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SYNTHETIC STUDIES ON ARENEOLEFIN CYCLOADDITIONS -VI- TWO SYNTHESES OF (±)-CORIOLIN.

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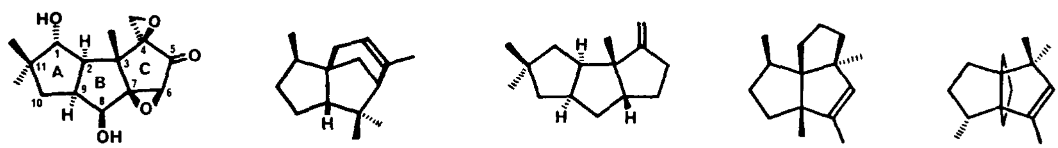
Abstract: The areneolefin photocyclization is shown to provide access to highly oxygenated natural products in an efficient and straightforward manner, as evidenced by the synthesis of coriolin via two separate routes; both proceed from 1-(2,6-dimethylphenyl)-1-acetoxy-2,2-dimethylpent-4-ene (**6a**) in 12 steps.

The areneolefin photocyclization has seen successful application in these laboratories to the total synthesis of several classes of polycyclic sesquiterpenes, such that its status as a general and flexible method for forming complex arrays of carbocyclic rings is now firmly established. The primary ring-forming event, a 1,3-cycloaddition of the S_1 excited state of a benzene nucleus to a ground-state olefin, proceeds both inter- and intramolecularly, providing access thus far to structures ranging from cedrene (**2**)[2a] and the tricyclopentanoids hirsutene (**3**)[2b] and isocomene(**4**)[2c], to the propellane modhephene (**5**)[2d]. We now wish to report the successful extension of the areneolefin method to the synthesis of a densely oxygenated sesquiterpene, (±)coriolin (**1**), whose derivatives have intriguing and possibly unique cytotoxic properties[3]. An attractive and novel feature of this approach is that it permits stereo-



1 **2** **3** **4** **5**

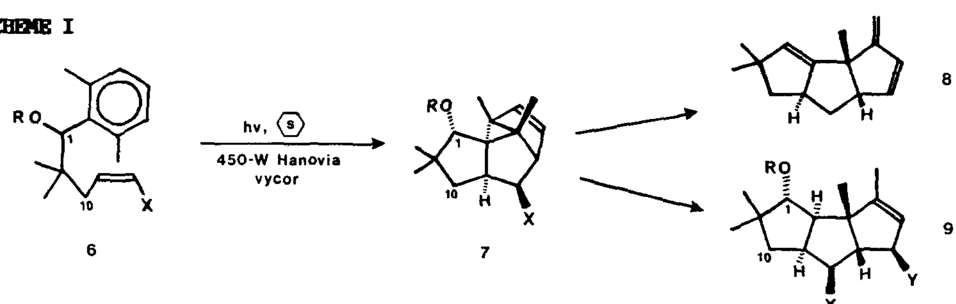
specific introduction of all of the groups pendant to two of the three target rings *at the level of the photocyclization itself.*

