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COBALT-MEDIATED PROPARGYLATION/ANNELATION: TOTAL SYNTHESIS OF (±)-CYCLOCOLORENONE

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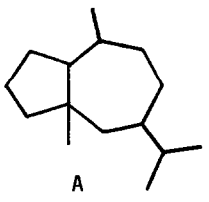
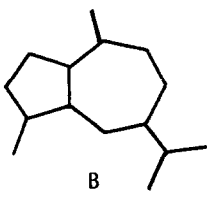
Summary. A recently developed cyclopentenone annelation sequence involving propargylation of ketone derivatives by $(RC{\equiv}CCR_2)Co_2(CO)_6^+$ complexes (1) followed by regiospecific hydration and cyclization has been employed in an efficient stereoselective synthesis of the guiane sesquiterpene cyclocolorenone (2).

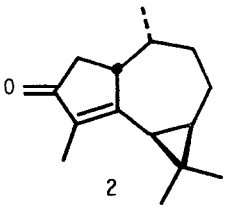
Although considerable progress has been made towards the development of synthetic methodologies for constructing the hydrozulenic skeleton of the pseudoguiane sesquiterpenes A, total syntheses of guiane sesquiterpenes B are notably few (1). To date, incorporation of the



A



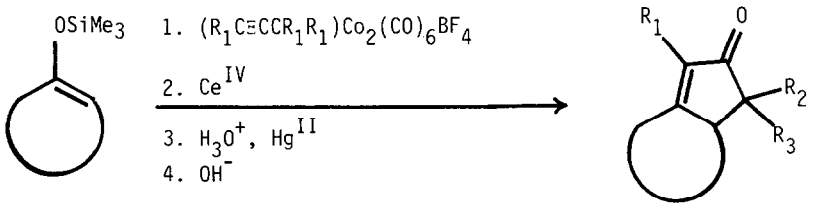
B



2

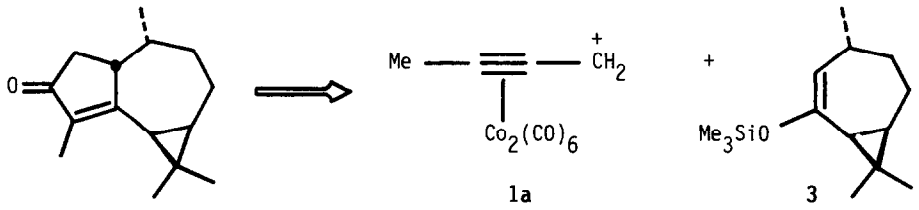
azulenic skeleton in either class generally has been accomplished by cyclization of cyclodecane derivatives or by rearrangement of bi- or tricyclic, non-hydroazulenic precursors (2). Surprisingly few approaches involving cyclopentannelation of cycloheptyl derivatives have been reported (3). Having recently developed a novel and efficient cyclopentenone annelation sequence featuring propargylation of enol derivatives by $(RC{\equiv}CCR_2)Co_2(CO)_6BF_4$ (1), regiospecific hydration to 1,4-diketones, and base induced cyclization (4, Scheme 1), we report here the successful utilization of this methodology in the total synthesis of the guiane cyclocolorenone **2** (5). The structure of cyclocolorenone is punctuated by four stereocenters, one of which (C1) is readily epimerized (6).

Scheme 1



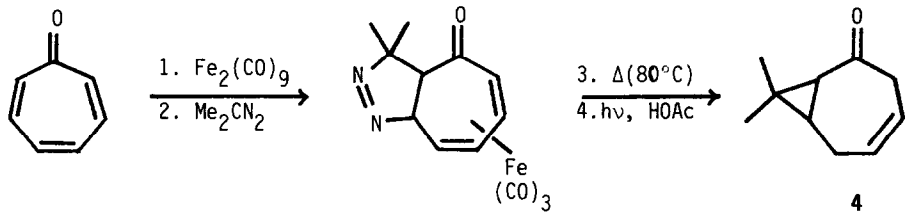
Retrosynthetic analysis of cyclocolorenone according to Scheme 1 calls for the coupling of $(CH_3C{\equiv}CCH_2)Co_2(CO)_6BF_4$ (**1a**) with silyl enol ether **3** (Scheme 2). Synthesis of **3** initially

Scheme 2



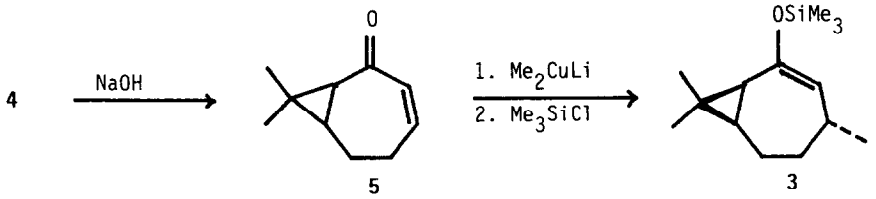
proved to be rather troublesome and several conventional methods failed including one which was thwarted by an unexpected and unprecedented cyclopropane mislocation reaction occurring in the reaction of $PhHgCBr_3$ with 2,6-cycloheptadienone ethylene ketal (7).

Eventually we turned our efforts to an alternative route to **3** (eq. 1) which rested largely upon a combination of previously reported reactions featuring use of the $-Fe(CO)_3$ unit as both a protecting and activating group for 1,3-dienes (8-10).



