Synthesis of 4-Substituted Hexahydro-2(3*H*)-benzofuranones by Addition of Hydrides or Trimethylaluminium to 2-Ethoxycarbonylmethyl-cyclohexanones†

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The addition of complex hydride and trimethyl aluminium to 3-substituted and 3,3-disubstituted-2-carboxymethylcyclohexanones to produce cyclohexanols which could be cyclized to the corresponding benzofuranones was investigated; the stereochemistry of the addition was strongly influenced by the nature and size of the added nucleofiles and by the cyclohexanone-substituent.

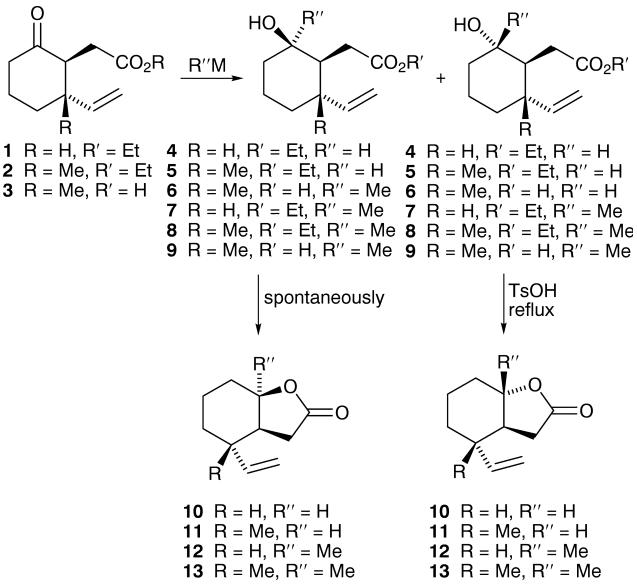
Hexahydro-2(3*H*)-benzofuranones constitute part of a number of biologically active natural products, including sesquiterpene lactones.[1] Synthetic methods for these compounds are the focus of attention of many chemists.[2] In the search for an alternative general method for the stereoselective synthesis of hexahydro-2(3*H*)-benzofurans, we present our results on the stereochemical course of the addition of hydrides and trimethylaluminium to and 3-R-3-vinyl-2-ethoxycarbonylmethylcyclohexanones (R = H or Me).

Although the addition of hydrides or organometallic compounds to cyclohexanones has been widely studied,[3] new methods are still sought.[4] The hydride addition stereochemistry depends both on the size of the hydride and the cyclohexanone substituents,[5] whereas the outcome of the addition of trimethylaluminium in hydrocarbon solvents depends on the substrate/organometallic reagent ratio.[6]

2-Ethoxycarbonylmethyl 3-R-3-vinylcyclohexanones (**1**, R = H) and (**2**, R = Me) were prepared by the addition of vinyl cuprate to cyclohex-2-en-1-one or to 3-methylcyclohex-2-en-1-one and subsequent trapping the enolate with ethyl iodoacetate according to Andriamialisoa.[7] The corresponding acid **3** was obtained in high yield by hydrolysis of a sample of the ketoester **2** with aqueous NaOH.

The addition of hydrides and trimethylaluminium to cyclohexanones **1**, **2** and **3** gave the corresponding alcohols **4**–**8** (Scheme 1, Table 1). The *cis* alcohols cyclize spontaneously to the *cis*-γ-lactones under the reaction conditions, while *trans* alcohols only cyclize under acidic conditions (toluene-*p*-sulfonic acid). The well-established chemical shifts of the γ-proton of hexahydro-(2*H*)-benzofuranones (*ca.* 4.5 ppm for the *cis* and 4.0 ppm for the *trans* fusion)[8] were used to support the assignment of the *cis* and *trans* diastereoisomers. The *cis*–lactones to *trans*-hydroxy esters ratios were determined from isolated products after column chromatography.

