A Novel Approach to the Rare 4- and 5-Alkylindan-2-ols†

J. Chem. Research (S), 1998, 590–591†

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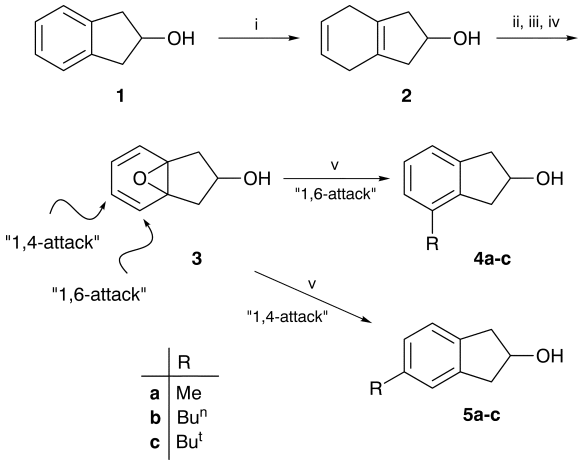
The rare 4- and 5-alkylindan-2-ols have been synthesized in 62–72% yields by formal 1,6- and 1,4-nucleophilic ring opening of the 2-hydroxyindan 3a,7a-oxide, respectively.

Only very few publications[1,2] deal with the preparation of 4- and 5-alkylindan-2-ols **4** and **5**. To the best of our knowledge, no general synthetic route to them, has yet been described. Thus, herein, we report on our efforts towards the development of a versatile general approach to these compounds.

We reasoned that the *syn*-2-hydroxyindan 3a,7a-oxide **3**, first described by Rastetter *et al.*,[3] should be a suitable intermediate on the way to **4a**–**4c** and **5a**–**5c** *via* formal 1,6- and 1,4-nucleophilic ring opening of the $\alpha,\beta-\gamma,\delta$ unsaturated epoxide **3**, respectively (Scheme 1). The *syn*-2-hydroxyindan 3a,7a-oxide **3** was synthesized with a 55% overall yield according to a slightly modified three-step literature procedure[3] which, starting with 4,7-dihydroindan-2-ol **2**, proceeds from a regioselective epoxidation, a bromination and a dehydrobromination. The diene **2** is obtained from indan-2-ol **1** by a Birch reduction.[4] We found that performing the Birch reduction twice in succession gave pure **2** in quantitative yields without any further purification.

Compound **3** was treated with alkyllithium‡ nucleophiles and, upon aromatising acidic work-up followed by filtration on a silica gel pad, the required mixture of regioisomers **4** and **5** was isolated in good yields ranging from 62 to 72%. since the **5a**–**5c** series shows a singlet signal for the 4-H proton, the aromatic substitution pattern could be assigned unambiguously and the composition of the mixture established by means of ^{1}H NMR spectroscopy. The composition has also been confirmed by GC.

As shown by the results in Table 1, the observed regioselectivities of the ring opening reaction were modest. However, if we assume that the reaction proceeds *via* 1,6- and 1,4-nucleophilic attack, without 'oxygen-walk',[5] comparing entries 1, 2 and 3 on the one hand and 5 and 6 on the other suggests that the reaction is kinetically controlled. Indeed, nucleophilic attack at the sterically less demanding



Scheme 1 i, NH_3 (l), MeOH; ii, *m*-CPBA, CH_2Cl_2, −10 °C to r.t., 1 h; iii, Br_2, CH_2Cl_2, −78 °C; iv, Bu^tOK, Et_2O, −15 °C; v, THF–Et_2O (1:1), RLi

5 position, yielding the 5-alkyl derivatives **5**, is favoured under milder conditions. Moreover, the stronger nucleophile alkyllanthanide[6] (entry 4) exhibited lower regioselectivity as compared to the corresponding alkyllithium, underlining this argument.