Coriolin is a member of the hirsutane class, whose fundamental skeleton has already been addressed with an areneolefin-based strategy in the synthesis of the parent hirsutene (**3**)[2b]. As outlined in Scheme I, intramolecular photocyclization of **6a** (available in one step) gave as the major product **7b** (22-23% after deacetylation with LAH), containing the correct vinylcyclopropane structure to undergo an acid-catalyzed dehydrative rearrangement to the pro-*cis-anti-cis*-fused tricyclopentanoid **8** (71%), from which **3** was derived. Direct adaptation of this strategy to coriolin seemed *a priori* quite feasible, provided that oxygenation in each of the three rings could be controlled. It was anticipated that the most elaborately adorned of these, C, could be efficiently developed from as little functionality as a single olefin, based on transformations suggested by previously reported syntheses[4e]. For both the A and B rings, a single alcohol of defined orientation is required. The former is potentially available from an adduct such as **7**, provided that cyclopropane cleavage can be effected without loss of the stereocenter at C-1. The remaining B-ring alcohol can be introduced at two distinct stages of the synthesis. In all routes to date[4], introduction subsequent to construction of the basic tricyclic skeleton has been employed, involving a relay of stereochemistry from the quaternary methyl center. In such a scheme, form **b** of intermediate **9** would suffice, and in fact, **9b** has already been prepared by Mehta[4e] and formally converted to coriolin. The alternative approach would exploit the known transfer of olefin geometry during areneolefin photocyclization into the stereochemistry of the products, e.g. a *cis* relationship between C-10 and the group **X** on the olefin in precursor **6** would be expected to produce the same *cis* geometry of these groups in products **7** and **9**. Thus if **X** were some appropriate oxygenated precursor, generation of the desired B-ring alcohol stereochemistry could be controlled as early as the cyclization. Both of these possibilities have been successfully explored and are detailed below.

Preliminary model work led swiftly to the interception of Mehta's intermediate, **9b**, thus providing a formal total synthesis of coriolin. The previously described photoadduct **7b**[2b], available in two steps, underwent oxidation with PDC to the corresponding ketone (74%), whose cyclopropane subunit was reductively cleaved in a stereoelectronically controlled process (Li/NH_3, Et_2O, EtOH; Scheme I). Protonation of the resultant enolate and subsequent *in situ* ketone reduction proceeded to give the more stable alpha-alcohol **9b** (92%), as observed by Danishefsky on a similar substrate[4a]. This preparation of **9b** (four steps, overall yield = 12%) reduces by more than one-half the number of steps previously required[4e], and displays the ring-building power of the areneolefin cyclization to advantage. A second, radical-based, method for converting **7b** to **9b** was also developed, which suggests a new and possibly general method for cleavage of vinylcyclopropanes. *Thus, heating **7b** neat with 1.0 eq. of thiophenol gave, via 1,5-free-radical addition, the adduct **9c**[10] as the sole product[5].* Reductive desulfurization provided **9b**, identical with that obtained from the first route.

The alternative route to coriolin, i.e. direct functionalization of ring B via photolysis of a substrate **6** where **X** = oxygen equivalent, was pursued initially in the most direct manner possible. Unfortunately, the substrates **6d** and **6e** gave only low yields of cyclized materials, possibly due to a poor match in the electronic character of the two reacting pi-systems in these substrates, as suggested by the Ionization Potential Rule[6] of Gilbert and Bryce-Smith. Since alkyl-substituted olefins are generally good partners for areneolefin additions, a substrate in which **X** was more carbon-like was selected, retaining, however, a level of

SCHEME I



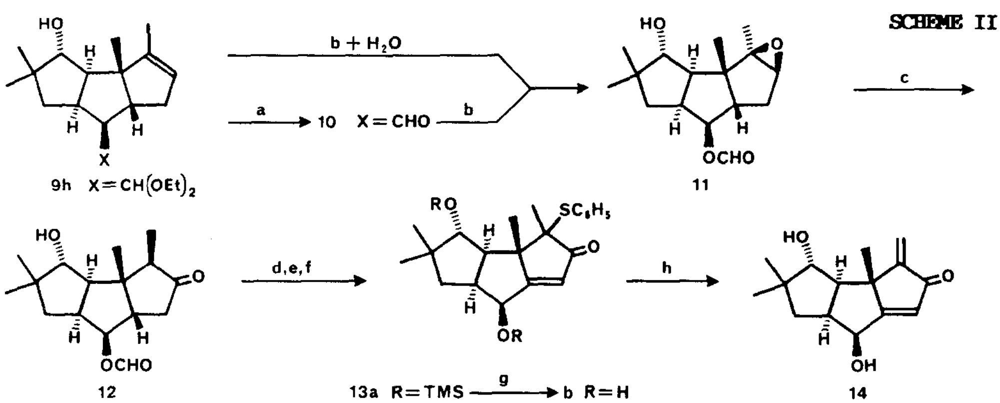
	R	X	Y
a	Ac	H	
b	H	H	H
c	H	H	SC_6H_5
d	Ac	OMe	
e	Ac	OAc	
f	Ac	$CH(OEt)_2$	H
g	Ac	$CH(OEt)_2$	SC_6H_5
h	H	$CH(OEt)_2$	H