The sodium tetrahydroborate reduction of the 3-vinyl-cyclohexanone **1** produced the corresponding axial and equatorial products **4** (Table 1, entry 1), in a 40:60 *cis*:*trans* ratio, the equatorial alcohol being the favoured product;[3a,b] whereas reduction of the 3-methyl-3-vinyl-cyclohexanone **2** gave the *cis* and *trans* cyclohexanols **5** in a 83:17 ratio, (Table 1, entry 2), the result of the stronger bulk effect of the substituents.[3c–e] In contrast to the last result, the lithium aluminium hydride reduction of the 3-methyl-3-vinyl-keto-acid **3** afforded the *cis*, and *trans* hydroxy-acids **6** in a 40:60 ratio (Table 1, entry 3). The electronic effect produced by the hydride complexation with the acid group and the subsequent hydride transfer from the same side of the acid substituent[9] might explain this result. The *cis*-**6** hydroxy-acid also cyclizes to the *cis*-**11** lactone, while the *trans*-**6** hydroxy-acid was isolated, esterified with diazomethane and cyclized by acid catalysis to the *trans*-**11** lactone.



Scheme 1

The reaction of trimethylaluminium with the ketoesters **1** and **2** and with the keto-acid **3** gave exclusively *cis* (axial) alcohols **7**, **8**, and **9**, which cyclize spontaneously to the respective *cis* lactones **12** and **13** (Table 1, entries 4–6). Apparently, the steric effect of the nucleophile and/or the 2- and 3-substituents determines the course of the addition by the equatorial side of the molecule, in spite of previous reports of trimethyl aluminium transfer of methyl group by the axial side of cyclohexanones.[6]

In summary, the addition of the trimethylaluminium to 2-ethoxycarbonylcyclohexanones leading to the corresponding *cis* alcohols, which cyclize spontaneously to the *cis*-γ-lactones, constitutes an alternative stereoselective synthesis for 4-substituted *cis*-hexahydro-2(3*H*)-benzofuranones. By addition of hydrides, mixtures are obtained, depending on the cyclohexanone substituents. The *trans* alcohols can be cyclized by refluxing in benzene with acid catalysis to give the corresponding *trans* benzofuranones.

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Table 1 Nucleophilic additions to substituted cyclohexanones **1**, **2** and **3**

Entry	Substrate[a]	Nucleophile	Product		Yield[b] (%)	Ratio[c] (*cis:trans*)
			Alcohol	Lactone		
1	**1**	$NaBH_4$	**4**	**10**	84	40:60
2	**2**	$NaBH_4$	**5**	**11**	68	83:17
3	**3**	$LiAlH_4$	**6**	**11**	45	40:60
4	**1**	$Al(CH_3)_3$[d]	**7**	**12**	84	100:0
5	**2**	$Al(CH_3)_3$[d]	**8**	**13**	56	100:0
6	**3**	$Al(CH_3)_3$[d]	**9**	**13**	76	100:0

[a]Structures in Scheme 1. [b]Isolated material after column chromatography. [c]*cis* Lactones:*trans* hydroxyesters. [d]Used as etherate [$4Al(CH_3)_3{\cdot}3OEt_2$].

Experimental

Reduction of Ketoester **1** *with* $NaBH_4$.—A solution of **1** (700 mg, 3.30 mmol) in 20 ml ethanol was stirred with (42.0 mg, 1.11 mmol) sodium tetrahydroborate at room temperature. After 4 h, the reaction was quenched with solid NH_4Cl, the ethanol was evaporated and the solid residue was extracted with diethyl ether. After column chromatography [silica gel; hexane/AcOEt (9:1)], 190 mg of *cis*-**10** and 354 mg of *trans*-**4** (40:60) was obtained. Total yield: 84%. *cis*-**10** Colourless oil; $\nu/cm^{-1} = 1778$ (C=O); δ_H (90 MHz, $CDCl_3$) 1.00–2.80 (m, 10 H), 4.57 (q, *J* 3.5 Hz, 1 H), 4.85–5.10 (m, 2 H), 5.45 (ddd, *J* 6.5, 7.9 and 18.0 Hz, 1 H); *m*/*z* (EI) 166 (M^+, 75%), 67 (100). *trans*-**4**: Colourless oil; ν/cm^{-1} 3450 (OH), 1730 (C=O); δ_H (90 MHz, $CDCl_3$) 1.00–2.60 (m, 14 H), 3.30 (dt, *J* 5.0 and 10.1 Hz, 1 H), 4.01 (q, *J* 7.1 Hz, 2 H), 4.90–5.15 (m, 2 H), 5.60 (ddd, *J* 6.5, 7.9 and 18.0 Hz, 1 H); *m*/*z* (EI) 212 (M^+, 3%), 67 (100).

