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SYNTHETIC STUDIES ON ARENE-OLEFIN CYCLOADDITIONS -III- TOTAL SYNTHESIS OF (±)-HIRSUTENE[1].

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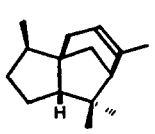
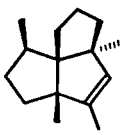
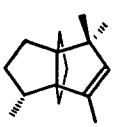
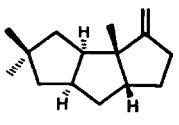
Abstract: The arene-olefin meta-cycloaddition is shown to provide a facile entry into linear tricyclopentanoid skeleta. Hirsutene is synthesized in seven steps by this method from 2,6-dimethylbromobenzene and 2,2-dimethylpent-4-enal.

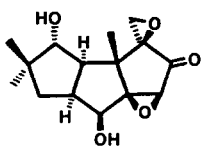
The problem of polyquinane synthesis has come to the forefront of interest in recent years, due largely to the proliferation of known natural products containing such structures[2]. To such classical examples as cedrene (**1**, containing a diquinane subunit) have been added a variety of triquinanes, of which the hirsutanes (**4,5**), isocomene (**2**), and modhephene (**3**) are representative. Topological analysis[3] and practical experience both


Cedrene
1


Isocomene
2

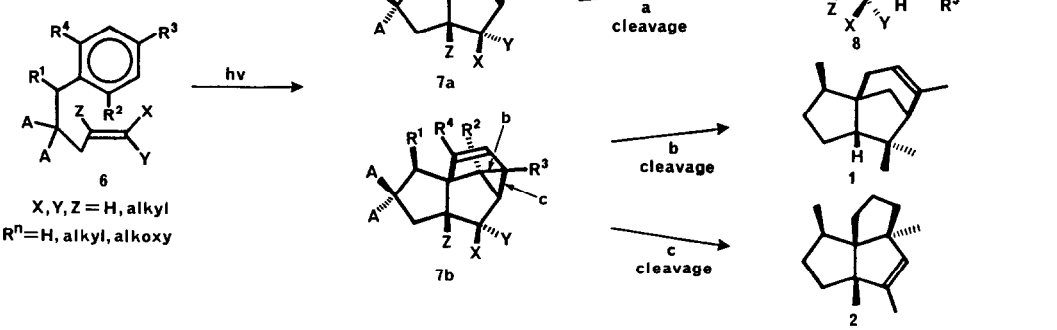

Modhephene
3


Hirsutene
4


Coriolin
5

suggest that the complexity inherent to these systems (or any general polycycle) is most efficiently developed from trivial precursors through a design in which several rings are established simultaneously. Intramolecular cyclizations hold special promise toward satisfying this dictum, and have been explored in our laboratories in the form of the arene-olefin cyclization (Scheme I). Thus, substrates of general structure **6**, in which three sp^3

SCHEME I



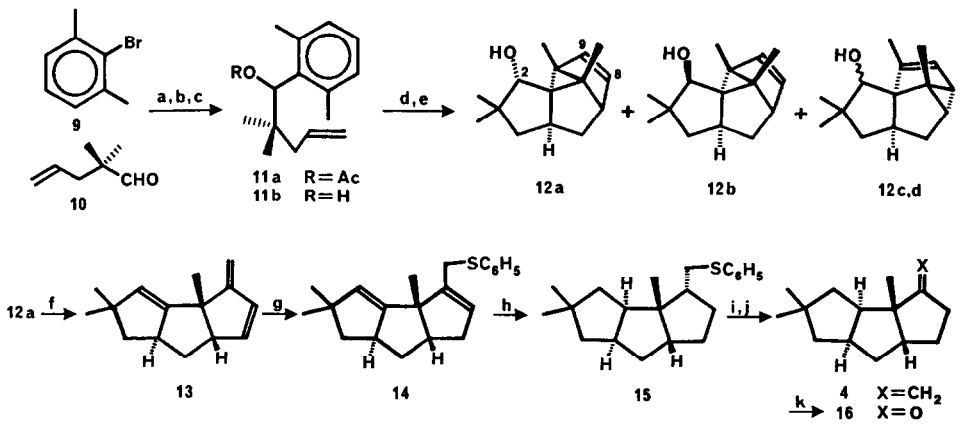
centers link the arene and olefin, undergo 1,3- (or "meta") cycloaddition upon singlet excitation of the arene, to give a mixture of adducts **7a** and **7b**. When substituents on **6** are restricted to those indicated, yields are moderate to high, olefin geometry is retained in the products, and little, if any, competition from other modes of addition (e.g. 1,2-) is seen. Furthermore, a high degree of stereoinduction is imparted by the benzylic center, giving the beta-orientation of R^1 shown[4]. The utility of this cyclization in the rapid assembly of polyquinanes was indicated in our previous reports of a five-step synthesis of isocomene (**2**)[5] and a four-step synthesis of cedrene (**1**)[6]. We now wish to report the extension of this method to linearly fused triquinanes, and the total synthesis of hirsutene (**4**), a natural product containing this type of skeleton.

