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

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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 acetoni 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 Csp3−Csp2 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. Potent mammalian squalene synthase inhibition originally propelled these natural products into the limelight as lead structures for cholesterol-lowering therapeutics. More recent studies include potential application for retinal degenerative disorders, new antimalarials, activity against hepatitis C, and antitumor agents. 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. Our approach has focused on construction of the core 3 of 6,7-dideoxysqualestatin H5 (2) 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 (CH2X = H), we considered the complexity-inducing pericyclic transformation attractive for further development as it delivers the correct stereochemistry at the desired tricic oxidation level. In the present work, we report the advancement of this chemistry to a synthesis of (−)-6,7-dideoxysqualestatin H5 (2). 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 Csp3−Csp2 cross-coupling 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.

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. 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" alkylation chemistry originally described by Seebach. Although Seebach reported that the limited stability of the lithium enolate of tartrate acetone 11 restricted feasible alkylation to reactive (methyl, allylic, benzylic) halides (~85:15 drs), 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 diionan,16 monobenzylation of the resulting symmetrical diol 13, and iodination of benzyl ether 14. Reaction of iodide 15 with

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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\textsuperscript{18} followed by acid-catalyzed elimination of acetone from the resulting hydroxyacetone 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.\textsuperscript{19} Also, under ozonolysis conditions, hydrazones are known to transform to ketones,\textsuperscript{20} but the rate of this currently undesired process is expected to be reduced by proximal electron deficiency\textsuperscript{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\textsuperscript{21} followed by addition of Et\textsubscript{3}N cleanly produced diazoketone 20 (80% yield);\textsuperscript{22} here, the Et\textsubscript{3}N functions as a base in two processes: facilitating anionic cycloreversion of the intermediate ozonide to the ketone (and triethylammonium formate)\textsuperscript{23} and in the Bamford–Stevens reaction.\textsuperscript{24}

Rh\textsubscript{2}(OAc)\textsubscript{4}-catalyzed tandem carbon ylide formation cycloaddition of diazoketone 20 with methyl glyoxylate followed the
The E-alkenyl iodide bearing side chain 4 required for attachment to the core was prepared from R-α-benzyl propionaldehyde, in three steps involving Corey–Fuchs homologation to the alkyne 6 and hydrozirconation–iodination. 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. After a lack of success with some more traditional approaches, we were attracted to recent methodological developments in reductive cross-electrophile coupling 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 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, operating at ambient temperature. Under optimized conditions (solvent, ratio of reactants, concentration, and additives were examined on model systems), a 1:1 mixture of hydroxy iodide 25 and alknyl iodide 4 in DMF (0.8 M) gave alkene 26 in 66% yield with complete stereoretention. Desilylation using TBAF was accompanied by hydrolysis of the C-3 ester to give the known diester 27 in 67% yield. Finally, hydrolysis of the remaining more-hindered esters using anhydrous KOH gave (−)-6,7-dideoxyxquelestatin HS 5 possessing spectral data in complete agreement with that previously reported.

In summary, a total synthesis of the natural product (−)-6,7-dideoxyxquelestatin HS (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. Noteworthy features include improvement in alkylation scope and stereocchemical 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 enolzolytic conversion of an unsaturated hydrazone to a diazoketone illustrates a new strategic entry to substrates for cyclic carbonyl ylide formation–cycloaddition chemistry. The current synthesis showcases the power of the latter pericyclic process to deliver high levels of stereoccontrol from functional group rich precursors. Finally, a late-stage ester and alcohol functional group-tolerant Ni-catalyzed Mn-mediated Csp3–Csp2 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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