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Research Article

The synthesis and characterisation of multi-labelled [D, ^{13}C] 2-deuterio-2-methyl aromatic ketones

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Summary

A series of multi-labelled aromatic ketones were efficiently synthesized using a deprotonation–deuteriation/alkylation strategy. The yields were high and the products are synthetically useful. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: chelating deuterium donor; deprotonation–deuteriation strategy; kinetic deuteriation; ketones; lithium amide bases and isotopic labels

Introduction

The development of new synthetic methods and the extension of existing methodology for the incorporation of non-radioactive isotopic labels is becoming an increasingly important area.[1] In many cases, the incorporation of a deuterium atom or a carbon-13 containing substituent has relied on simple carbon-hydrogen bond exchange reactions.[2] These exchange processes have been shown to occur readily

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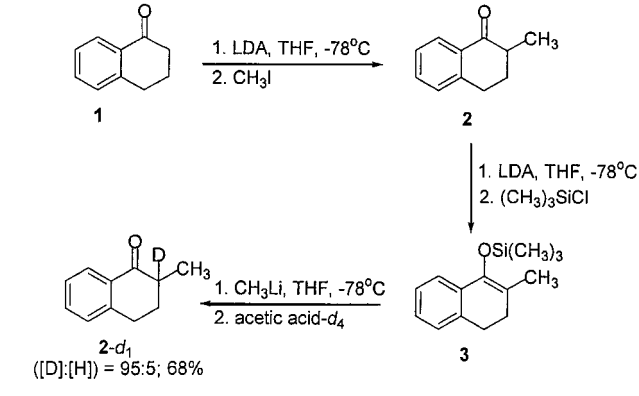
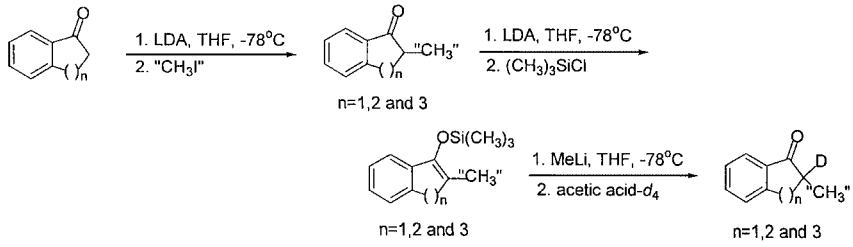
at relatively acidic positions,[3] most notably those adjacent to a carbonyl group.[4] Many of these transformations are generally performed under thermodynamic control[5] to improve the level of isotopic incorporation.[6] However, there are problems associated with this approach, such as product separation due to incomplete substitution or in some cases over-incorporation,[7] whereas, isotopic incorporation under kinetic control[8] has the potential to solve many of these non-selective incorporations. 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 deuterium donor, such as 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* the complementary 'base-free' enolate since the level of *D*-incorporation was found to be significantly lower due to *initial proton return*[10] when using traditional 'base' enolates.[9]

We originally chose this aromatic ketone framework due to its UV activity, non-volatile nature and predictable enolate chemistry.[9] This predictability is particularly 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 2-deuterio-2-methyl-aromatic ketones containing combinations of deuterium and carbon-13 isotopic labelled substituents.

We chose to synthesise these multi-labelled [D, ^{13}C] ketones using isotopically labelled 2-methyl ketones **5a-b**, **8a-c** and **12a-b** which



Scheme 1. Synthesis of 2-methyltetralone 2-d1.



Scheme 2.

