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A Succinct Route to the Synthesis of Multi-Labelled [D, ^{13}C] α-Methyl Aromatic Ketones

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A series of multi-labelled aromatic ketones were efficiently synthesized using a simple deprotonation–deuteriation/alkylation strategy. The yields were high and the pro ducts are synthetically useful.

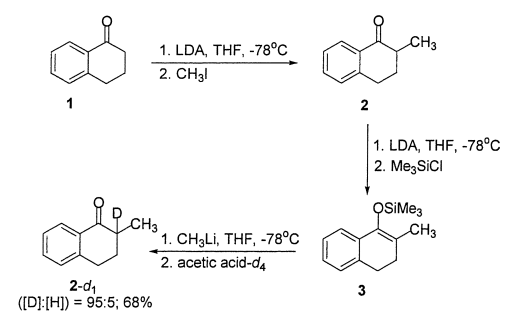
The development of novel synthetic methods and the extension of existing methodology for the incorporation of non-radioactive isotopic labels within organic molecules is an important area.[1] In many cases, the incorporation of a [D] or [^{13}C] isotopic label has relied on simple carbon-hydrogen bond exchange reactions.[2] This exchange occurs readily at relatively acidic positions,[3] most notably those adjacent to a carbonyl group.[4] Many of these reactions are under thermodynamic control[5] to enhance the incorporation.[6] However, there are problems associated with this approach, such as product separation primarily due to incomplete substitution or in some cases over-incorporation.[7] Whereas, isotopic incorporation under kinetic control[8] could potentially solve many of these associated problems. We have recently reported an efficient and reliable method for the regioselective *C*-deuteriation of enolates under "base-free" conditions (Scheme 1).[9] Treatment of the silyl enol ether, e.g., (**3**) [derived from the 2-methyltetralone (**2**) in 76% yield] with MeLi, followed by the addition of a suitable carbonyl directing deuterium donor like acetic acid-d_4, gave the isotopically labelled 2-deuterio-2-methyltetralone (**2**-d_1) with near complete *D*-incorporation ([D]:[H] = 95:5; 68%). This deuteriation step must proceed via a "base-free" enolate and does relies on the efficient synthesis of the silyl enol ether **3** as the enolate precursor, otherwise the levels of D-incorporation is significantly lower due to proton return when using traditional "base" enolates.[9]

We originally chose this aromatic ketone framework due to its UV activity, non-volatile nature and predictable enolate configuration. This predictability is important, in that it allows further incorporation to occur on the same α-carbon atom. We now report an extension of this methodology in the synthesis of multi-labelled aromatic ketones containing combinations of both [D] and [^{13}C] labels.

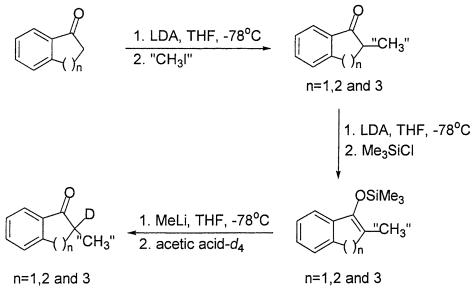
We chose to synthesise these multi-labelled ([D] and [^{13}C]) variants using related α-methyl aromatic ketone based skeletons involving different isotopically labelled methyl groups (e.g., CD_3, $^{13}CH_3$ and $^{13}CD_3$) (Scheme 2). We assumed that incorporation of these different methyl substituents could be efficiently achieved using the appropriate commercially available isotopically labelled methyl iodide, CD_3I, $^{13}CH_3I$ and $^{13}CD_3I$. This strategy allows simple and selective incorporation to occur through kinetic control, which we believed, would minimize over-incorporation. We were initially required to synthesise a series of 2-trideuteriomethyl (CD_3), 2-trideuteriomethyl-[^{13}C] ($^{13}CD_3$) and methyl-[^{13}C] ($^{13}CH_3$) isotopically labelled methyl aromatic ketones (**5a,b**), (**8a–c**) and (**12a,b**). This method is ideal since quantitative incorporation must occur through simple carbon-carbon bond formation. The required aryl aromatic (**5a,b**), (**8a–c**) and (**12a,b**) were synthesized in excellent yield by methylation of the enolate [derived from indanone (**4**), tetralone (**1**), benzosuberone (**11**) and LDA] with the corresponding labelled methyl iodide (CD_3I, $^{13}CH_3I$ and $^{13}CD_3I$). These ketones were efficiently converted into the related silyl enol ethers **6**, **9** and **13** by addition of LDA in THF at −78 °C, followed by the addition of neat Me_3SiCl.

Deuteriation of these silyl enol ethers (**6**), (**9**) and (**13**) were achieved using our standard procedure,[9] by initially converting these into their corresponding "base-free" enolate, by the direct addition of MeLi using Stork's protocol.[10] Simple addition of acetic acid-d_4 (2 molar amounts) to a stirred solution of each enolate at −78 °C gave the multi-labelled aromatic ketones (**7a,b**), (**10a–c**) and (**14a,b**) in excellent yield (Table 1) with near complete *D*-incorporation (determined by ^{1}H NMR).