6a $\xrightarrow{a,b}$ **6f**   **7b** $\xrightarrow{c}$ **9c** $\xrightarrow{d}$ **9d**

7b $\xrightarrow{e}$ **8**   **7f** $\xrightarrow{c}$ **9g** $\xrightarrow{d}$ **9h**

a) O_3, MeOH, -78°; 61% b) $(C_6H_5)_3P^+$ OEt Br^-, NaOEt, CH_2Cl_2/THF, RT; 55% c) C_6H_5SH, 1 eq, neat, 100° d) Li/NH_3, Et_2O e) camphorsulfonic acid, C_6H_6, RT oxidation required for its eventual conversion to an alcohol. Acetal **6f** was prepared from **6a** in two steps via the method of Bestmann[7], with very high _cis_-selectivity (>40:1) (Scheme I). By analogy with the results in the hirsutene synthesis, photocyclization of **6f** gave as the major product (~15%) adduct **7f** . Cleavage of **7f** using the thiyl radical chemistry alluded to previously led, in two further steps (72%, 80%), to the sought-after intermediate **9h**.

The utility of **9h** is, of course, contingent on the ease with which conversion of its acetal into a B-ring oxygen substituent can be achieved. It was discovered that elaboration of **9h** into a methyl ketone for Baeyer-Villiger oxidation was superfluous, since the aldehyde functionality in **10** could be converted under the same conditions to a formate in superior yield (**11**, 83%; epoxidation occurs concommitantly); competing formation of carboxylic acid products occurred only to a minor extent (~ 6%)[8] (Scheme II). In a further simplification, acetal **9h** could be used directly in the oxidation (67%) without prior hydrolysis when a small amount of water (15 eq.) was added to promote _in situ_ conversion to **10**. Thus the acetal group ultimately proved equivalent to a protected alcohol (formate), since it was "liberated" in a single synthetic operation.



a) SiO_2, H_2O, H^+; 98% b) MCBPA, CH_2Cl_2, RT c) BF_3, C_6H_6, RT; 86% d) LDA, TMSCl e) $Pd(OAc)_2$, CH_3CN f) LDA, $C_6H_5SSO_2C_6H_5$ g) $HOAc/H_2O/THF$, 3:1:1; 100% h) MCPBA; EtOAc, Δ

The remaining steps of the synthesis proceeded as anticipated (Scheme II); rearrangement of the epoxide to a ketone, followed by its oxidation to an enone and alpha-sulfenylation, produced a single isomer of the compound **13a** (42% from **11**), which gave upon desilylation the diol **13b**, having spectral properties in agreement with those previously reported by Danishefsky[4a]. Since Danishefsky has successfully converted **13b** to coriolin in two steps[4a], the present route represents a second formal areneolefin synthesis of coriolin. Modification of our **13b** according to the first of those two steps gave **14** and permitted unequivocal correlation (TLC, NMR, IR, and MS) with authentic **14**, a sample of which was kindly provided by Prof. Danishefsky.

In accord with the high oxidation level of the cycloadducts, the areneolefin photocyclization proves eminently capable of delivering highly oxygenated products with good stereocontrol, building significantly on its already potent ring-forming capabilities. Applications in other classes of oxygen-rich natural products, as well as potentially active analogs of coriolin, are underway.

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†A. P. Sloan Foundation Fellow; Camille and Henry Dreyfus Teacher-Scholar Award Recipient.

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