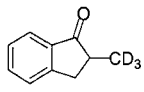
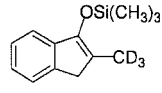
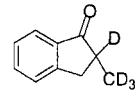
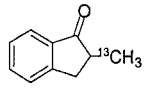
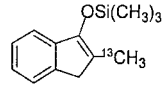
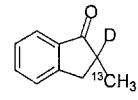
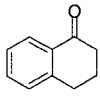
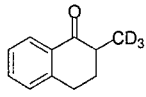
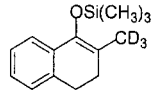
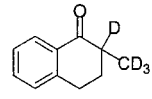
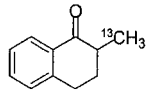
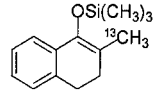
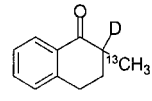
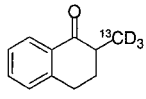
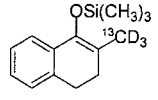
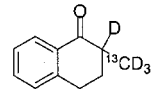
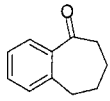
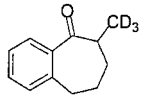
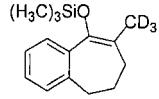
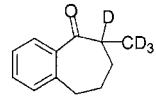
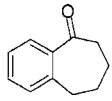
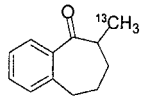
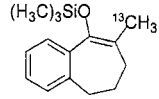
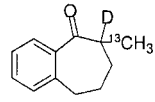
contain an isotopically labelled methyl group (e.g. CD_3, $^{13}CH_3$ and $^{13}CD_3$) (Scheme 2 and Table 1). We assumed that incorporation of these different methyl labelled substituents could be efficiently achieved by deprotonation of the parent ketone, tetralone **1**, indanone **4** and benzosuberone **11** (using LDA) and methylation of the corresponding enolate with appropriately labelled methyl iodide; CD_3I, $^{13}CH_3I$ and $^{13}CD_3I$. This strategy is ideal since quantitative incorporation must occur through carbon-carbon bond formation. The required 2-methyl aromatic ketones **5a-b**, **8a-c** and **12a-b** were synthesized in good yield by methylation of the enolate [derived from indanone **4**, tetralone **1**, benzosuberone **11** and LDA] with the corresponding isotopically labelled methyl iodide (CD_3I, $^{13}CH_3I$ and $^{13}CD_3I$). These ketones were efficiently converted into the corresponding silyl enol ethers **6a-b**, **9a-c** and **13a-b** by the sequential addition of LDA and Me_3SiCl.

Deuteriation of these silyl enol ethers **6a-b**, **9a-c** and **13a-b** were achieved using our standard procedure,[9] by initially converting them into their corresponding 'base-free' enolates, by the direct addition of MeLi using Stork's methodology.[11] Simple addition of acetic acid-d_4 (**2** equivalents) to a stirred solution of each enolate in THF at –78°C gave the multi-labelled aromatic ketones **7a-b**, **10a-c** and **14a-b** in excellent yields (Table 1) with near complete *D*-incorporation (determined by ^1H NMR).[†]

In conclusion, we report an efficient route to the selective isotopic exchange of C-H bonds adjacent to a carbonyl motif. For those cases, which involved the substituent combination [D, CD_3] and [D, $^{13}CD_3$] this resulted in the removal of their associated signals in the ^1H NMR spectra relative to the non-isotopic variant. Those involving a

[†] Determined by integration of the ^1H NMR spectrum of the corresponding methyl doublet versus the methyl singlet (for the $^{13}CH_3$ labelled derivatives) and by the disappearance of the adjacent C(2) proton.

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

Entry	Ketone	1. LDA / 2. "CH_3"I	Methyl ketone	1. LDA / 2. $(CH_3)_3SiCl$	Silyl enol ether	1. CH_3Li / 2. CD_3CO_2D	Labelled ketone
1							
	4		**5a**; 67%		**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%

combination of [D, $^{13}CH_3$] gave a characteristic doublet ($^1J_{C,H} = 127.4$ Hz) for the methyl group in the ^{1}H NMR spectra. The synthesis of related multi-labelled 2,2-[D, ^{13}C] ketones using a deprotonation strategy under thermodynamic control has previously been reported.[‡,12,13] Virtually all these reports deal with the synthesis of fully deuteriated carbonyl derivatives,[12] whereas reports into the

[‡] For methods involving 2,2-[D, CD_3] incorporation, see ref. 12.

synthesis of selective 2,2-[D, ^{13}C] labelled ketones are much rarer.[§,13] However, there are some reports into the synthesis of related ketones using a different carbon-carbon bond forming strategy.[¶, ‖,14]

Experimental

All solvents were distilled before use. Tetrahydrofuran (THF) and ether were freshly distilled from $LiAlH_4$. Triphenylmethane was used as the indicator for THF. All reactions were carried out under nitrogen using oven-dried glassware. Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$ silica). Proton and carbon NMR spectra were recorded on a JEOL EX 270 and Bruker AM 250, AMX 400 and AM 600 Fourier transform spectrometer (using an internal deuterium lock). Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Infrared spectra were recorded on a Shimadzu 8300 FTIR instrument and mass spectra were recorded on a Kratos 50MSTC instrument using a DS503 data system for high-resolution analysis.

