

2-Aryl-5-epoxynitrile Anion Cyclizations : Total Syntheses of ($\pm$)- α -Cuparenone and ($\pm$)-Epilaurene

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Total syntheses of the cyclopentane sesquiterpenes of the title using an epoxynitrile anion cyclization reaction as key step, are described. The preferential formation of the cyclopentane ring from a terminal disubstituted 5-epoxynitrile (*e.g.* **2b**) had not previously been observed. The 2-aryl substituent is reasonably assumed to be responsible for this divergence.

The 5-epoxynitrile anion cyclizations were originally proposed by Stork and coworkers in 1974 as a general method for cyclobutane formation and this was exemplified by a simple synthesis of the monoterpene grandisol.¹⁻³ Shortly afterwards, Lallemand and Onanga in 1975 made the important observation that the ring size of the cyclized product was dependent of the geometry of the epoxide: epoxides from *cis*-olefins give exclusively cyclobutanes and those from *trans*-olefins give mixtures of cyclobutanes and cyclopentanes, predominating the latter.⁴

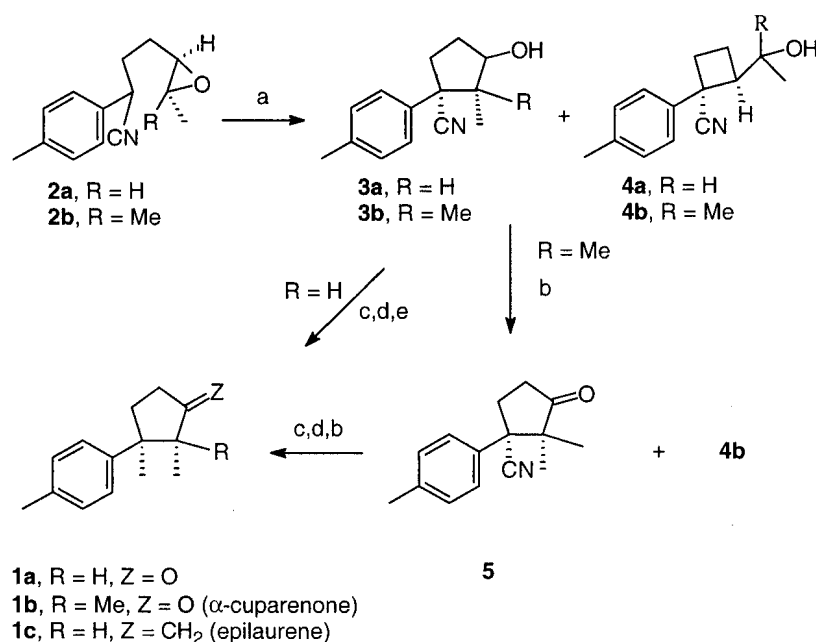
From the above studies it is clear that until now a special attention has been given to the epoxide environment, but investigations concerning the influence of large substituents in the α -position of the nitrile group towards the regiochemistry of

cyclization are unknown. Now we wish to report an interesting deviation of the expected result in the cyclization of a substrate containing an α -aryl group as substituent, which has led us to a simple, new total synthesis of ($\pm$)- α -cuparenone **1b**.⁵ From these studies, a total synthesis of ($\pm$)-epilaurene **1c** has also been achieved.⁶

Cyclization of several acyclic and cyclic 6,6-disubstituted-5-epoxynitrile anions was reported by Stork and Cohen^{1b} to give cyclobutanes in good yields (58-80%). No cyclopentanes were detected in these experiments. However, in our hands cyclization of epoxynitrile **2b**⁷ with 2.5 eq of lithium hexamethyldisilazide (LHMDS) in refluxing C₆H₆ for 1 h gave a 60% yield of a 2:1 mixture of the cyclopentane (**3b**) and the cyclobutane (**4b**) isomers, respectively.⁸ Although the isomers could be separated by preparative tlc in silica gel (hexanes-ethyl acetate, 4:1, 5 elutions), for practical purposes PCC oxidation (3 eq, rt, CH₂Cl₂) of the cyclized crude mixture gave cyclopentanone **5** and unreacted cyclobutylcarbinol **4b**, more easily separated by flash column chromatography in silica gel (hexanes-ethyl acetate, 7:3) (see Scheme 1).

