Tetrahedron Letters,Vol.29,No.14,pp 1645-1648,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ON THE QUESTION OF REVERSIBILITY IN THE INTRAMOLECULAR ADDITION OF RADICALS TO ALDEHYDES TO FORM CYCLOALKANOLS

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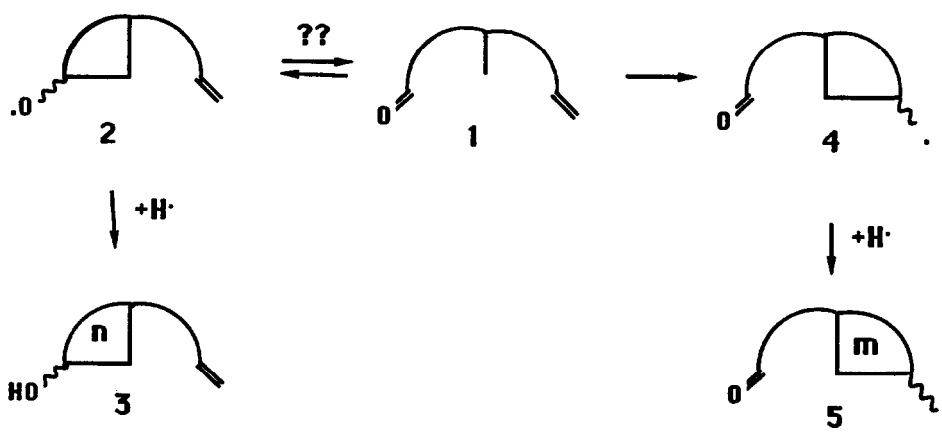
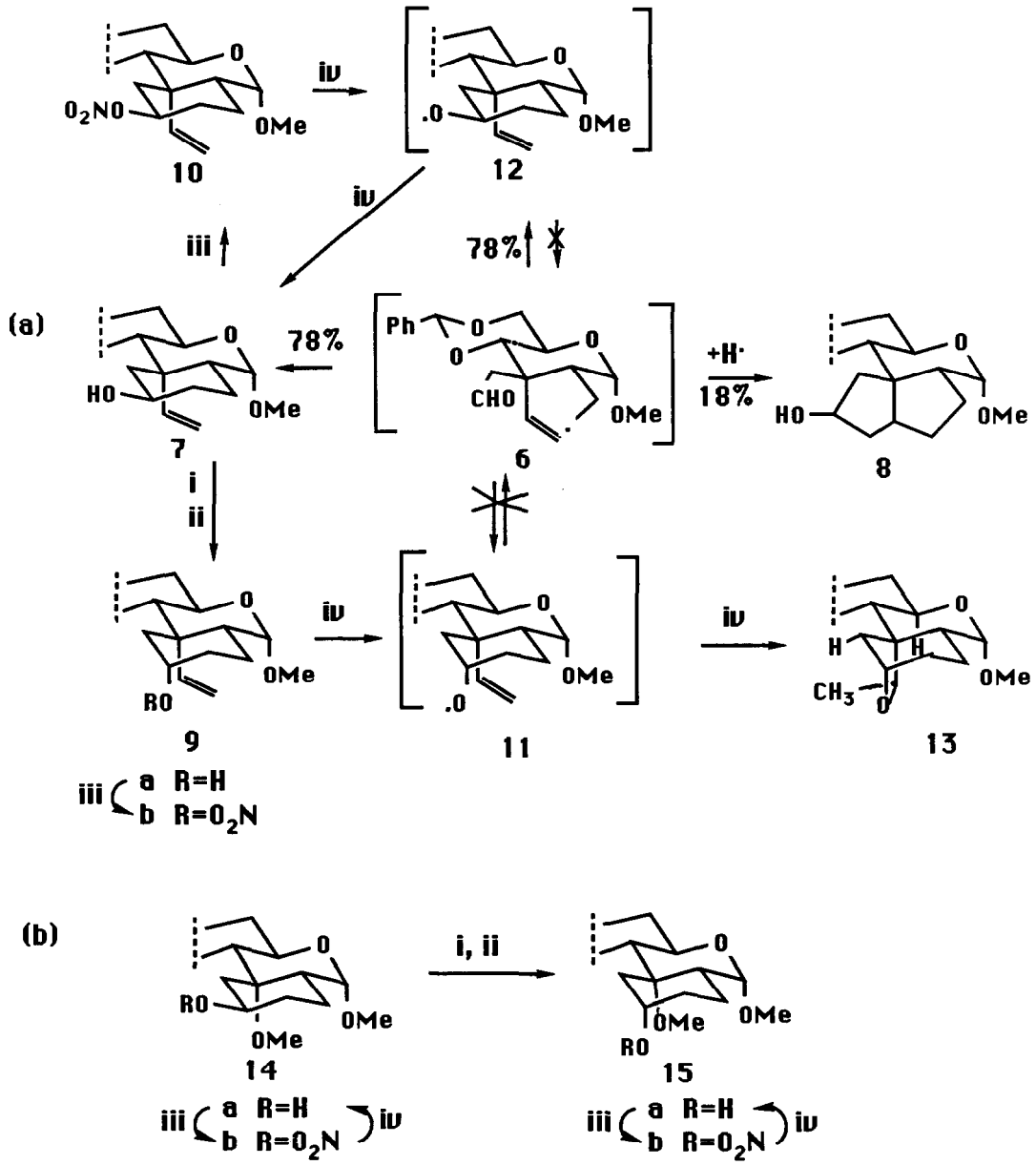
Experiments with two pairs of epimeric alcohols establish conclusively that the intramolecular addition of a primary radical to an aldehyde to give a cycloalkanoxyl radical is not a reversible process.