2-Trideuteriomethylindanone **5a**-d_3

Indanone **4** (0.24 g, 1.5 mmol) was slowly added dropwise to a stirred solution of LDA (2.0 ml, 1.5 M in THF, 3.0 mmol) in THF (20 ml) at –78°C and stirred for a further 20 min. Methyl iodide-d_3 (0.43 g, 0.2 ml, 3.0 mmol) was added and the resulting solution was stirred for 12 h. A solution of NH_4Cl (saturated, 10 ml) was then added and the mixture was extracted with ether (3 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum (b.p. 40–60°C)-ether (19:1) to give *2-trideuteriomethylindanone* **5a**-d_3 (0.33 g, 67%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.2; ν_{max} (film)/cm^{-1} 2136 (CD) and 1735 (CO); δ_H

[§] For related methods involving 2,2-[D, ^{13}CD] incorporation, see ref. 13.
[¶] For methods involving 2,2-[D, ^{13}C] incorporation, see ref. 14.
[‖] For related methods involving 2,2-[D, ^{13}CD] incorporation, see ref. 15.

(270 MHz, $CDCl_3$) 7.75 (1 H, d, $^3J_{H,H} = 7.5$, CH; Ar), 7.58 (1 H, t, $^3J_{H,H} = 7.5$, CH; Ar), 7.44 (1 H, d, $^3J_{H,H} = 7.5$, CH; Ar), 7.36 (1 H, t, $^3J_{H,H} = 7.5$, CH; Ar), 3.39 (1 H, dd, $^3J_{H,H} = 17.9$ and 8.7, CH_AH_B) and 2.70 (2 H, m, CH_AH_B and $CHCD_3$); δ_C (67.5 MHz, $CDCl_3$) 210.4, 154.2, 137.0, 135.3, 128.1, 127.2, 124.7, 42.5, 35.6 and 15.5 (1 C, triplet [6:7:6], $^1J_{C,D} = 9.8$, CD_3) (Found M^+, 149.0912. $C_{10}H_7D_3$ requires M, 149.0920). The intensity of the CD_3 signal in the ^{13}C NMR spectrum was particularly weak due to the long T_1 relaxation time associated with this substituent.[16]

2-Methyl-[^{13}C]-indanone **5b**

In the same way as 2-methylindanone **5a**, indanone **4** (0.49 g, 3.75 mmol), LDA (2.5 ml, 1.5 M in THF, 3.75 mmol) and methyl-[^{13}C]-iodide (0.53 g, 0.2 ml, 3.75 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), *2-methyl-[^{13}C]-indanone* **5b** (0.31 g, 57%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.2; ν_{max} (film)/cm^{-1} 1731 (CO); δ_H (270 MHz, $CDCl_3$) 7.76 (1 H, d, $^3J_{H,H} = 7.5$, CH; Ar), 7.62 (1 H, t, $^3J_{H,H} = 7.5$, CH; Ar), 7.46 (1 H, d, $^3J_{H,H} = 7.5$, CH, Ar), 7.35 (1 H, t, $^3J_{H,H} = 7.5$, CH; Ar), 3.40 (1 H, dd, $^3J_{H,H} = 17.7$ and 8.7; CH_AH_B), 2.79-2.63 (2 H, m, CH_AH_B and $CH^{13}CH_3$) and 1.32 (3 H, dd, $^1J_{C,H} = 128.2$ and $^3J_{H,H} = 7.3$, $^{13}CH_3$); δ_C (67.5 MHz, $CDCl_3$) 209.6, 153.5, 134.7, 134.6, 127.3, 126.6, 124.0, 41.9 (1 C, doublet [1:1], $^1J_{C,C} = 31.2$, $C^{13}CH_3$), 32.6 and 16.7 ($^{13}CH_3$) (Found M^+, 147.0760. $C_9{}^{13}CH_{10}O$ requires M, 147.0765).