The structure of cyanocyclopentanone **5** was easily

Scheme 1



a : LHMDS or LDA (see text); b : PCC, then flash column chromatography; c : DIBAL (toluene), then H₃O⁺; d : NH₂NH₂·H₂O, KOH (ethyleneglycol), Δ ; e : Jones (acetone)

assigned from spectroscopic data [IR (film) 2232, 1747 cm^{-1} ; $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 7.27 (m, 4H), 2.80-2.50 (m, 4H), 2.35 (s, 3H), 1.32 (s, 3H, *anti*- CH_3 to the aryl group), 0.63 (s, 3H, *syn*- CH_3 to the aryl group)] and by its eventual conversion to α -cuparenone **1b** following the standard reactions shown in the Scheme (40% overall yield from **5**).

The cyclization reaction was next studied with substrate **2a**^{7,9} (LDA, THF, rt, 7 h) but in this case no influence by the aryl substituent was found, since a 3:1 mixture of cyclopentanol **3a** and cyclobutylcarbinol **4a** was obtained in good accord with the results of Lallemand and Onanga⁴ for α -unsubstituted substrates. Yields were 44 and 15% respectively (59 and 20% based on recovered epoxide). The *anti* relationship of the aryl and methyl groups in **3a** was established by the normal chemical shift observed for the CH_3 doublet (δ 1.12) in the $^1\text{H-NMR}$ spectrum. If this relationship were *syn*, it would be expected a strong high field shift of this signal due to the aromatic ring (*cf.* the *syn*- CH_3 chemical shift in the $^1\text{H-NMR}$ spectrum of compound **5**). Finally, the conversion of **3a** into the known ketone **1a**¹¹ (35% overall yield) completed the formal syntheses of epilaurene **1c** and also α -cuparenone **1b**.^{5b}

The reaction mechanism to explain the preference for the cyclopentane formation in the cyclization of **2b** is unclear, but steric interference between the aryl group and the gem-dimethyl group in the transition state leading to the cyclobutane isomer should play a significant role. On the other hand, the similar results obtained in the cyclization reaction with other aryl substituted substrates (phenyl and 3-methoxy-4-methylphenyl) suggest a negligible electronic effect caused by the aryl substituent. Finally, in the case of cyanocyclopentanol **3a** the observed stereochemistry can be explained as the result of minimum steric interactions in the transition state for the cyclization (preferred Ar,H eclipsing vs. Ar, CH_3 eclipsing).¹²

In summary, we have achieved new total syntheses of ($\pm$)- α -cuparenone **1b** and ($\pm$)-epilaurene **1c** using the previously unobserved 2-aryl-5-epoxynitrile anion cyclization as key step. The potential use of the results described in this paper for the enantioselective syntheses of these sesquiterpenes, is being investigated in our laboratories.

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References and Notes

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- 2-Aryl-5-epoxynitriles **2a** and **2b** were obtained in ~60% yields by alkylating the 4-methylphenylacetone nitrile carbanion (LDA, THF, -78°) with the corresponding alkenyl iodides ($-78^\circ \rightarrow$ rt, overnight), followed by epoxidation (mcpba, CH_2Cl_2 , rt). Some dialkylated product (5-10%) was also isolated in the alkylation reaction.
- With LDA in THF at rt only traces of epoxide ring opening products were detected after 24 h. Hence, the base and solvent were changed to allow heating.
- Since the alkenyl iodides were obtained by the cyclopropylcarbinyl-homoallyl cation rearrangement in the presence of iodide anion,¹⁰ the geometry of the olefin precursor was reasonably assumed to be *E*.
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- In the case of cyclobutylcarbinols **4a** and **4b** the indicated stereochemistry is proposed based on that found, by X-ray analysis, for the derived carboxamide of the phenyl analogue of **4b**: G. Avila, L. A. Maldonado, and R. A. Toscano, *J. Chem. Cryst.*, **27**, 125 (1997).