THE INTRAMOLECULAR OPENING OF THE OXIRANE RING IN BUTYL 4,5-EPOXY-2-HYDROXYHEXANOATE. A NEW SIMPLE SYNTHESIS OF RACEMIC ALLOMUSCARINE

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Abstract - The new simple synthesis of racemic allomuscarine via the intramolecular opening of the trans substituted epoxide ring in butyl 4,5-epoxy-2-hydroxyhexanoate is described.

The intramolecular opening of the epoxide ring in esters of 4,5-epoxy-2-hydroxyhexanoic acid by the hydroxyl group to a tetrahydrofuran derivative is a new way to C-glycofuranosides. The model \(\beta\)-hydroxyepoxide grouping \(1\) can be obtained via an ene reaction between butyl glyoxylate and but-1-ene followed by the epoxidation of the double bond with m-chloroperoxybenzoic acid, \(1\).

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\begin{align*}
\text{CHCO}_2\text{Bu} + \text{SnCl}_4 & \xrightarrow{\text{CH}_2\text{Cl}_2, \text{O}^\circ} \text{CHCO}_2\text{Bu} \quad \text{CO}_2\text{Bu} \\
& \xrightarrow{\text{m-CPBA}} \text{OH} \quad \text{CHCl}_3 \\
& \xrightarrow{\text{OH}} \text{CO}_2\text{Bu}
\end{align*}
\]

The mixture of diastereomeric epoxides \(1\) (6:4) treated with 0.5 equiv. of stannic chloride in methylene chloride at \(-40^\circ\text{C}\) undergoes intramolecular opening of the epoxide ring to afford \(2\) as the major product (40%); \(^1\)H NMR (CDCl\(_3\)): 0.8-1.9(m, 7H, CH\(_3\)), 1.19(d, 3H, CH\(_3\)), 2.11(m, 1H, \(J_{4,4} = 14.0\)), 2.50(m, 1H, \(J_{4,5} = 3.6\text{Hz}\)), 3.45-4.01(m, 1H, H\(_4\)), 4.1-4.4(m, 3H, \(H_2, CH_2\)), 4.63(dd, 1H, H\(_5\)).

\[
\begin{align*}
\text{CH}_2\text{N(CH}_3)_3^- & \quad \text{OH} \\
\text{CO}_2\text{Bu} & \xrightarrow{\text{SnCl}_4, \text{CH}_2\text{Cl}_2, -40^\circ} \text{OH} \\
& \xrightarrow{\text{CO}_2\text{Bu}} \text{OH} \\
& \xrightarrow{\text{CH}_2\text{N(CH}_3)_3^-} \text{OH}
\end{align*}
\]
To demonstrate the potential synthetic value of the presented reaction we have performed a new simple synthesis of racemic allomuscarnine 3. The synthesis of racemic and natural D-(-)-allo-muscarnine which occurs in Amanita muscaria 3 has been attempted several times in the past. 4

The ester 2 was treated with freshly prepared dimethylamide magnesium bromide in THF solution to yield amide 4 (90%), mp 74-75°C; $^1$H NMR (CDCl$_3$): 1.19(d, 3H, CH$_3$), 2.1-2.6(m, 2H, H$_4$, H$_5$), 3.06, 3.25[2s, 6H, N(CH$_3$)$_2$], 4.03(m, 1H, H$_3$), 4.27(dq, 1H, J$_{23}$=7.7Hz, H$_2$), 5.03(dd, 1H, J$_{45}$=2.8, J$_{45}$=7.4Hz, H$_5$).

Reaction of 4 using LAH in boiling THF solution for 1h gave dimethylamine derivative 5 (95%); $^1$H NMR (CDCl$_3$): 1.08(d, 3H, CH$_3$), 1.75(bd, 1H, J$_{44}$=13.5Hz, H$_4$), 2.2-2.8(m, 3H, CH$_2$N$^+$), 4.28[2s, 6H, N(CH$_3$)$_2$], 3.94(bd, 1H, J$_{34}$=5.5Hz, H$_3$), 4.22(bq, 1H, H$_2$), 4.42(bq, 1H, H$_5$). Quaternization of 5 was performed using the high pressure technique which allows to obtain a pure crystalline quaternary salt with almost quantitative yield. 5 Treatment of 5 with equiv. of methyl iodide in acetone solution under 11 kbar at room temperature for 16h afforded allomuscarnine iodide 3, mp 131-132°C (lit.131-132°C); $^1$H NMR (D$_2$O): 1.22(d, 3H, CH$_3$), 1.67(dt, 1H, J$_{44}$=11.8, J$_{34}$=9.8Hz, H$_4$), 2.61(dd, 1H, J$_{34}$+J$_{45}$=13Hz, H$_5$), 3.23[2s, 9H, N(CH$_3$)$_2$], 3.46(dd, 1H, J$_{gem}$=13.0, J$_{vic}$=2.3Hz, -CHH$^+$), 3.71(dd, 1H, J$_{vic}$=8.8Hz, -CHH$^+$), 4.10(m, 2H, H$_2$H$_3$), 4.73(m, 1H, H$_5$).

The $^1$H NMR data of 3 are identical with those published ones. 4 Further studies on the intramolecular opening of the oxirane ring in 1 are currently in progress.

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REFERENCES
2. The configuration of 2 was proved by its transformation into racemic allomuscarnine. Micro-analytical (combustion) data for 2 and all subsequent products (3-5) are in full accord with the proposed structures.
5. The experiment was performed with cooperation of Dr. J. Jurczak according to the known procedure [M. Pietraszkiewicz, P. Słański and J. Jurczak, J. Chem. Soc., Chem. Commun., in press].

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