(1)

Utilizing the sequence of eq. 1 we were able to prepare the non-conjugated ketone **4** in 40-45% overall yield from tropone. Isomerization of **4** to the conjugated isomer **5** was found to occur readily under basic conditions ($NaOH/H_2O$, pH 11, 20°C, 2 hr; 91%yield, 11). Treatment of **5** with Me_2CuLi (THF/ -78°C) followed by quenching with excess Me_3SiCl (-78° → 0°C) and rapid aqueous workup produced the crude TMS enol ether **3** which appeared to be almost entirely a single isomer (>95%) based on its ^{13}C NMR spectrum (eq. 2).

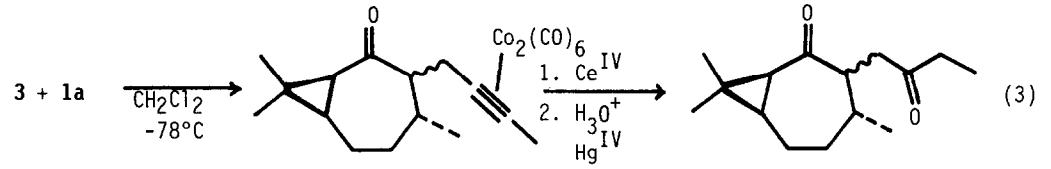


(2)

Examination of molecular models of **5** suggests significant shielding of one face of the enone by the dimethylcyclopropane unit and the results of subsequent transformations (vide infra) lead us to assign a **trans** stereochemistry to **3**.

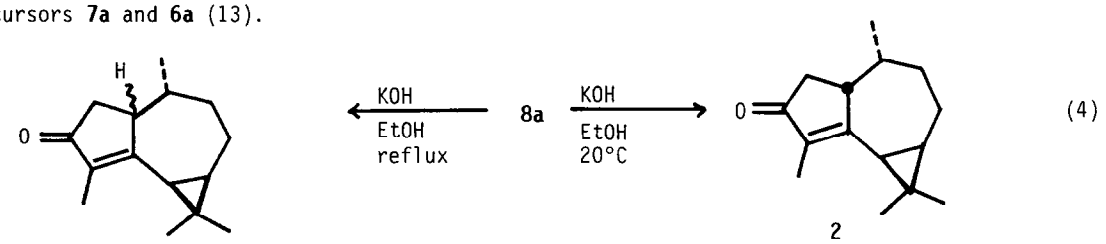
With the key intermediate **3** in hand the annelation sequence of Scheme 1 was executed. Alkylation of **3** by complex **1a** proceeded in moderate yield (45%, unoptimized) to give the cor-

responding α-propargylated complex **6a,b**, predominantly as one diastereomer (ca. 3:1 by ^{13}C NMR). Demetalation of the mixture **6a,b** [$(NH_4)_2Ce(NO_3)_6$, acetone, -78°C] gave approximately a 1.5:1.0 mixture of butynyl ketones **7a,b** (90%) which, in turn, was subjected to hydration (H_2SO_4, H_2O, MeOH, $HgSO_4$, 50°C) affording an 8:1 mixture of diketones **8a,b** (80%) which was separated by preparative TLC (1:4 Et_2O:petroleum ether).



6a,b **8a,b** (3)

The major diketone isomer **8a**, when refluxed with ethanolic KOH (3 hr), gave a separable 1:3 mixture of cyclocolorenone and epi-cyclocolorenone (71% combined yield). Satisfyingly, **the same reaction conducted at room temperature (14 hr) yielded cyclocolorenone exclusively** (72%, 12). This result, in addition to successfully completing our synthetic venture, implicates a **cis**-2,3 geometry for the major diketone **8a** and probably for the major isomeric precursors **7a** and **6a** (13).



(4)

In contrast, the minor diketone **8b** under identical reaction conditions produced a complex product mixture which was devoid of either cyclocolorenone or its epimer. Inspection of models of **8b** reveals that attack of the enolate side chain on the cycloheptanone carbonyl leading to epi-CC would be impeded by a cyclopropane methyl group.

Acknowledgements. Helpful discussions with Prof. Frank-Neumann (Strasbourg) regarding the preparation of **4** were appreciated. Financial support was provided by NIH (GM 34799).

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5. Only one previous synthesis of cyclocolorenone has been reported (2d); photochemical rearrangement of a decalenone derivative was employed to generate the hydroazulenic skeleton.
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8. D.F. Hunt, C.C. Farrant and G.T. Rodeheaver, J. Organometal. Chem., 1973, 38, 362.
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10. All new compounds gave satisfactory IR, NMR and MS (high resolution) spectra.
11. Data for synthetic **2** (cyclocolorenone): IR (thin film) 1694, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.96 (bs, 1H), 2.47 (dd, J=18 Hz, 6 Hz, 1H), 2.10 (bd, 1H), 1.9 (m, 1H), 1.72 (d, J=2 Hz, 3H), 1.70-0.80 (b envelope, ca. 6H), 1.24 (s, 3H), 1.02 (s, 3H), 0.79 (d, J=7 Hz, dH); λ_{max} 261 nm; MS (m/e) 218 (M^+). Data identical to that reported for the authentic **2** in ref.6.
12. Apparently some epimerization occurs in the sequence **6** → **7** → **8**. At this time we cannot assign with certainty the stereochemistry of the major isomers **6a** and **7a**. However, examination of molecular models suggests that the less hindered approach of **1a** to **3** would give rise to the **cis**-2,3-substituted isomer **6a**. Experimental efforts are underway to address this issue.

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