2-Trimethylsilyoxy-2-trideuteriomethylindan-1-ene **6**-d_3

2-Trideuteriomethylindanone **5a** (0.3 g, 2.02 mmol) was slowly added dropwise to a stirred solution of LDA (2.0 ml, 1.5 M in THF, 2.02 mmol) in THF (10 ml) at –78°C and stirred for 20 min. Me_3SiCl (0.24 g, 0.28 ml, 2.22 mmol) was added and this solution was stirred for 3 hours. A solution of NH_4Cl (10 ml) was added and the mixture was extracted with ether (3 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum (b.p. 40–60°C)-ether (19:1) to give the *1-trimethylsiloxy-2-trideuteriomethylindan-1-ene* **6a**-d_3 (0.27 g, 78%) as a colourless oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.75; ν_{max} (film)/cm^{-1} 2125 (CD) and 1634 (C=C); δ_H (270 MHz, $CDCl_3$) 7.32-7.09 (4 H, m, 4 × CH;

Ar), 3.18 (2 H, s, CH_2) and 0.26 (9 H, s, Me_3Si); δ_C (67.5 MHz, $CDCl_3$) 142.8, 140.9, 128.3, 125.9, 124.0, 123.1, 119.9, 117.2, 38.4 and 0.73 (Found MH^+, 221.1232. $C_{13}H_{15}D_3OSi$ requires M, 221.1237). The absence of the septet [1:3:6:7:6:3:1] around 15 ppm for the CD_3 substituent in the ^{13}C NMR spectrum is common due to the long T_1 relaxation time associated with this substituent.[16]

1-Trimethylsilyoxy-2-methyl-[^{13}C]-indan-1-ene **6b**

In the same way as silyl enol ether **5a**, 2-methyl-[^{13}C]-indanone **5b** (0.10 g, 0.68 mmol), LDA (0.5 ml, 1.5 M in THF, 0.68 mmol) and Me_3SiCl (80 mg, 93 µl, 0.74 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), the *1-trimethylsilyoxy-2-methyl-[^{13}C]-indan-1-ene* **6b** (0.11 g, 72%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.75; ν_{max} (film)/cm^{-1} 1625 (C = C); δ_H(270 MHz, $CDCl_3$) 7.32-7.01 (4 H, m, 4 × CH; Ar), 3.18 (2 H, s, CH_2), 1.97 (3 H, d, $^1J_{C,H} = 126.1$, $^{13}CH_3$) and 0.26 (9 H, s, Me_3Si); δ_C(67.5 MHz, $CDCl_3$) 142.4, 140.9, 126.2, 124.0, 123.8, 117.3, 38.4, 12.4 ($^{13}CH_3$) and 0.77 (Found M^+, 219.1152. $C_{12}^{13}CH_{18}OSi$ requires M, 219.1160).

2-Deuterio-2-trideuteriomethylindanone **7a**-d_4

A solution of MeLi (0.3 ml, 1.6 M in ether, 0.45 mmol) was added dropwise to the silyl enol ether **6a** (0.10 g, 0.45 mmol) at room temperature. This resulting solution was stirred for 1 hour at room temperature and then cooled to –78°C. Acetic acid-d_4 (57 mg, 51 µl, 0.90 mmol) in THF (1 ml) was added dropwise to this solution and the resulting solution 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 the *2-deuterio-2-trideuteriomethylindanone* **7a**-d_4 (48 mg, 71%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.2; ν_{max} (film)/cm^{-1} 2072 (CD) and 1715 (CO); δ_H (270 MHz, $CDCl_3$) 7.76 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.58 (1 H, t, $^3J_{H,H} = 7.6$, CH; Ar), 7.44 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.36 (1 H, t, $^3J_{H,H} = 7.6$, CH; Ar), 3.40 (1 H, AB quartet, $^3J_{H,H} = 17.2$, CH_AH_B) and 2.85 (1 H, AB quartet, $^3J_{H,H} = 17.2$, CH_AH_B); δ_C (67.5 MHz, $CDCl_3$) 209.5, 153.5, 136.4, 134.6, 127.3, 126.5, 123.9,

41.5 (1 H, triplet [1:1:1:], $^{1}J_{C,D} = 19.7$, *C*DCH$_3$) and 34.2 (Found M$^+$, 150.0789. $C_{10}H_6D_4O$ requires M, 150.0793). The negative isotopic shift was 0.42 ppm (42.6 Hz at 100.6 MHz).