In conclusion, we have report an efficient route to the selective isotopic exchange of both C–H bonds adjacent to a carbonyl motif. For those cases, which involved the substituent combination [CD_3, D] and [$^{13}CD_3$, D] resulted in the removal of their associated signal in the ^{1}H NMR with respect to the

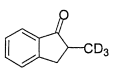
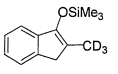
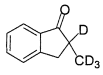
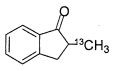
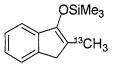
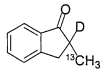
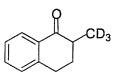
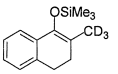
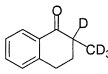
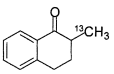
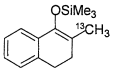
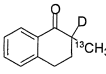
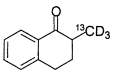
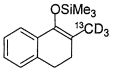
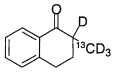
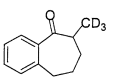
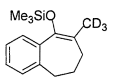
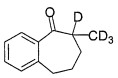
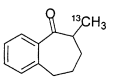
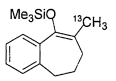
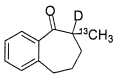


Scheme 1. Synthesis of 2-methyltetralone **2**-d_1.



Scheme 2.

Table 1. The synthesis of multi-labelled ketones **7a**,**b**, **10a–c**, and **14a**,**b**.

Entry	Starting material	Methyl ketone	Silyl enol ether	Labelled ketone
1	 **4**	 **5a**; 56%	 **6a**; 78%	 **7a**; ([D]:[H]) = 83:17; 71%
2	 **4**	 **5b**; 57%	 **6b**; 72%	 **7b**; ([D]:[H]) = 85:15; 72%
3	 **1**	 **8a**; 58%	 **9a**; 78%	 **10a**; ([D]:[H]) = 95:5; 61%
4	 **1**	 **8b**; 48%	 **9b**; 89%	 **10b**; ([D]:[H]) = 98:2; 72%
5	 **1**	 **8c**; 57%	 **9c**; 88%	 **10c**; ([D]:[H]) = 79:21; 82%
6	 **11**	 **12a**; 56%	 **13a**; 76%	 **14a**; ([D]:[H]) = 95:5; 73%
7	 **11**	 **12b**; 61%	 **13b**; 81%	 **14b**; ([D]:[H]) = 95:5;77%

non-isotopic variant. Whereas, those involving a combination of [$^{13}CH_3$, D] gave a characteristic double (J = 127.4 Hz) for the methyl group in the ^{1}H NMR spectrum. The synthesis of related multi-labelled 2,2-[D, ^{13}C] ketones using a deprotonation strategy under thermodynamic control has previously been reported.[11,12] Virtually, all these reports deal with the synthesis of fully deuteriated carbonyl derivatives,[11] whereas reports into the synthesis of selective 2,2-[D, ^{13}C] labelled ketones are much rarer.[12] However, there are some reports into the synthesis of related ketones using a different carbon-carbon bond forming strategy.[13]

Typical procedure: A solution of MeLi (0.1 mL, 1.6 M in diethyl ether, 0.16 mmol) was added drop-wise to the silyl enol ether (**9a**) (40 mg, 0.15 mmol), at room temperature. This resulting solution was stirred for 1 hour at room temperature and then cooled at −78 °C. Acetic acid-d_4 (10 mg, 10 µL, 0.3 mmol) in THF (1 mL) was added drop-wise to this solution and stirred for a further 30 minutes. The reaction was quenched by the addition of water (10 mL). The solution was extracted with ether (3 × 20 mL), dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum (40–60 °C):ether (9:1) to give 2-deuterio-2-trideuteriomethyltetralone (**10a**-d_4) (20 mg, 61%) as an oil; R_f [light petroleum (40–60 °C):ether (9:1)] 0.5; ν_{max}(film)/cm^{-1} 2059 (CD) and 1680 (CO); δ_H (600 MHz, $CDCl_3$) 8.04 (1 H, dd, J = 7.7 and 1.5 Hz, CH; Ar), 7.45 (1 H, td, J = 7.7 and 1.5 Hz, CH; Ar), 7.31 (1 H, t, J = 7.7 Hz, CH; Ar), 7.23 (1 H, d, J = 7.7 Hz, CH; Ar), 3.02 (2 H, m, CH_2), 2.19 (1H, dt, J = 8.8 and 4.4 Hz, CH_ACH_B) and 1.88 (1H, m, CH_ACH_B); δ_c (150 MHz, $CDCl_3$) 200.8, 144.1, 133.0, 132.3, 128.6, 127.3, 126.8, 41.8 ($J_{C\text{-}D}$ = 19.5 Hz), 31.8 and 28.7; *m*/*z* 164 (100%, M). The absence of the septet at around 17 ppm for CD_3 signal in the ^{13}C NMR spectra is common due to a long relaxation time associated with this substituent.

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