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

J. Gustavo Avila-Zárraga and Luis A. Maldonado*
Instituto de Química and División de Estudios de Posgrado, Facultad de Quìmica, UNAM, Ciudad Universitaria, Coyoacán, 04510 México D.F., México

(Received February 14, 2000; CL-000154)

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.

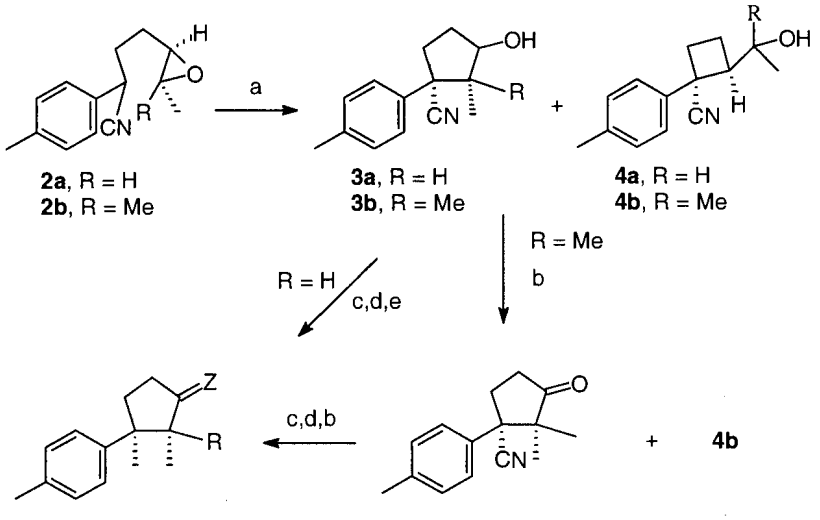
The 5-epoxynitrile anion cyclizations were originally proposed by Stork and coworkers in 1974 as a general method for cyclobutane formation and this was exemplified by a simple synthesis of the monoterpene grandisol.[1-3] Shortly afterwards, Lallemand and Onanga in 1975 made the important observation 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 (±)-α-cuparenone **1b**.[5] From these studies, a total synthesis of (±)-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 C_6H_6 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, CH_2Cl_2) 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 H_3O^+; d : $NH_2NH_2.H_2O$, KOH (ethyleneglycol), Δ; e : Jones (acetone)

assigned from spectroscopic data [IR (film) 2232, 1747 cm^{-1}; ^{1}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 Onanga[4] 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}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}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 (±)-α-cuparenone **1b** and (±)-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.

We are grateful to Alejandrina Acosta, Marisela Gutiérrez, Graciela Chávez, Claudia Contreras, Luis Velasco, Javier Pérez-Flores and Wilber Matus, for their assistance in acquiring spectral data. We also thank DGAPA-UNAM for a fellowship financial support.

References and Notes

1 a) G. Stork, L. D. Cama, and R. D. Coulson, *J. Am. Chem.Soc.*, **96**, 5268 (1974). b) G. Stork and J. F. Cohen, *J. Am. Chem. Soc.*, **96**, 5270 (1974).

2 For examples of the closely related 6-epoxynitrile anion cyclization see Ref. 1 and R. Achini and W. Oppolzer, *Tetrahedron Lett.*, **1975**, 369. Recently, a 7-epoxynitrile anion cyclization has also been reported: A. Nitta, A. Ishiwata, T. Noda, and M. Hirama, *Synlett*, **1999**, 695.

3 For a review on reactions of nitrile carbanions see: S. Arseniyadis, K. S. Kyler, and D. S. Watt, *Org. React.* (N.Y.), **31**, 1 (1984).

4 J. Y. Lallemand and M. Onanga, *Tetrahedron Lett.*, **1975,** 585.

5 For previous synthesis of α-cuparenone see: a) M. G. Kulkarni and D. S. Pendharkar, *Tetrahedron*, **53**, 3167 (1997). b) J. Cossy, B. Gille, S. BouzBouz, and V. Bellosta, *Tetrahedron Lett.*, **38**, 4069 (1997) and references cited in these papers.

6 For previous synthesis of epilaurene see: A. Fadel, J.-L. Canet, and J. Salaun, *Tetrahedron : Asymmetry*, **4**, 27 (1993) and references cited therein. For a recent synthesis of a 1:1 mixture of epilaurene and laurene see: M. G. Kulkarni and D. S. Pendharkar, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3127.

7 2-Aryl-5-epoxynitriles **2a** and **2b** were obtained in ~60% yields by alkylating the 4-methylphenylacetonitrile carbanion (LDA, THF, -78°) with the corresponding alkenyl iodides (-78°→ rt, overnight), followed by epoxidation (mcpba, CH_2Cl_2, rt). Some dialkylated product (5-10%) was also isolated in the alkylation reaction.

8 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.

9 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*.

10 W. Biernacki and A. Gdula, *Synthesis*, **1979,** 37.

11 Cyclopentanone **1a** was first prepared by T. Irie, T. Suzuki, Y. Yasunari, E. Kurosawa, and T. Masamune, *Tetrahedron*, **25**, 459 (1969), but in this paper the relative stereochemistry of the 2-methyl and 3-(*p*-tolyl) groups was incorrectly assigned as *syn*. See: J. E. McMurry and L. A. von Beroldingen, *Tetrahedron*, **30**, 2027 (1974). See also Ref. 5b for an alternative synthesis of **1a**.

12 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).