2-Deuterio-2-methyl-[^{13}C]-indanone **7b**-d_1

In the same way as 2-trideuteriomethylindanone **7a**-d_4, silyl enol ether **6b** (0.10 g, 0.54 mmol), MeLi (0.34 ml, 1.6 M in ether, 0.54 mmol) and acetic acid-d_4 (69 mg, 61 µl, 1.08 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), *2-deuterio-2-methyl-[^{13}C]-indanone* **7b**-d_1 (58 mg, 72%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.2; ν_{max} (film)/cm^{-1} 2072 (CD) and 1715 (CO); δ_H (270 MHz, $CDCl_3$) 7.76 (1 H, d, $^{3}J_{H,H} = 7.5$, CH; Ar), 7.62 (1 H, t, $^{3}J_{H,H} = 7.5$, CH; Ar), 7.46 (1 H, d, $^{3}J_{H,H} = 7.5$, CH; Ar), 7.39 (1 H, t, $^{3}J_{H,H} = 7.5$, CH; Ar), 3.45 (1 H, AB quartet, $^{3}J_{H,H} = 17.0$, C*H*$_A$H$_B$), 2.85 (1 H, AB quartet, $^{3}J_{H,H} = 17.0$, CH$_A$*H*$_B$) and 1.33 (3 H, d, $^{1}J_{C,H} = 128.1$, ^{13}CH$_3$); δ_C (67.5 MHz, $CDCl_3$) 209.4, 154.0, 137.2, 135.2, 128.4, 127.1, 124.8 and 41.7 (1 C, m, *C*DCO) (Found MH$^+$, 149.0914. $C_9{}^{13}CH_{10}DO$ requires M, 149.0906). The negative isotopic shift could not be determined due to the multiplicity of the ^{13}C NMR signal at 41.7 ppm.

2-Trideuteriomethyltetralone **8a**-d_3

In the same way as 2-methylindanone **5a**, tetralone **1** (0.99 g, 6.8 mmol), LDA (4.5 ml, 1.5 M in THF, 6.8 mmol) and methyl iodide–d_3 (0.98 g, 0.42 µl. 6.8 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (19:1), the *2-trideuteriomethyltetralone* **8a**-d_3 (0.64 g, 58%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.5; ν_{max} (film)/cm^{-1} 2061 (CD) and 1681 (CO); δ_H (250 MHz, $CDCl_3$) 8.05 (1 H, d, $^{3}J_{H,H} = 7.7$, CH; Ar), 7.45 (1 H, t, $^{3}J_{H,H} = 7.7$, CH; Ar), 7.31 (1 H, d, $^{3}J_{H,H} = 7.7$, CH; Ar), 7.22 (1 H, d, $^{3}J_{H,H} = 7.7$, CH; Ar), 3.10-2.93 (2 H, m, CH$_2$), 2.62-2.54 (1 H, dd, $^{3}J_{H,H} = 11.9$ and 4.4, CD$_3$CH), 2.25-2.15 (1 H, m, C*H*$_A$CH$_B$) and 1.96-1.80 (1 H, m, CH$_A$C*H*$_B$); δ_C (100.6 MHz, $CDCl_3$) 200.7, 144.2, 133.0, 132.4, 128.7, 127.4, 126.5, 42.4, 31.3 and 28.8 (Found M$^+$, 163.1083. $C_{11}H_9D_3O$ requires M, 163.1076); *m/z* 164 (100%, M + H) and 163 (60, M). The absence of the septet [1:3:6:7:6:3:1] around 15 ppm for the CD$_3$ substituent in the ^{13}C NMR spectrum is common due to the long T_1 relaxation time associated with this substituent.[16]

