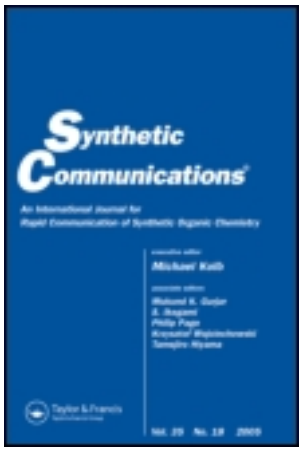

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$ZnI_2/NaCNBH_3$ as an Efficient Reagent for Regioselective Ring Opening of the Benzylic Epoxide Moiety

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ABSTRACT

In the presence of zinc iodide, sodium cyanoborohydride was found to produce regioselective ring opening of benzylic epoxides in mild reaction conditions.

Key Words: Sodium cyanoborohydride; Zinc iodide; Benzylic epoxide; α-Chloroketone; β-Chlorohydrin.

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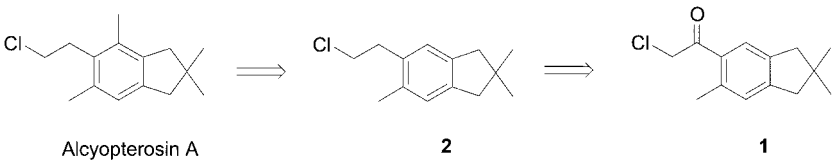

Figure 1. Synthetic pathway of alcyopterosins.

In an attempt to find a synthetic route to the natural occurring sesquiterpenes named alcyopterosins,[1] we needed to reduce α-chloroketone **1** to the indanic compound **2** (Fig. 1). To this end, we chose sodium cyanoborohydride in the presence of zinc iodide. This system afford reductive deoxygenation of aryl aldehydes and ketones[2] and benzylic alcohols[3] to the corresponding hydrocarbons.

When the reaction was carried out with zinc iodide/sodium cyanoborohydride at room temperature, compound **1** cleanly furnished the corresponding halohydrin **3** in good yield, but when the reaction was performed under reflux conditions, the main product isolated was alcohol **4**. To generalize this reaction, several examples were performed, and results are given in Table 1.

The obtention of alcohols **4, 9**, and **13** prompted us to consider the possibility of *in situ* epoxide formation, whereby the epoxide would be opened by attack of the hydride moiety to afford the primary alcohol.

To test this hypothesis, we synthesized several epoxides, which were then treated with $ZnI_2/NaCNBH_3$ in the same conditions used for reductive deoxygenation reaction. It was found that this mixture of reagents is able to perform ring opening of the epoxide moiety to render, in all examples, the less substituted alcohol in an efficient manner (see Table 2), better than when the starting material was the α-chloroketone or β-chlorohydrin. The presence of a Lewis acid is required to activate the epoxide toward nucleophilic attack, since this moiety is essentially inert to sodium cyanoborohydride. Hydride is trapped at the site best able to accommodate a carbonium ion, and thus the less substituted alcohol is preferentially obtained.

When the reaction was carried out starting from either α-chloroketone or β-chlorohydrin at reflux conditions, an iododerivative was also obtained in all cases. In an early publication, Lau et al.[2] proposed the formation of a spiro cyclopropyl intermediate when 4-methoxyphenethyl alcohol was treated with $ZnI_2/NaCNBH_3$. Such an intermediate, favored by the electron donor effect of the methoxyl group, is then attacked by an iodide anion to produce 4-methoxyphenethyl iodide. Our results would seem to indicate that the production of the iododerivative is not entirely due to the formation of this intermediate. As the epoxide is formed, starting from the β-chlorohydrin or

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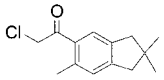
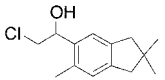
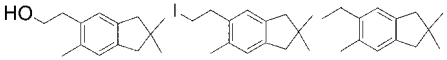
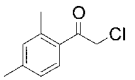
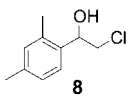
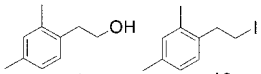
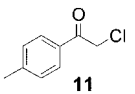
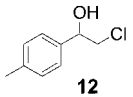
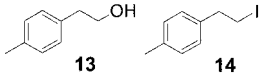
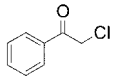
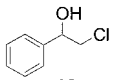
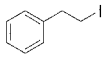
Table 1. Reduction of α-chloroketones and β-chlorohydrins with $ZnI_2/NaCNBH_3$.

