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Synthetic Studies on Arene-Olefin Cycloadditions-VIII.[1,2] Total Syntheses of (±)-Silphiperfol-6-ene, (±)-7αH-Silphiperfol-5-ene and (±)-7βH-Silphiperfol-5-ene

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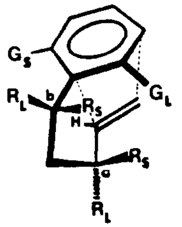
Dedicated to Professor Harry Wasserman on the occasion of his 65th birthday

Abstract: Total syntheses of (±)-silphiperfol-6-ene, (±)-7αH-silphiperfol-5-ene and (±)-7βH-silphiperfol-5-ene are described in which a new element of stereoinduction in arene-olefin meta cycloadditions was tested and a new method for cycloadduct transformation was developed.

Since our report in 1981 on the initial application of the arene-olefin meta-photocycloaddition to complex natural product synthesis, we have been involved with investigations aimed at elucidating those structural features which govern the often impressive selectivities observed for this strategy level reaction.[2] Based on the parallel plane exciplex model[3] represented by 1, a working hypothesis has emerged from these studies which allows for a prediction of the sense and degree of stereoinduction that a chiral benzylic center (b in arene olefin 1) will impart on the course of the cycloaddition. Without exception, thus far,[2a,b,f,g] the product stereochemistry observed in such cases is consistent with cycloaddition proceeding via exciplex 1 in which the larger of the two benzylic substituents (R_L and R_S) is preferentially oriented away from the larger of the two ortho substituents (G_L and G_S) of the



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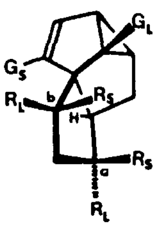

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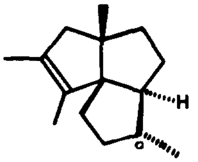

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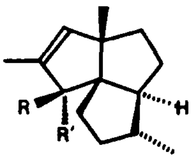

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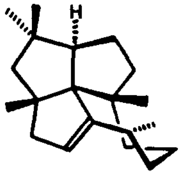
a: R'=H , R =CH_3
b: R'=CH_3, R =H



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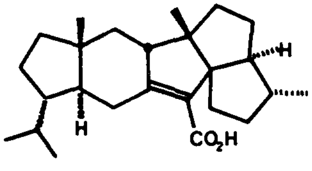

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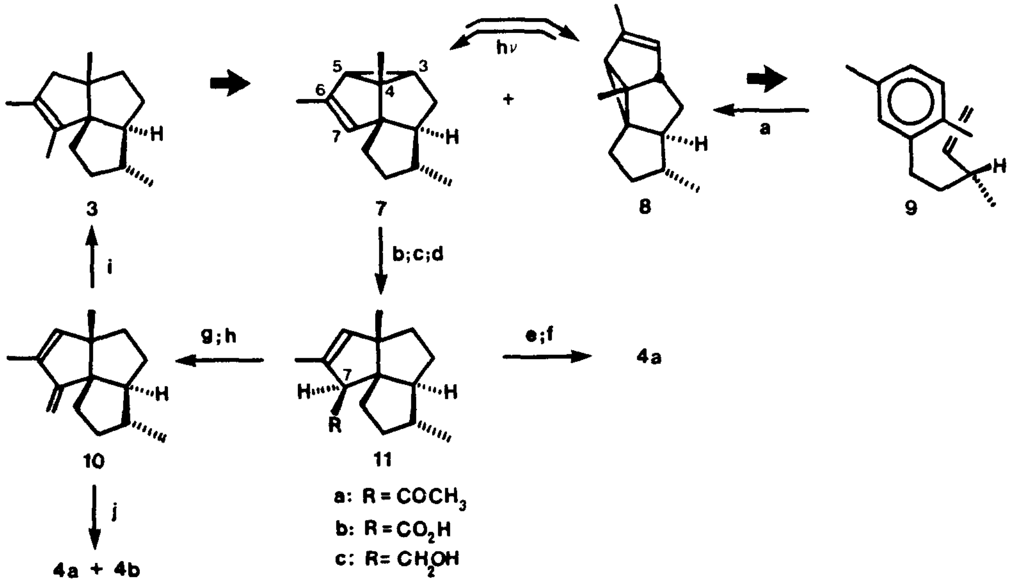
aromatic ring in order to minimize steric strain. To the extent that the remaining structural elements of this exciplex conform to structure 1, it would follow that substituents at the allylic site (a) in the tether connecting the arene and olefin should preferentially orient with the larger group (R_L) orthogonal to the plane of the olefinic carbons and directed away from the approaching arene subunit. This orientation would minimize steric interactions in the exciplex and would also direct the larger substituent to the sterically less congested convex face of the local bicyclo[3.3.0]octane subunit which develops as the exciplex evolves to product 2. At present, however, the influence of allylic substituents on the course of the cycloaddition has not been tested experimentally even though this issue bears fundamentally on the mechanism of the cycloaddition and the broader use of this process in synthesis. In this Letter, we describe our studies on this subject of stereopredictability which have been developed in the context of total syntheses of (±)-silphiperfol-6-ene (3), (±)-7βH-silphiperfol-5-ene (4a) and (±)-7αH-silphiperfol-5-ene (4b)[4,5] and which have produced a new radical-based method for the regiocontrolled cleavage of the photocycloadducts.

