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RAPID CONSTRUCTION OF THE TETRACYCLIC NUCLEUS OF CERORUBENIC ACID-III BY OXYANIONIC COPE CHEMISTRY

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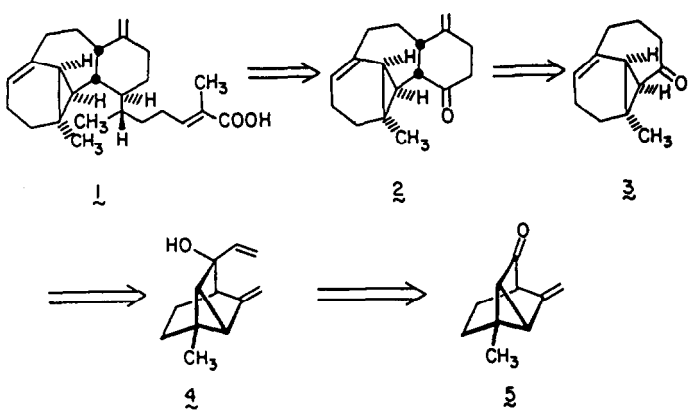
Summary: Ketone 3, produced directly by anionic oxy-Cope rearrangement of 4, was crafted into silyloxydiene 8, Diels-Alder condensation of which with methyl acrylate under high pressure permitted arrival at 2, a tetracyclic precursor to cerorubenic acid-III.

Cerorubenic acid-III (1), a principal component of secretions produced by the scale insect *Ceroplastes rubens* Maskell,[2] is recognized to play an important role in communication between these wasps.[3] The molecular architecture of 1, especially its tricyclic ABC vinylcyclopropane subunit, and the need for reasonable quantities of 1 to enable broad-scale pharmacologic evaluation have intrigued us. From the retrosynthetic perspective, 1 was viewed as being capable of sequential dismantling in the sense 1 → 2 → 3 (Scheme I). Attractively, tricyclic ketone 3 was envisioned as being accessible *in a single step* by anionic oxy-Cope rearrangement of 4. The feasibility of preparing its progenitor β,γ-unsaturated ketone 5 in racemic and optically pure condition is described in the accompanying Letter.[4]