Reduction of Ketoester **2** *with* $NaBH_4$.—Using the previous method, *cis*-**11** and *trans*-**5** were obtained. *cis*-**11**: Colourless oil; ν/cm^{-1} 1780 (C=O); δ_H (90 MHz, $CDCl_3$) 0.99 (s, 3 H), 1.00–2.70 (m, 9 H), 4.60 (m, 1 H), 5.00–5.20 (m, 2 H), 5.8 (dd, *J* 12.0 and 18.0 Hz, 1 H). *m*/*z* (EI) 180 (M^+, 36%), 81 (100). *trans*-**5**: Colourless oil; ν/cm^{-1} 3450 (OH), 1740 (C=O); δ_H (90 MHz, $CDCl_3$) 0.87 (s, 3 H), 0.98–2.30 (m, 13 H), 3.40 (dt, *J* 5.0 and 10.2 Hz, 1 H), 4.00 (q, *J* 7.1 Hz, 2 H), 4.80–5.10 (m, 2 H), 5.60 (dd, *J* 10.2 and 17.3 Hz, 1 H).

trans-*Hexahydro*-4-*vinyl*-2(3H)*benzofuranone* **10**.—A mixture of *trans*-**4** (200 mg, 0.94 mmol) and toluene-*p*-sulfonic acid (*ca.* 5 mg) was boiled under reflux in 20 ml benzene for 2 h. After cooling to room temperature, the product was extracted with 30 ml of diethyl ether. Column chromatography [silica gel; hexane/AcOEt (9:1)] produced 131 mg (84%) of *trans*-**10** as colourless oil. ν/cm^{-1} 1780 (C=O); δ_H (90 MHz, $CDCl_3$) 1.00–2.60 (m, 10 H), 3.95 (dt, *J* 4.0 and 10.0 Hz, 1 H), 5.00–5.30 (m, 2 H), 5.8 (ddd, *J* 6.5, 7.9 and 18.0 Hz, 1 H); *m*/*z* (EI) 166 (M^+, 69%), 67 (100).

trans-*Hexahydro*-4-*methyl*-4-*vinyl*-2(3H)*benzofuranone* **11**.—Using the previous method, *trans*-**11** was obtained as colourless oil. ν/cm^{-1} 1775 (C=O); δ_H (90 MHz, $CDCl_3$) 1.00 (s, 3 H), 1.20–2.60 (m, 10 H), 4.05 (m, 1 H), 4.85–5.30 (m, 2 H), 5.60 (dd, *J* 12.0 and 18.0 Hz, 1 H). *m*/*z* (EI) 180 (M^+, 52%), 81 (100).

Addition of $Al(CH_3)_3$ *to Ketoester* **1**.—cis-*Hexahydro*-7*a*-*methyl*-4-*vinyl*-2(3H)*benzofuranone* **12**. To a solution of **1** (1.00 g, 4.76 mmol) in 20 ml benzene was added $4Al(CH_3)_3{\cdot}3Et_2O$[10] (1.37 g, 4.75 mmol) at room temperature. After the addition, the reaction mixture was heated at 50 °C for 3 days. The reaction was allowed to cool to room temperature, diluted with 50 ml diethyl ether and quenched by addition of 30 ml water. The NaCl saturated aqueous phase was extracted with diethyl ether (3 × 50 ml). After column chromatography of the organic extracts [silica gel; hexane/AcOEt (95:5)], 7.20 mg (84%) of *cis*-**12** was obtained as colourless oil. ν/cm^{-1} 1770 (C=O); δ_H (90 MHz, $CDCl_3$, TMS) 1.10–2.50 (m, 13 H), 4.90–5.10 (m, 2 H), 5.45 (ddd, *J* 6.5, 7.9 and 18.0 Hz, 1 H); *m*/*z* (EI) 180 (M^+, 23%), 165 (100).

cis-*Hexahydro*-4,7*a*-*dimethyl*-4-*vinyl*-2(3H)*benzofuranone* **13**.—Using the previous method, *cis*-**13** was obtained as colourless oil. ν/cm^{-1} 1780 (C=O); δ_H (90 MHz, $DCCl_3$) 0.85 (s, 3 H), 1.05–2.40 (m, 12 H), 4.65–5.00 (m, 2 H), 5.60 (dd, *J* 12.0 and 18.0 Hz, 1 H). *m*/*z* (EI) 194 (M^+, 45%), 81 (100%).

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