Hirsutene and its more highly oxidized congener coriolin (**5**) were isolated from the Basidomycete **Coriolus Consors**. The antibiotic and antitumor activity[7] of several members of the class have prompted widespread efforts at their synthesis[8]. Two main issues have had to be dealt with in each case: establishment of the required **cis, anti, cis** pattern of ring fusion, and elaboration of the rich array of substituents. The first would be solved in a straightforward manner using the arene-olefin cyclization if cleavage of bond **a** in an adduct of type **7a** (to give a structure of type **8**) could be achieved. The substituents in the specific case of hirsutene are sufficiently simple that it is reasonable to propose their inclusion in the uncyclized precursor. The retrosynthetic analysis then becomes quite direct: **4** → **8** → **7a** → **6** (Scheme I: R^1,R^3,X,Y,Z=H; R^2,R^4,A=Me)[9]. Its implementation proved equally straightforward.

Arene-olefin **11a**[10] was prepared in one operation by condensation of the Grignard reagent derived from **9** with aldehyde **10**[11], followed by an in situ quench of the alkoxide with Ac_2O (79%, distilled). The benzylic oxygenation was left in place to act as a control element for the later cyclopropane cleavage. Photolysis of **11a** under standard conditions gave, after deacetylation of the crude mixture, four identifiable cycloadducts, **12a-d**, in yields of 22-23%, 7%, 1%, and 1%, respectively. Photolysis of the unprotected alcohol precursor **11b** gave an identical mixture of **12a-d** directly, but in somewhat reduced yield (c. 18-19% for **12a**). The low yield, relative to that seen in previous arene-olefin syntheses[5,6], undoubtedly stems from steric congestion in the transition state leading to **12a-b**, in which three contiguous quaternary centers are developed.

It was anticipated that the crucial cyclopropane cleavage could be induced by development of electron deficiency (either cationic or radical) at C-2 or C-9 (see **12a**). Although models show approximately equal overlap with both adjacent cyclopropane bonds for C-2, one might expect allylic stabilization involving the olefin at C-8,C-9 to provide a bias toward the desired cleavage. This indeed proved to be the case. Dehydrative acid-catalyzed rearrangement of **12a** led cleanly to triene **13** in 71% yield.

Completion of a synthesis of hirsutene required selective saturation of two of the olefins in **13**. The desired exomethylene group was "protected" via 1,4-free radical



a Mg^0, Et_2O; **b** **9**; **c** Ac_2O, DMAP; **d** h (450W Hanovia medium-pressure Hg lamp), cyclohexane, vycor filter; **e** LAH, Et_2O; **f** 10-camphorsulfonic acid, ØH, RT; **g** 1.0 eq. ØSH, neat, 100°; **h** H_2, $[Ir(cod)pyPCy_3]PF_6$, CH_2Cl_2; **i** $NaIO_4$, MeOH; **j** 170°, ØH, $(MeO)_3P$; **k** O_3, MeOH, -78°

addition of thiophenol[12] (78%). Subsequent hydrogenation of **14** was troublesome due to catalyst poisoning by the sulfide, but could be achieved, after several cyclings, with the Crabtree-Suggs catalyst[13]. Oxidation of **15** to a sulfoxide (86%), followed by elimination under standard conditions, regenerated the exocyclic olefin (yield ~60%) to give hirsutene (**4**). The analytical and spectral properties of this material agreed with the assigned structure and with available literature data[14]. Unequivocal identification was made through conversion of **4** to norketone **16**, whose TLC, NMR, IR, MS, and m.p. were identical with those of an authentic sample[14].

The utility of the arene-olefin cyclization in the synthesis of polycycles has thus been expanded to include another skeletal class, the linear tricyclopentanoids. Applications to more highly oxidized members of the class (e.g. **5**), and to more complex 5- and 7-membered ring-containing polycycles, are being explored.

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References and Notes.

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

[1]Portions of this work were presented at the French Chemical Society Meeting, Palaiseau, 1981; the Royal Society of Chemistry Autumn Meeting, Univ. of Leeds, 1981; the American Chemical Society Meeting, Atlanta, 1981; and the Middle Atlantic Regional ACS Meeting, Wilmington, 1982.

[2]A comprehensive review of polyquinane syntheses has been collected by L. A. Paquette, "Topics in Current Chem.", **79**, p. 41 (1979).

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[4]See refs. 5 and 6 for a discussion of the origins of this stereoinduction.

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[9]An added benefit of this approach is the symmetrical substitution of the arene, which reduces the number of possible regioisomers in the cyclization.

[10]All new compounds displayed satisfactory NMR, IR, and low-resolution mass spectra, and satisfactory elemental analysis and/or high-resolution MS.

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[14]A sample of synthetic **16** was kindly provided by Prof. Tom Hudlicky. He also provided copies of the MS and NMR of **4** taken by Prof. Tatsuta during his synthesis (see ref. 7), which were used to correlate our synthetic **4.**

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