Scheme I

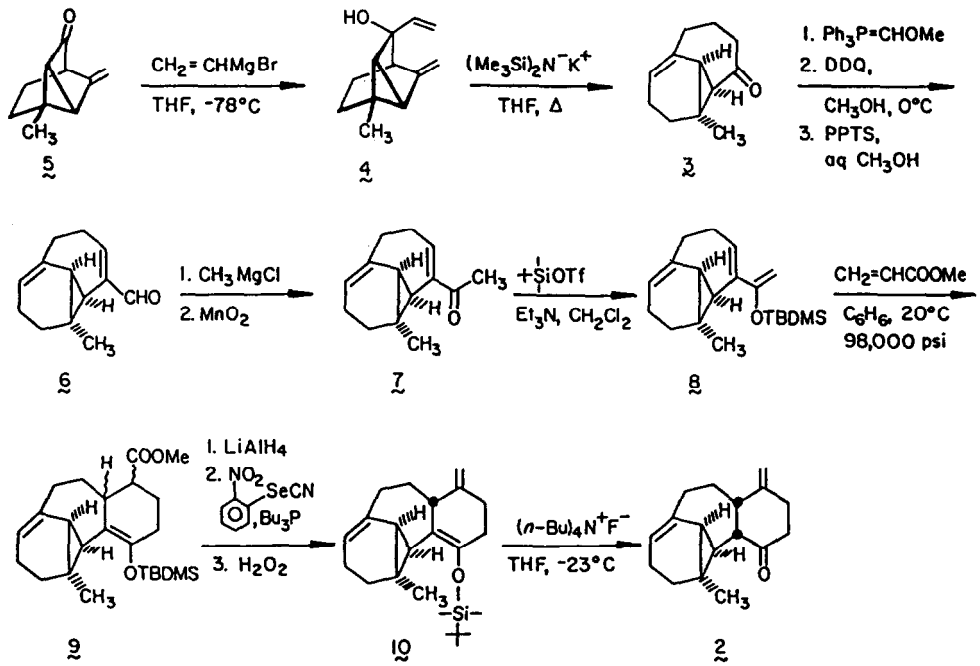


1 2 3

4 5

Early success rested on our ability to add vinylmagnesium bromide to 5 in the proper stereochemical direction. Here we took advantage of the outward splaying of the trigonal centers,[4] a structural feature that permits the acquisition of 4 in 98% yield (Scheme II). To our delight, heating 4 with an excess of potassium hexamethyldisilazide in tetrahydrofuran for 24 h yielded exclusively 3 (90%), a colorless oil.[5] Consequently, the three contiguous stereocenters present in the western sector of 1 are capable of rapidly being set in their proper relative configuration.

Scheme II



Attention was next focused on the annulation of ring D as in 2. A major consideration here was the need to avoid strongly acidic reagents in order to avoid protonation of the strained bridgehead double bond in 3. Generation of the cyclopropylcarbinyl cation was guaranteed to promote destruction of the carbobicyclic framework. The one-carbon homologation found most serviceable in providing aldehyde 6 consisted of reaction with methoxymethyltriphenylphosphorane and oxidation of the vinyl ether mixture (E/Z = 6:4) with DDQ in methanol

at 0 °C.[6] Brief stirring with pyridinium tosylate in methanol-water (9:1) prior to isolation was adequate to hydrolyze any dimethyl acetal that had formed. In this way, a 50% yield of **6** could be realized. Subsequent condensation with the methyl Grignard reagent followed by manganese dioxide oxidation[7] provided **7** (80%). Quite unexpectedly, both **6** and **7** proved to be strikingly poor Michael acceptors. To illustrate, **7** was recovered intact following exposure to a functionalized vinylcopper reagent [LiC(=CH_2)CH_2CH_2OTBDMS, CuBr•SMe_2],[8] lithium divinylcuprate, and the phenylselenide anion.[9] The geometrically fixed relationship of the double bond relative to the cyclopropane ring may be a major contributing factor to this intrinsic lack of reactivity.

Accordingly, silyl enol ether **8** was prepared[11] and subjected directly to Diels-Alder reaction with methyl acrylate in a high-pressure reactor at 20 °C. The structural features unique to the conjugated diene unit in **8** appear nicely conducive to [4+2] cycloaddition, in that a stereoisomeric 8:2 mixture of tetracyclic esters could be obtained in 68% yield. Due consideration of those steric control elements operative during capture of diene **8** suggested that appproach of the dienophile should occur preferentially from the exterior of the molecular fold as in **9**.

Following the acquisition of **9**, its ester functionality was transformed into an exocyclic double bond (73% overall)[12] and the carbonyl group was unmasked with tetra-*n*-butylammonium fluoride in anhydrous tetrahydrofuran at -23 °C (64%). These conditions gave rise to a 7:3 mixture of **2** and the corresponding trans isomer.[13] The greater thermodynamic stability of the latter substance was ascertained by stirring **2** in acetonitrile containing silica gel at room temperature.

In summary, this study establishes a straightforward route to the cerorubenic acid-III ring system and, more generally, extends the significant synthetic potential of the oxy-Cope rearrangement.[14] We are currently working on streamlining the sequence such that epimerizations of the sort witnessed in **2** do not introduce unnecessary complication in the late stages of the synthetic scheme.

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(5) IR (CH_2Cl_2, cm^{-1}) 1680; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (m, 1 H), 2.47-1.93 (seris of m, 6 H), 1.83-1.58 (m, 4 H), 1.55-1.44 (m, 1 H), 1.28 (d, J = 9.0 Hz, 1 H), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.65, 137.28, 127.86, 42.97, 40.58, 34.66, 27.64, 26.31, 23.77, 23.41, 22.65, 22.62; MS *m/z* (M^+) calcd 176.1201, obsd 176.1202.
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