The regioisomers **4a**–**4c** and **5a**–**5c** were inseparable by normal pressure column chromatography, but we were able to separate **4b**, **4c** from **5b**, **5c** by normal phase Lobar® Si 60 chromatography using cyclohexane–ethyl acetate (4:1) as eluent, making the synthetic route practicable for preparative purposes. The **4a**/**5a** mixture could be separated by means of preparative HPLC on Si 60 material eluted with a cyclohexane–ethyl acetate (17:3).

Table 1 Results of the nucleophilic ring opening of compound **3**

Entry	Products[a]	*T*/°C	Nucleophile[b]	% Yield[c]	**4**/**5** ratio[d]
1	**4a**, **5a**	0 to r.t.	MeLi (8)	65	45/55
2	**4a**, **5a**	−40 to r.t.	MeLi (8)	65	43/57
3	**4a**, **5a**	−78 to r.t.	MeLi (8)	62	30/70
4	**4a**, **5a**	−78 to r.t.	MeLi/$CeCl_3$ (8)	68	42/58
5	**4b**, **5b**	−40	Bu^nLi (4)	68	44/56
6	**4b**, **5b**	−78	Bu^nLi (4)	64	32/68
7	**4c**, **5c**	−78	Bu^tLi (2.2)	72	19/81

[a]All new compounds gave satisfactory spectral data. [b]Number of equivalents of nucleophile with respect to the substrate given in parentheses. [c]Isolated and reproducible yields are given. [d]The reactions were quenched after 2 h at the end temperature. [d]Determined by GC and by 300 MHz ^{1}H NMR spectroscopy.

In summary, we have devised a new synthetic route for the rare 4- and 5-alkylindan-2-ols **4** and **5** the strength of which is the flexibility of the alkyl side chain.

Experimental

Column chromatography was performed on Merck silica gel (70–230 mesh ASTM), Lobar® chromatography on a LiChroprep®

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡1.6 M MeLi in diethyl ether, 2 M Bu^nLi in cyclohexane and 1.6 M Bu^tLi in diethyl ether (Aldrich) were stored under an inert atmosphere.

Si 60 silica gel column (Merck KGaA), and preparative HPLC on a LiChrosorb® Si-60 column (Merck KGaA) equipped with a Waters 501 pump and 486 absorbance detector. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard on a Varian Unity 300 spectrometer. The GC-MS measurements were performed on a Perkin-Elmer auto System N-610 chromatograph combined with a Q-mass 910 spectrometer.

General Procedure for the Ring-opening Reaction.—Epoxide **3** (400 mg, 2.66 mmol) was taken up in THF-diethyl ether (1:1, 12 mL), and cooled to the given temperature (see Table 1). The alkyllithium (2.2 to 8 equivalents, see Table 1) was added and stirring maintained upon completion of the TLC monitored reaction. The orange solution was then diluted with ethyl acetate (40 mL) and quenched with 1 M HCl (20 mL), washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was filtered over a silica gel pad (eluted with cyclohexane–ethyl acetate 4:1), dried and concentrated to give the **4**/**5** mixture in yield varying from 62 to 72% (see Table 1). The regioisomers (200 mg of the respective mixtures) were then purified either by means of Lobar® chromatography (**4b**/**5b** and **4c**/**5c**) (elution at 0.8 mL min^{-1} with cyclohexane–ethyl acetate 8:2), or by preparative HPLC (**4a**/**5a**) (elution at 1.0 mL min^{-1} with cyclohexane–ethyl acetate 9:1).