2-Methyl-[^{13}C]-tetralone **8b**

In the same way as 2-methylindanone **5a**, tetralone **1** (0.9 g, 6.2 mmol), LDA (4.1 ml, 1.5 M in THF, 6.2 mmol) and methyl-[^{13}C]-iodide (0.88 g, 0.38 ml, 6.2 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (19:1), *2-methyl-[^{13}C]-tetralone* **8b** (0.48 g, 48%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.5; ν_{max} (film)/cm^{-1} 1682 (CO); δ_H (250 MHz, $CDCl_3$) 8.05 (1 H, d, $^3J_{H,H} = 7.7$ CH; Ar), 7.46 (1 H, t, $^3J_{H,H} = 7.7$, CH; Ar), 7.21 (1 H, d, $^3J_{H,H} = 7.7$, CH; Ar), 7.23 (1 H, d, $^3J_{H,H} = 7.7$, CH; Ar), 3.12-2.93 (2 H, m, CH_2), 2.69-2.51 (1 H, m, $^{13}CH_3CH$), 2.26-2.14 (1 H, m, CH_ACH_B), 1.97-1.80 (1 H, m, CH_ACH_B) and 1.30 (3 H, dd, $^1J_{C,H} = 127.4$ and $^3J_{H,H} = 6.8$, $^{13}CH_3$); δ_C (62.5 MHz, $CDCl_3$) 202.9, 133.3, 131.8, 128.6, 127.9, 126.2, 125.2, 42.0 (1 C, triplet [1:1:1], $^1J_{C,C} = 36.2$, $C^{13}CH_3$), 31.2, 28.7 and 16.5 ($^{13}CH_3$) (Found M^+, 161.0913. $C_{10}^{13}CH_{12}O$ requires M, 161.0922).

2-Trideuteriomethyl-[^{13}C]-tetralone **8c**-d_3

In the same way as 2-methylindanone **5a**, tetralone **1** (1.4 g, 9.8 mmol), LDA (6.5 ml, 1.5 M in THF, 9.8 mmol) and methyl-[^{13}C]-iodide–d_3 (1.43 g, 0.61 ml, 9.8 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (19:1), *2-trideuteriomethyl-[^{13}C]-tetralone* **8c**-d_3 (0.91 g, 57%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.5; ν_{max} (film)/cm^{-1} 2065 (CD) and 1685 (CO); δ_H (250 MHz, $CDCl_3$) 8.05 (1 H, d, $^3J_{H,H} = 7.7$, CH; Ar), 7.45 (1 H, t, $^3J_{H,H} = 7.7$, CH; Ar), 7.32 (1 H, d, $^3J_{H,H} = 7.7$, CH; Ar), 7.24 (1 H, d, $^3J_{H,H} = 7.7$, CH; Ar), 3.12-2.93 (2 H, m, CH_2), 2.62-2.58 (1 H, m, $^{13}CD_3CH$), 2.26-2.14 (1 H, m, CH_ACH_B) and 1.89 (1 H, m, CH_ACH_B); δ_C (67.5 MHz, $CDCl_3$) 200.7, 144.2, 133.1, 132.7, 128.7, 127.4, 126.6, 42.4 (1 C, doublet [1:1], $^1J_{C,C} = 36.1$, $C^{13}CH_3$), 31.3, 28.8 and 14.6 (1 C, septet [1:3:6:7:6:3:1], $^1J_{C,D} = 19.4$, CD_3) (Found MH^+, 165.1212. $C_{10}^{13}CH_{10}D_3O$ requires M, 165.1217).

2-Trimethylsilyoxy-2-trideuteriomethyl-tetra-1-ene **9a**

In the same way as the silyl enol ether **6a**, 2-trideuteriomethyl-[^{13}C]-tetralone **8a** (0.81 g, 5.5 mmol), LDA (4.75 ml, 1.5 M in THF, 11.0 mmol) and Me_3SiCl (1.31 g, 1.53 ml, 12.1 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether

(19:1), the *1-trimethylsilyoxy-2-trideuteriomethyl-tetra-1-ene* **9a** (0.77 g, 78%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.9; ν_{max} (film)/cm^{-1} 2090 (CD) and 1590 (C=C); δ_H (250 MHz, $CDCl_3$) 7.33-7.07 (4 H, m, 4 × CH; Ar), 2.74 (2 H, t, $^3J_{H,H}$ = 8.4, CH_2), 2.26 (2 H, t, $^3J_{H,H}$ = 8.4, CH_2) and 0.20 (9 H, s, Me_3Si); δ_C (62.5 MHz, $CDCl_3$) 144.5, 135.9, 134.4, 128.8, 126.1, 125.5, 121.5, 116.8, 29.1, 28.3 and 0.62 (Found M^+, 235.1480. $C_{14}H_{17}D_3OSi$ requires M, 235.1472). The absence of the septet [1:3:6:7:6:3:1] around 15 ppm for the CD_3 substituent in ^{13}C NMR spectrum is common due to the long T_1 relaxation time associated with this substituent.[16]

