## SYNTHETIC STUDIES ON ARENE-OLEFIN CYCLOADDITIONS-VII:<sup>1</sup> A THREE-STEP TOTAL SYNTHESIS OF $(\pm)$ -SILPHINENE

Paul A. Wender\* and Robert J. Ternansky Department of Chemistry, Stanford University, Stanford, California 94305

<u>Abstract</u>: A three-step total synthesis of  $(\pm)$ -silphinene  $(\underline{1})$  is described which illustrates the high process selectivity attainable with the arene-olefin meta-photocycloaddition and a method for selective transformation of meta-cycloadducts.

Notwithstanding the major advances and impressive efficacy of contemporary synthesis, a considerable gap exists between current realities and the routine realization of ideal syntheses, i.e., those in which the target molecule is assembled from readily available starting materials in one simple, safe, economical, and efficient operation. The discovery or design and development of strategy level reactions figure significantly in reducing this disparity, particularly in the case of those transformations which allow for a great increase in structural complexity since the judicious use of such processes invariably results in a decrease in the number of operations needed to convert simple starting materials to complex targets.<sup>2</sup> In this Letter, we describe our continuing studies on a representative of this special reaction class, the arene-olefin meta-photocycloaddition, 1,3 which further underscore the considerable design simplification achievable with this reaction producing in the present study a three-step total synthesis of silphinene (1).

Silphinene (1), the first member of a new family of triquinane natural products, was initially reported by Bohlmann and Jakupovic<sup>4</sup> in 1980 and its synthesis has been achieved by three groups.<sup>5</sup> Our plan for the synthesis of silphinene (Scheme I) was influenced, in part, by an interest in improving our understanding of those factors which bear on the selectivity of the meta-cycloaddition  $(4 \rightarrow 2)^{1,3}$  and in developing processes for the selective cleavage of the peripheral cyclopropane bond of meta-cycloadducts (2: C-3, C-5), matters

2625



C. 5 + Li (1% Na), Et<sub>2</sub>O, rm. temp; 6 , ∆ ; N H<sub>3</sub> , -78° → -33° ; NH<sub>4</sub>Cl B. hv (vycor), pentane, 25° A. Li , CH<sub>3</sub>NH<sub>2</sub> , -78° \$ = commercially available



which bear on the broader synthetic uses of this reaction. The arene olefin  $4^6$  required for the present study was prepared in multigram quantity from commercially available starting materials (5 and 6) in one operation and in 87% yield by using the procedure of Hall and coworkers.<sup>7</sup> Irradiation of 4 with Vycor-filtered light from a Hanovia medium pressure, mercury arc lamp gave photoadducts 2 and 3 as a 1:1 mixture in 70% yield. This result<sup>1,3</sup> is consistent with a cycloaddition proceeding from exciplex <u>8a</u> (Scheme II) in which the larger C-9 substituent (CH<sub>3</sub> vs H) is oriented away from the larger

ortho substituent (C-4 CH<sub>3</sub> vs C-1H) thereby favoring a pro-beta, C-9 methyl orientation over the pro-alpha conformer (8b). The magnitude of this preference is suggested by the absence of products arising from 8b and the finding in the case of ortho isopropyl toluene that the conformer (<u>9a</u>) corresponding to the beta-methyl exciplex <u>8a</u> is greater than 2 kcal/mole lower in energy than its <u>9b</u> isomer. The exo orientation required for the formation of 2 and 3 is attributable to the better overlap between the reacting pi and arene centers in exciplex 8a relative to its endo counterpart. Finally, the regioselectivity observed emphasizes the directing influence of donor groups with meta addition across alkyl groups (C-4) being preferred over addition across hydrogen substituted centers (C-1). The absence of products arising from addition across the C-8 alkyl group is presumably due to the destabilizing C-10, C-13 interaction involved in the formation and/or further transformation of exciplex 10.1 On the practical side, it is noteworthy that the cycloaddition reaction provides milligram to multigram quantities of cycloadducts. The irradiation time required for these reactions increased with sample size from 2 hours for 85% conversion of a 3g sample of 4 to 6 hours for similar conversion (82%) of a 7g sample.

The third and final step in our plan required regioselective, reductive cleavage of the cyclopropane bond of 2 which we intended to accomplish by dissolving metal reduction.<sup>8</sup> It was expected that formation of the double bond radical anion would lead to preferential cleavage of the cyclopropane bond aligned parallel (2: C-3, C-5) to the radical anion orbitals relative to the orthogonally aligned cyclopropane bond (2: C-3, C-4). In practice, while this reductive cleavage could not be effected with lithium in ether/ammonia at  $-33^{\circ}$ C, it was observed when ammonia was replaced with an alkylamine solvent. Optimal conditions were realized with lithium in monomethylamine at  $-78^{\circ}$ C, which provided (±)-silphinene (1) along with its positional olefin isomer 7 in a ratio of 9:1 (73.5% combined yield).<sup>9</sup> Silphinene prepared in this fashion could be purified by preparative GC or by chromatography on silver nitrate impregnated silica gel. The identity of the isolated sample of synthetic (1) was established by comparison of its spectra with spectra of (±)-silphinene (1)

provided by Professors Paquette (Ohio State University) and ShôItô(Tohoku University). Furthermore, our synthetic silphinene was converted with MCPBA to an epoxide whose spectroscopic data were fully in accord with those reported for this derivative of silphinene.<sup>4</sup>

This study extends the general utility of the arene olefin metacycloaddition to a preparatively useful synthesis of a new natural product class and provides an expanded data base for the interpretation and predictive use of this reaction in future work. Moreover, at the level of synthesis design, it clearly illustrates the highly significant relationship between reaction complexity and design brevity. Further studies are in progress.

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## References and Notes

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- 6. All compounds reported herein exhibited NMR, IR, MS and where relevant UV spectra in full accord with the assigned structure. Satisfactory combustion analyses were obtained on all compounds.
- 7. Hall, S.S.; McEnroe, F.J.; J. Org. Chem., 1975, 40, 271.
- For a discussion of reductive cleavages of vinylcyclopropanes, see Staley, S.W.; Heyn, A.S.; <u>Tetrahedron</u>, 1974, <u>30</u>, 3671.
- 9. While the factors influencing this result are not fully defined, it is noteworthy that the major product (1) is calculated (MM2) as being 2.6 kcal/mole lower in energy than  $\underline{7}$ .

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