minimize interactions with the out-of-plane (β-) ester group. Acid-catalyzed transketalization (best carried out after debenzylation) with concomitant desilylation gave a 60:40 ratio of unrearranged and rearranged cores (**23** and **24**, respectively). In the model system (Scheme 1, CH_2X = H), the rearranged core was favored (34:66).[9] These results indicate the equilibrium position is sensitive to variation in the C-1 chain. Nevertheless, the unrearranged diol **23** could be separated and resubmitted to the reaction conditions, and after two cycles, the desired diol **24** was obtained in 68% overall yield.

The *E*-alkenyl iodide bearing side chain **4** required for attachment to the core was prepared from *R*-α-benzyl propionaldehyde[26] in three steps involving Corey–Fuchs homologation to the alkyne **6** and hydrozirconation–iodination[27] (Scheme 1).[25] In preparation for cross-coupling, the primary alcohol of diol **24** was activated as the iodide **25**; however, iodide **25** (and the corresponding bromide) displayed unexpected thermal instability on moving to 40 °C or above which, along with the pre-existing functionality on the core, significantly limited the cross-coupling protocols that could potentially be investigated.[12] After a lack of success with some more traditional approaches,[28] we were attracted to recent methodological developments in reductive cross-electrophile coupling[29] where prior generation of one of the partners as a carbon nucleophile is redundant. In particular, we focused on the Ni-catalyzed technology pioneered by Weix[30] due to the chemistry showing promise for reasonable stereoretention with an internal *E*-alkenyl halide being tolerant of ester functionality and, in the most recent report,[30c] operating at ambient temperature. Under optimized conditions (solvent, ratio of reactants, concentration, and additives were examined on model systems),[25] a 1:1 mixture of hydroxy iodide **25** and alkenyl iodide **4** in DMF (0.8 M) gave alkene **26** in 66% yield with complete stereoretention. Desilylation using TBAF was accompanied by hydrolysis[31] of the C-3 ester to give the known[8c] diester **27** in 67% yield. Finally, hydrolysis of the remaining more-hindered esters using anhydrous KOH[32] gave (−)-6,7-dideoxysqualestatin H5 **2** possessing spectral data in complete agreement with that previously reported.[8]

In summary, a total synthesis of the natural product (−)-6,7-dideoxysqualestatin H5 (**2**) was completed starting from the bulk chemical isoprenol (**12**); the 16-step sequence compares favorably with Martin's previous 14- and 17-step routes.[8c] Noteworthy features include improvement in alkylation scope and stereochemical efficiency from the enolate of a commercially available tartrate acetonide **11**, leading to a new entry to the β-hydroxy-α-ketoester motif in an asymmetric manner. Also, the direct ozonolytic conversion of an unsaturated hydrazone to a diazoketone illustrates a new strategic entry to substrates for cyclic carbonyl ylide formation–cycloaddition chemistry.[10] The current synthesis showcases the power of the latter pericyclic process to deliver high levels of stereocontrol from functional group rich precursors. Finally, a late-stage ester and alcohol functional group-tolerant Ni-catalyzed Mn-mediated Csp^3–Csp^2 cross-electrophile coupling involving equimolar quantities of the halide partners and occurring at room temperature with geometrical integrity at the internal alkenyl halide demonstrates the utility of this emerging technology in complex natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01513.

Detailed experimental procedures, spectral data and X-ray crystallographic data (PDF)

X-ray data for compound **22** (CIF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX–XXX

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Org. Lett. XXXX, XXX, XXX−XXX