4-*Methylindan*-2-*ol* **4a**.—Yield 85 mg; MS (EI) *m*/*z* 148; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (s br, 1 H), 2.32 (s, 3 H), 2.82 (dd, $J = 3.2$, 16.5, 1 H), 2.94 (dd, $J = 3.2$, 16.4, 1 H), 3.14 (dd, $J = 6.1$, $J = 16.6$, 1 H), 3.22 (dd, $J = 6.2$, 16.6 Hz, 1 H), 4.70 (m, 1 H) and 7.05–7.20 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 42.3, 42.7, 73.2, 124.7, 125.7, 127.4, 136.3, 137.7 and 140.8. 5-*Methylindan*-2-*ol* **5a**: yield 104 mg; MS (EI) *m*/*z* 148; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (s br, 1 H), 2.26 (s, 3 H), 2.84 (dd, $J = 3.18$, 16.6, 1 H), 2.91 (dd, $J = 3.17$, 16.36, 1 H); 3.15 (dd, $J = 6.11$, 16.61, 1 H), 3.23 (dd, $J = 6.1$, 16.6, 1 H), 4.72 (m, 1 H), 6.98 (d, $J = 6.10$, 1 H), 7.07 (s, 1 H) and 7.09 (d, $J = 6.15$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 41.3, 43.0, 72.8, 122.26, 126.8, 127.5, 134.4, 139.6 and 140.5.

4-n-*Butylindan*-2-*ol* **4b**.—Yield 84 mg; MS (EI) *m*/*z* 190; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.33$, 3 H), 1.36 (sex, $J = 7.82$, 2 H), 1.55 (m, 2 H), 1.72 (s br, 1 H), 2.57 (t, $J = 7.56$, 2 H), 2.87 (dd, $J = 3.18$, 8.8, 1 H), 2.92 (dd, $J = 3.2$, 8.8, 1 H), 3.16 (dd, $J = 5.86$, 17.1, 1 H), 3.22 (dd, $J = 16.4$, 6.11, 1 H), 4.70 (m, 1 H), 7.00 (d, $J = 7.8$ Hz, 1 H) and 7.06–7.15 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 22.4, 32.1, 33.0, 40.8, 42.7, 72.7, 122.1, 126.4, 126.6, 138.9, 139.0 and 140.4. 5-n-*Butylindan*-2-*ol* **5b**: yield 105 mg; MS (EI) *m*/*z* 190; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.4$, 3 H), 1.36 (sex, $J = 7.4$, 2 H), 1.57 (m, 2 H), 1.66 (s br, 1 H), 2.57 (t, $J = 7.57$, 2 H), 2.84 (dd, $J = 3.18$, 2.93, 1 H), 2.89 (dd, $J = 3.18$, 2.93, 1 H), 3.15 (dd, $J = 2.2$, $J = 5.86$, 1 H), 3.21 (dd, $J = 2.2$, 5.85, 1 H), 4.69 (m, 1 H), 6.99 (d, $J = 7.81$, 1 H), 7.06 (s, 1 H) and 7.13 (d, $J = 7.56$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 21.9, 33.5, 35.1, 41.9, 42.2, 73.0, 124.3, 124.6, 126.5, 137.5, 140.4 and 141.1.

4-*tert*-*Butylindan*-2-*ol* **4c**.—Yield 38 mg; MS (EI) *m*/*z* 190; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9 H), 1.65 (s br, 1 H), 2.88 (dd, $J = 3.35$, 16.18, 1 H), 3.18 (m, 2 H), 3.36 (dd, $J = 5.65$, 16.03, 1 H), 4.65 (m, 1 H), 7.12 (d, $J = 7.0$, 1 H), 7.15 (t, $J = 7.0$, 1 H) and 7.22 (dd, $J = 2.29$, 6.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.4, 35.4, 42.2, 44.4, 72.9, 122.9, 123.8, 126.8, 137.9, 141.8 and 147.3. 5-tert-*Butylindan*-2-*ol* **5c**: yield 146 mg; MS (EI) *m*/*z* 190; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9 H), 1.59 (s br, 1 H), 2.89 (ddd, $J = 3.2$, 8.24, 16.17, 2 H), 3.20 (m, 2 H), 4.71 (m, 1 H), 7.17 (d, $J = 8.0$, 1 H), 7.23 (dd, $J = 1.8$, 7.94 Hz, 1 H) and 7.28 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 34.3, 42.1, 42.6, 73.3, 121.7, 123.6, 124.2, 137.5, 140.3 and 149.7.

Received, 19th May 1998; Accepted, 2nd June 1998
Paper E/8/03785J

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