The synthetic focus of this study, silphiperfolenes 3, 4a, and 4b,[4] are sesquiterpenes characterized by a tricyclo[6.3.0.0^{1,5}]undecane ring system common to a growing list of other terpenoid families represented by natural products such as isocomene, silphinene, pentalenene, laurenene (5) and retigeranic acid (6).[6] Synthetic access to this group based on the meta cycloaddition was expected to arise from cycloadduct 7 which, in turn, would be derived from arene olefin 9 if the above postulate on allylic stereocontrol were to prevail. In our effort to test this approach, we found that the requisite cycloaddition precursor 9 was readily prepared in 92% yield by reaction of commercially available bromo p-xylene with lithium metal (8 equiv.) in Et_2O (1 h at 25°) followed by sequential addition of 3-methyl-4-pentenal and ammonia.[7,8] Gratifyingly, when this compound (9, 0.017M cyclohexane) was irradiated at room temperature for 30 minutes with a Hanovia medium pressure mercury arc source filtered through Vycor, a mixture of photoadduct 7 and its vinylcyclopropane isomer 8 was obtained in a 1:1.88 ratio and in a combined yield of 72% as determined by internal standard (adamantane) capillary GC analysis. It is mechanistically and synthetically noteworthy that 7 and 8 are photochemically interconvertible.[9] Consequently, they result from the same sense of allylic stereo induction which is in complete agreement with predictions based on model 1 and which indicate that the difference between the CH_3 and H groups is sufficient to induce virtually complete stereocontrol during the cycloaddition.

Illustrative of the rapid structural complexity-building character of meta cycloaddition based strategies, cycloadduct 7, available in only two steps, required for its conversion to the target structures only introduction of the C7 methyl and cleavage of the C5-C3 bond. In principle, the reaction of a carbon radical with the vinylcyclopropane subunit of 7 could service both of these requirements since addition to C7 would produce a C6 radical which should induce selective cleavage of the C5-C3 bond relative to the unfavorably aligned C5-C4 bond. In the event, irradiation of 7 in acetaldehyde[10] (Pyrex filter, 0°, 2 h) provided in 60% yield a product (11a) which exhibited a C4 methyl singlet in its ^1H NMR spectrum in accord with the assigned structure. The stereochemistry at C7 is that expected from convex face addition to the

C6-C7 olefin and was confirmed by conversion of **11a** to (±)-7βH-silphiperfol-5-ene (**4a**). For this purpose, the C7 methyl ketone **11a** was converted by a haloform cleavage[11] to the C7 carboxylic acid **11b** which was reduced to provide alcohol **11c**. Deoxygenation[12] of **11c** afforded (±)-7βH-silphiperfol-5-ene (**4a**), whose identity was confirmed by Professor Bohlmann[13] through spectroscopic comparison with natural **4a** and its epimer **4b**.[14] For the synthesis of (±)-silphiperfol-6-ene (**3**), alcohol **11c** was first dehydrated (78%) to the diene **10** which was then reduced to furnish in 91% yield racemic **3** as a colorless oil. Spectroscopic comparison of this product and authentic **3** unequivocally established the identity of the synthetic material.[13] Finally, reduction of diene **10** afforded (±)-7αH-silphiperfol-5-ene (**4b**) along with its isomer (**4a**) in a 2.8:1 ratio.[13,14]