2-Trimethylsilyoxy-2-methyl-[^{13}C]-tetra-1-ene **9b**

In the same way as silyl enol ether **6a**, 2-methyl-[^{13}C]-tetralone **8b** (0.21 g, 1.2 mmol), LDA (0.6 ml, 2 M in THF, 1.2 mmol) and Me_3SiCl (0.14 g, 0.16 ml, 1.32 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (19:1), the *1-trimethylsilyoxy-2-methyl-[^{13}C]-tetra-1-ene* **9b** (0.26 g, 89%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.9; ν_{max} (film)/cm^{-1} 1588 (C=C); δ_H (250 MHz, $CDCl_3$) 7.34-7.17 (4 H, m, 4 × CH; Ar), 3.30-2.80 (2 H, m, CH_2), 2.35-2.00 (2 H, m, CH_2), 1.44 (3 H, d, $^1J_{C,H}$ = 127.6, $^{13}CH_3$) and 0.8 (9 H, s, Me_3Si); δ_C (62.5 MHz, $CDCl_3$) 143.3, 133.0, 132.9, 128.7, 127.3, 126.3, 122.1, 117.5, 28.7, 27.4 ($^{13}CH_3$), 23.6 and 1.3 (Found M^+, 233.1381. $C^{13}_{13}CH_{20}SiO$ requires M, 233.1386).

1-Trimethylsilyoxy-2-trideuteriomethyl-[^{13}C]-tetra-1-ene **9c**-d_3

In the same way as the silyl enol ether **6a**, 2-trideuteriomethyl-[^{13}C]-tetralone **8c** (0.4 g, 2.43 mmol), LDA (1.6 ml, 1.5 M in THF, 2.43 mmol) and Me_3SiCl (0.29 g, 0.33 ml, 2.63 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (19:1), the *1-trimethylsilyoxy-2-trideuteriomethyl-[^{13}C]-tetra-1-ene* **9c**-d_3 (0.51 g, 88%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.9; ν_{max} (film)/cm^{-1} 2065 (CD) and 1599 (C=C); δ_H (270 MHz, $CDCl_3$) 7.50-7.25 (4 H, m, 4 × CH; Ar), 3.34-3.01 (2 H, m, CH_2), 2.46 (2 H, m, CH_2), 2.46-2.13 (2 H, m, CH_2) and 0.20 (9 H, s, Me_3Si); δ_C (67.5 MHz, $CDCl_3$) 143.5, 133.2, 131.3, 128.5, 128.0, 126.4, 122.1, 117.5, 29.4, 26.3, 23.4 (1 C, septet [1:3:6:7:6:3:1], $^1J_{C,D}$ = 19.6, CD_3) and 2.2 (Found MH^+, 237.1576. $C^{13}_{13}CH_{18}D_3OSi$ requires M, 237.1584).

2-Deuterio-2-trideuteriomethyltetralone **10a**-d_4

In the same way as 2-trideuteriomethylindanone **7a**-d_4, silyl enol ether **9a** (35 mg, 0.15 mmol), MeLi (93 µl, 1.6 M in ether, 0.15 mmol) and acetic acid–d_4 (19 mg, 17 µl, 0.3 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (19:1), *2-deuterio-2-trideuteriomethyltetralone* **10a**-d_4 (15 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 (250 MHz, $CDCl_3$) 8.04 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.45 (1 H, t, $^3J_{H,H} = 7.6$, CH; Ar), 7.31 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.23 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 3.02-2.96 (2 H, m, CH_2), 2.22-2.18 (1 H, m, CH_ACH_B) and 1.92-1.87 (1 H, m, CH_ACH_B); δ_C (67.5 MHz, $CDCl_3$) 201.6, 144.9, 133.7, 133.1, 129.4, 128.5, 127.2, 42.6 (1 C, triplet [1:1:1], $^1J_{C,D} = 19.5$, *C*DCO), 32.1 and 30.4 (Found MH$^+$, 165.1212. $C_{11}H_9D_4O$ requires M, 165.1217). The negative isotopic shift was 0.5 ppm (75.4 Hz at 150.9 MHz).