α-Chloroketone	Products[a]	Yield (%)	Time (h)	Products[b]	Yield (%)	Time (h)
 **1**	 **3**	74	16	 **4** **5** **6**	42, 4, 6[c]	16
 **7**	 **8**	84	16	 **9** **10**	22, 7[c,d]	16
 **11**	 **12**	83	16	 **13** **14**	8, 21[c,d]	36
 **15**	 **16**	78	16	 **17**	14[c,d]	110

[a]Reaction carried out in dichloromethane at room temperature.
[b]Reaction carried out in dichloroethane under reflux conditions.
[c]Yields refer to chromatographically pure products.
[d]All the products exhibited spectral data consistent with their structures.

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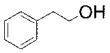
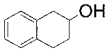
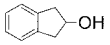
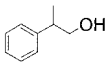
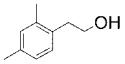
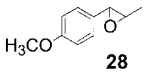
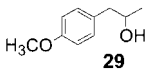
Table 2. Ring opening of benzylic epoxides with ZnI_2/$NaCNBH_3$.

Epoxide	Product[a]	Yield (%)[b]
 **18**	 **19**	76[c]
 **20**	 **21**	81[c]
 **22**	 **23**	85[c]
 **24**	 **25**	79[c]
 **26**	 **27**	82[c]
 **28**	 **29**	80[d]

[a]Reaction time: 16 h.
[b]Yields refer to isolate and chromatographically pure products. All the products exhibited spectral data consistent with their structures carried out.
[c]Reaction carried out in dichloroethane under reflux conditions.
[d]Reaction carried out in dichloroethane at room temperature.

α-chloroketone, the former is rapidly cleaved to render the corresponding alcohol. When epoxide formation is more difficult, as in the case of compound **12** and **16**, required reaction times are greater. In such conditions, the substitution of the alcohol by the iodide occurs, thus leading to the iodo-derivative. In support, when phenethyl alcohol was treated in the same conditions used for compound **16**, the corresponding iododerivative was obtained (yield: 91%). Throughout, the progress of the reaction was monitored by tlc.

In conclusion, the combination of ZnI_2 and $NaCNBH_3$ is capable of achieving the formation and cleavage of epoxides starting from α-chloro-

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ketones and β-chlorohydrins. The mixture of reagents proves also a convenient and efficient method for ring opening of benzylic epoxides. The reaction is invariably regioselective and proceeds in mild conditions. Due to, the ease in handling and inertness toward other functional groups, this method is recommended when chemoselectivity is crucial. Full investigation of ring opening of diverse classes of epoxides, with this reagent, are under way.

EXPERIMENTAL

The epoxides used were prepared from the corresponding alkenes and *m*-chloroperbenzoic acid in $CHCl_3$.[4] ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-300 spectrometer with $CDCl_3$ as solvent, employing Me_4Si as internal standard (δ: 0.00), J values are given in Hz. Mass spectra were obtained by direct injection of the sample as chloroform solution by using Shimadzu GCQP 1000 mass spectrometer operating at an ionizing electron energy of 70 eV. Elemental analysis was carried out in our laboratories with a Colleman Analyser. Melting point (uncorrected) was obtained with a Thomas Hoover apparatus. Preparative thin layer chromatography (*p*-tlc) was performed on a 20 × 20 cm glass coated with silica gel 60 F_{254} (0.50 mm).

General Procedure for Reaction of $ZnI_2/NaCNBH_3$ with α-Chloroketones, β-Chlorohydrins and Epoxides

To a solution of α-chloroketone, β-chlorohydrin or epoxide (2 mmol) in ethylene dichloride (10 mL) at room temperature were added zinc iodide (3 mmol) and sodium cyanoborohydride (15 mmol). The reaction mixture was stirred at room temperature or refluxed and, after completion of the reaction (monitored by tlc), the mixture was then cooled and poured onto a solution of 6N HCl (40 mL). Lastly, the mixture was extracted with dichloromethane (20 mL) and the organic extract was washed with water (15 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The residue obtained was chromatographed using hexane–ethyl acetate (4 : 1) as eluent.

General Procedure for the Preparation of α-Chloroketones

To a magnetically stirred cold solution of corresponding aromatic compound (2 mmol) and chloroacetyl chloride (2.5 mmol) in carbon disulfide (10 mL) was added $AlCl_3$ (15 mmol) in small portions. The reaction mixture was then refluxed for 30 min, cooled to room temperature, and carefully poured onto ice. The product was extracted into dichloromethane (25 mL) and

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then washed with water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by *p*-tlc using hexane-ethyl acetate (4 : 1) as eluent.

