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ANNELATION VIA CYCLOPROPYL KETONES. I. SYNTHESIS OF THE SPIRO SESQUITERPENE (±)-α-CHAMIGRENE

James D. White*
Department of Chemistry, Oregon State University
Corvallis, Oregon 97331

Sigeru Torii and Junzo Nogami
Department of Industrial Chemistry, Okayama University
Okayama, Japan

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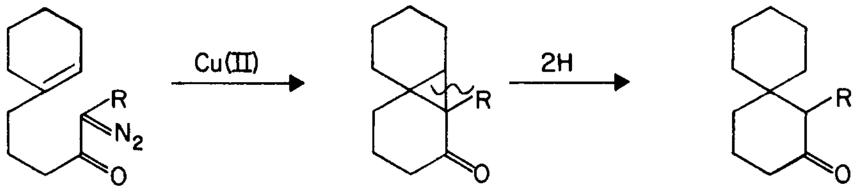
Although several novel schemes for the construction of spiro ring systems have been devised recently,[1] there remains a need for a method of general applicability in this area. One approach which offers attractive versatility for spiroannelation is the intramolecular addition of a diazoketone to an olefin,[2] followed by reductive cleavage of the peripheral ring bond of the resulting cyclopropyl ketone (Scheme I).[3,4] We here report the synthesis of the sesquiterpene (±)-α-chamigrene (**1**)[5] as an illustration of this concept.

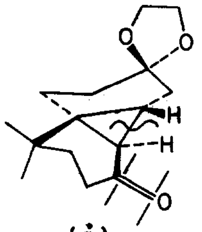
Scheme I



4-Methyl-4(p-methoxyphenyl)pentanoic acid (**2**)[6] was reduced under Birch conditions to give, after hydrolysis of the resulting enol ether (3% HCl, 5-10°), the keto acid **3**[7] in 94% yield. After protection of the ketone as its ethylene ketal **4** (66.5%), **3** was converted to the acyl chloride **5** by treatment of its <u>anhydrous</u> sodium salt (NaH, benzene) with oxalyl chloride in benzene (5°, 1 hr). Slow addition of **5** to an ethereal solution of diazoethane[8] at 0° gave diazoketone **6** (2050, 1640 cm^{-1}), which was purified by passage through an alumina column.

Homogeneous decomposition of 6 in the presence of the soluble catalyst bis-(N-n-propylsalicylideneaminate)copper(II)[9] (cyclohexane, 75-80°, 12 hr) resulted in formation of tricyclic ketone 7 (1672 cm^{-1}; 45% yield from 5).[10]

The dissolving metal reduction of fused cyclopropyl ketones has been convincingly shown to fall under powerful stereoelectronic control.[11] An examination of the tricyclic system 7 indicates quite decisively that the conformation (i), with the peripheral cyclopropane bond parallel to the carbonyl π axis, is much the more stable; hence this bond should undergo preferential reductive scission. In the event, treatment of 7 with lithium in ammonia-ether gave spiroketone 8 (1708 cm^{-1}) in quantitative yield.



(i)

Reduction of 8 (LiAlH(t-BuO)$_3$, THF, 0°, 2 hr) produced the cis alcohol 9 with high stereoselectivity, and the latter was converted to the spiroundecene 11 (δ 1.90 (3 H), 5.35 (1 H)) in 80% yield by warming the corresponding mesylate 10 (MsCl, py, 0°, 2 hr) in dimethylsulfoxide (60°, 7 hr).[12] The ketal function of 11 was hydrolyzed (1.5 M HClO$_4$, THF, 0°, 1 hr), and the resulting ketone 12 (96% after chromatography on silica gel) was treated with methyl lithium (Et$_2$O, 0°, 1 hr) to afford a pair of diastereomeric carbinols 13 (3300 cm^{-1}; δ 0.90 (6 H), 1.20 (3 H)) which cocrystallized (mp 73-74°). Without separation, the mixture of carbinols underwent dehydration (dimethylsulfoxide, 80°, 2 hr)[13] to give a hydrocarbon (65%); after purification by glpc (polyneopentyl succinate), this was shown to be identical by spectral comparison with an authentic specimen of (±)-α-chamigrene (1).[14] A minor amount (ca 5%) of exo olefin 14 accompanied α-chamigrene from dehydration.

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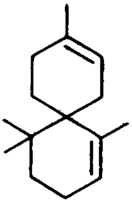

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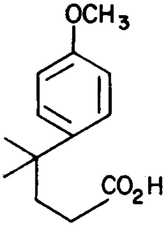

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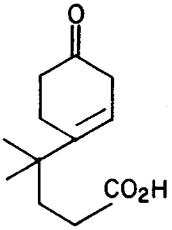

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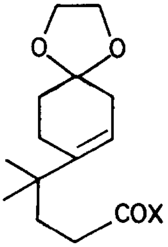
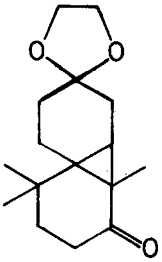


4, X = OH
5, X = Cl
6, $X = CN_2CH_3$



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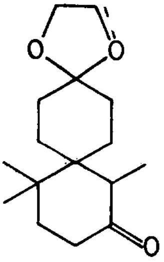

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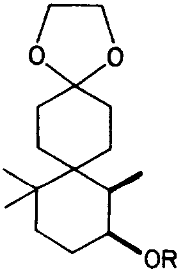
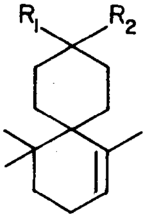
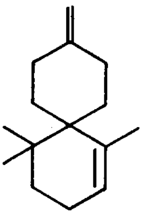


9, R = H
10, R = Ms



11, $R_1, R_2 = OCH_2CH_2O$
12, $R_1, R_2 = O$
13, $R_1 = CH_3, R_2 = OH$



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14. We are grateful to Professor A. Yoshikoshi, Tohoku University, for providing spectra of (±)-α-chamigrene.