In summary, concise syntheses (7-8 steps) of (±)-silphiperfol-6-ene (**3**), (±)-7β H-silphiperfol-5-ene (**4a**), and (±)-7αH-silphilperfolene (**4b**) are described which proceed in 8.4%, 5.0% and 6.0% overall yields, respectively. These studies demonstrate that a high degree of stereoinduction by allylic substituents can be achieved in arene olefin cycloadditions. Finally, carbon radical additions to the cycloadducts provides a new method for their



a) hν, Vycor filter, cyclohexane, 30 min., 25°C, 72%, **8**:**7** = 1.88:1; b) hν, CH_3CHO, Pyrex filter, 2 hrs, 0°C, 60%; c) 3.3 eq. Br_2, 13.1 eq. NaOH, 1:2 H_2O-dioxane, 0°C, 4 hrs, Na_2SO_4 quench, reflux 2.5 hrs, 95%; d) 1.5 eq. LAH, THF, 2 hrs, reflux, 91%; e) 2.5 eq. n-BuLi, 3.3 eq. $(EtO)_2POCl$, 4:1 THF-TMEDA, 12 hrs, 25°C, 76%; f) excess Li, t-BuOH, $EtNH_2$, THF, 1 hr, 0°C, 55%; g) 1.3 eq. $PhNO_2SeCN$, 1.3 eq. n-Bu_3P, THF, 25°C, 6 days, 99%; h) 10 eq. H_2O_2, THF, 25°C, 3.5 hrs, 78%; i) excess Li, NH_3, Et_2O, -33°C, .5 hrs, 91%; j) 1 eq. $(Ph_3P)_3RhCl/H_2$, 3:1 PhH-EtOH, 24 hrs, 25°C, 89% based on recovered starting material, **4a**:**4b** = 1:2.8.

regiocontrolled cleavage and a facile entry to the triquinane subunits of laurenene (5) and retigeranic acid (6). Further studies are in progress.

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References and Notes

1. This work was presented at the 20th Western Regional ACS meeting, October, 1984; Paper XI: Total Synthesis of the Silphiperfolenes.
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3. For discussions on this subject and recent reviews pertinent to the mechanism and synthetic applications of this reaction, see a) references 2a,b,f and g; b) Welzel, P. Nachr. Chem. Tech. Lab. 1983, 31, 262; c) Wender, P.A. in "Selectivity--A Goal for Synthetic Efficiency," Bartmann, W. and Trost, B., eds. Verlag Chemie 1984; d) Houk, K.N. Pure Appl. Chem. 1982, 54, 1633; e) Reedich, D.E.; Sheridan, R.S. J. Am. Chem. Soc. 1985, 107, 3360; f) Morrison, H. Accts. Chem. Res. 1973, 12, 383; g) Gilbert, A. Photochemistry 1984, 15, 291.
4. Bohlmann, F.; Jakupovic, J. Phytochemistry 1980, 19, 259. All compounds prepared in this work were racemic. The absolute stereochemistry depicted for 4 conforms to that established for 3 (ref. 5). The relative stereochemistry of 4a and 4b are those originally assigned as 7βH- and 7αH-silphiperfol-5-ene, respectively.
5. Since initial disclosure of this work (ref. 1), a synthesis of 3 has been reported: Paquette, L.A.; Roberts, R.A.; Drtina, G.J. J. Am. Chem. Soc. 1984, 106, 6690.
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8. Compounds 7-11 gave satisfactory ^{1}H NMR, IR, low resolution mass spectra and combustion or exact mass analysis.
9. Irradiation (Hanovia medium pressure lamp) of either 7 or 8 allowed for their interconversion although complete equilibration was not possible due to competing decomposition of these compounds.
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13. Institut fur Organische Chemie der Technischen Universitat Berlin, W. Germany. We thank Professor Bohlmann for making spectroscopic comparisons of our synthetic material with authentic compounds.
14. The NMR data for 7αH- and 7βH-silphiperfol-5-ene are reversed in the literature (see reference 4; private communication, Professor F. Bohlmann).

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