2-Chloro-1-(2,2,6-trimethylindan-5-yl)ethan-1-one 1

White solid, m.p. 61–63°C. ^{1}H NMR δ 1.14 (s, 6H), 2.49 (s, 3H), 2.72 (s, 4H), 4.64 (s, 2H), 7.09 (s, 1H), 7.43 (s, 1H). ^{13}C NMR δ 22.3, 29.3, 41.1, 47.7, 48.4, 48.6, 125.8, 129.9, 133.2, 138.6, 141.9, 149.8, 194.5. MS (m/z): 236 (9, M^+), 237 (2, $M^+ + 1$), 238 (3, $M^+ + 2$), 187 (100, $M^+ - CH_2Cl$). Calcd. for $C_{14}H_{17}ClO$: C, 71.03; H, 7.24; Cl, 14.98. Found: C, 71.24; H, 7.18; Cl, 15.09.

2-Chloro-1-(2,2,6-trimethyl-5-yl)ethan-1-ol 3

Oil. ^{1}H NMR δ 1.11 (s, 3H), 1.15 (s, 3H), 2.30 (s, 3H), 2.60–2.69 (m, 4H), 3.59 (dd, *J*: 9.2, *J*: 11.4, 1H), 3.68 (dd, *J*: 3.0, *J*: 11.4, 1H), 5.07 (dd, *J*: 3.0, *J*: 9.2, 1H), 6.96 (s, 1H), 7.31 (s, 1H). ^{13}C NMR δ 19.7, 29.5, 40.9, 48.1, 50.8, 71.8, 122.3, 127.5, 133.1, 136.3, 142.5, 144.4. MS (m/z): 238 (11, M^+), 239 (2, $M^+ + 1$), 240 (4, $M^+ + 2$), 189 (100, $M^+ - CH_2Cl$). Calcd. for $C_{14}H_{19}ClO$: C, 70.43; H, 8.02; Cl, 14.85. Found: C, 70.39; H, 7.88; Cl, 15.02.

2-(2,2,6-Trimethylindan-5-yl)ethan-1-ol 4

Oil. ^{1}H NMR δ 1.15 (s, 6H), 2.30 (s, 3H), 2.68 (s, 4H), 2.86 (t, *J*: 6.8, 2H), 3.82 (t, *J*: 6.8, 2H), 6.92 (s, 2H). ^{13}C NMR δ 20.1, 29.5, 29.6, 37.1, 40.8, 48.1, 63.4, 126.6, 127.3, 134.6, 142.0, 142.6. MS (m/z): 204 (19, M^+), 205 (3, $M^+ + 1$), 173 (100, $M^+ - CH_2OH$). Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C,82.46; H, 9.73.

5-(2-Iodoethyl)-2,2,6-trimethylindane 5

Oil. ^{1}H NMR δ 1.13 (s, 6H), 2.27 (s, 3H), 2.64 (s, 2H), 2.67 (s, 2H), 3.11–3.19 (m, 2H), 3.23–3.29 (m, 2H), 6.95 (s, 1H), 6.98 (s, 1H). ^{13}C NMR δ 5.1, 19.8, 29.5, 39.1, 40.9, 48.1, 48.2, 126.0, 127.5, 134.0, 137.6, 142.3, 143.2. MS (m/z): 314 (10, M^+), 315 (2, $M^+ + 1$), 187 (100, $M^+ - I$). Calcd. for $C_{14}H_{19}I$: C, 53.52; H, 6.10; I, 40.39. Found: C, 53.45; H, 6.22; I, 40.65.

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5-Ethyl-2,2,6-trimethylindane 6

Oil. ^{1}H NMR ó 1.15 (s, 6H), 1.21 (t, *J*: 7.5, 3H), 2.28 (s, 3H), 2.60 (q, *J*: 7.5, 2H), 2.68 (s, 4H), 6.96 (s, 1H), 6.98 (s, 1H). ^{13}C NMR δ 15.3, 19.8, 26.9, 29.7, 40.8, 48.2, 124.9, 127.0, 134.0, 140.7, 141.6, 141.9. MS (m/z): 188 (53, M^+), 189 (8, $M^+ + 1$), 173 (81, $M^+ - CH_3$), 159 (100, $M^+ - CH_2CH_3$). Calcd. for $C_{14}H_{20}$: C, 89.30; H, 10.17. Found: C, 89.17; H, 10.81.

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