Recent publications from this laboratory have shown that radical cyclization of aldehydes is frequently a highly efficient reaction which can, in some circumstances, compete with ring closure of a 5-hexenyl radical.[1,2,3] Thus, for a system such as **1**, a cyclohexanol (**3**, n = 6) was formed predominantly (and often exclusively) even when a methylcyclopentane (**5**, m = 5) was a plausible alternative.[3] However, when n = m = 5, the cyclopentanol, **3**, and

Scheme 1



Scheme 2



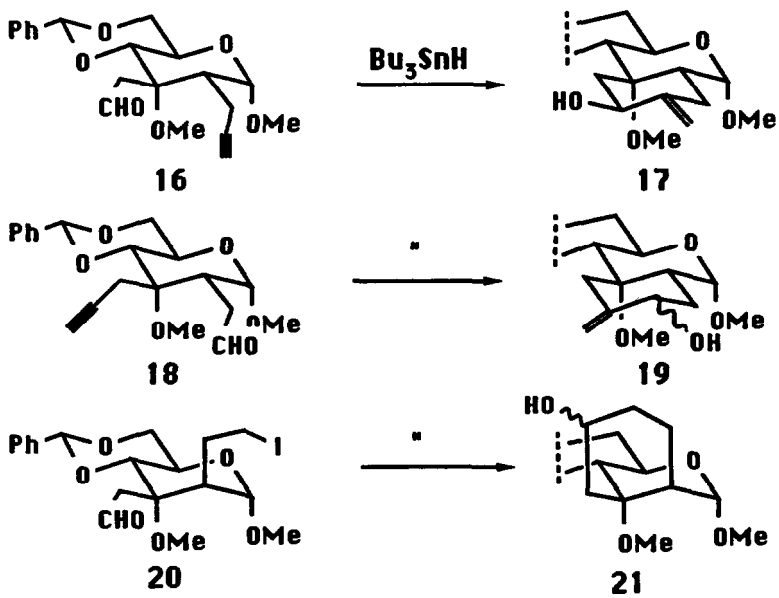
(i) PCC. (ii) L-Selectride. (iii) Ac_2O/HNO_3 [5]. (iv) Bu_3SnH [7]

methylcyclopentane, **5**, were both formed in appreciable amounts.[3] We are attempting to explore the generality and synthetic utility of the ring closure **1** ---> **3**, and it seemed prudent to examine the question of reversibility of cycloalkanol formation in view of the excellent precedents from Nickon's seminal study on α-caryophyllene alcohol,[4] and Binkley's studies on furanose sugar derivatives.[5] Thus these precedents show that β-scission of intermediate alkoxyl radical, **2**, provides a ready means for equilibrating the epimeric forms of the cycloalkanol, **3**.[4,5]

The question of isomerization/equilibration of the alcohols was particularly pertinent in our studies since the equatorial cyclohexanol, **7**, and the diquinane, **8**, were the only products isolated from the cyclization of **6** (Scheme 2a) the latter being generated from the corresponding iodide.[1] Conceivably, the axial counterpart, **9a**, could have been formed in the reaction, but was isomerized to **7** by the radical intermediates **11**, **6**, and **12**.

Compound **9a** was therefore prepared from **7** by pyridinium chlorochromate oxidation, followed by reduction with L-selectride. Both alcohols were converted into the nitrate esters, **10** and **9b**, respectively, according to Binkley's procedure,[5] and were treated with tri-*n*-butyltin hydride to generate the alkoxy radicals according to our recently developed procedure.[7] Compound **9b** led exclusively to the furan **13**,[6] thereby establishing conclusively that the axial alkoxy radical, **11**, is not formed during the cyclization of **6**. With nitrate **10**, the alcohol, **7**, was regenerated exclusively, **thereby establishing conclusively that the intermediate alkoxy radical 12 does not revert to 6, since this would have produced approximately 18% of the diquinane, 8.**

Scheme 3



If the vinyl group of **11** had not been present to trap the alkoxy radical, would axial ---> equatorial equilibration of the alkoxyl radical have occurred? This question was examined by using the methoxy analogs **14** and **15**.[3] Thus, the nitrate esters, **14b** and **15b**, were found to regenerate the corresponding alcohols, **14a** and **15a**, respectively, exclusively.

The results in Scheme 2 establish that the cyclizations are irreversible and that under our experimental conditions, the equatorial alcohols (e.g., **7** and **14a**) are formed under kinetic, rather than thermodynamic control.

However, this favorable stereoselectivity appears to be substrate specific. Thus, compound **16** gave only the equatorial alcohol **17**, comparable to **7** and **14**. However, the regioisomer, **18**, gave a 2:1 mixture of axial and equatorial forms of **19**, as did compound **20**, which gave the mixture of **21**.[3]

Therefore, these results show that the cyclohexanols **7** and **14a**[3] were formed irreversibly, and that in these and comparable systems in our recent report,[3] cyclohexanol formation is faster than 5-hexenyl radical ring closure.

Acknowledgements We are grateful to the National Institutes of Health (GM 37380) and the National Science Foundation (CHE 8703913) for financial support and we thank Mme Katherine Tachdjian for her help.

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6. The configuration of the methyl group in **13** was assigned on the basis of strong nOe effects (~10%) in the protons shown, when the CH_3 group was irradiated.
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(Received in USA 9 December 1987)