2-Deuterio-2-methyl-[^{13}C]-tetralone **10b**-d_1

In the same way as 2-trideuteriomethylindanone **7a**-d_4, silyl enol ether **9b** (0.1 g, 0.43 mmol), MeLi (0.27 ml, 1.6 M in diethyl ether, 0.43 mmol) and acetic acid–d_4 (55 mg, 49 µl, 0.86 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (19:1), *2-deuterio-2-methyl-[^{13}C]-tetralone* **10**-d_1 (50 mg, 72%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.5; ν_{max} (film)/cm^{-1} 2103 (CD) and 1618 (CO); δ_H (250 MHz, $CDCl_3$) 8.05 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.47 (1 H, t, $^3J_{H,H} = 7.6$, CH; Ar), 7.32 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.22 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 3.09-2.93 (2 H, m, CH_2), 2.25-2.15 (1 H, m, CH_ACH_B), 1.95-1.81 (1 H, m, CH_ACH_B) and 1.26 (3 H, d, $^1J_{C,H} = 127.4$, $^{13}CH_3$); δ_C (67.5 MHz, $CDCl_3$) 202.9, 143.3, 133.0, 132.9, 128.7, 127.3, 126.5, 41.8 (1 C, m, *C*D^{13}CH$_3$), 31.2, 28.7, and 15.6 ($^{13}CH_3$) (Found MH$^+$, 163.1060. $C_{10}^{13}CH_{12}DO$ requires M, 163.1063). The negative isotopic shift could not be determined due to the multiplicity of the ^{13}C NMR signal at 41.8 ppm.

2-Deuterio-2-trideuteriomethyl-[^{13}C]-tetralone **10c**-d_4

In the same way as 2-trideuteriomethylindanone **7a**-d_4, silyl enol ether **9c** (0.1 g, 0.42 mmol), MeLi (0.3 ml, 1.6 M in diethyl ether, 0.42 mmol) and acetic acid–d_4 (53 mg, 48 µl, 0.84 mmol) gave, after column

chromatography on silica gel eluting with light petroleum ether–ether (19:1), *2-deuterio-2-trideuteriomethyl-[^{13}C]-tetralone* **10c**-d_4 (57 mg, 82%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.5; ν_{max} (film)/cm^{-1} 2069 (CD) and 1685 (CO); δ_H (250 MHz, $CDCl_3$) 8.04 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.45 (1 H, t, $^3J_{H,H} = 7.6$, CH; Ar), 7.31 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.25 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 3.04-2.93 (2 H, m, CH_2), 2.24-2.14 (1 H, m, CH_ACH_B) and 1.94-1.81 (1 H, m, CH_ACH_B); δ_C (100.6 MHz, $CDCl_3$) 200.9, 144.2, 133.0, 132.4, 128.7, 127.4, 126.5, 42.5 (1 C, dt, $^1J_{C,C} = 36.2$ and $^1J_{C,D} = 18.1$), 31.2, 28.7 and 14.4 (1 C, septet [1:3:6:7:6:3:1], $^1J_{C,D} = 11$, $^{13}CD_3$) (Found M^+, 165.1180. $C_{10}^{13}CH_8D_4O$ requires M, 165.1173). The negative isotopic shift could not be determined due to the multiplicity of the ^{13}C NMR signal at 42.5 ppm.

2-Trideuteriomethylbenzosuberone **12a**-d_3

In the same way as 2-trideuteriomethylindanone **5a**, benzosuberone **11** (0.6 g, 3.74 mmol), LDA (2.3 ml, 1.5 M in THF, 3.74 mmol) and methyl iodide-d_3 (0.54 g, 0.23 ml, 0.24 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), the *2-trideuteriomethylbenzosuberone* **12a**-d_3 (0.36 g, 56%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.31; ν_{max} (film)/cm^{-1} 2069 (CD) and 1681 (CO); δ_H (400 MHz, $CDCl_3$) 7.68 (1 H, d, $^3J_{H,H} = 7.7$, CH; Ar), 7.38 (1 H, t, $^3J_{H,H} = 7.7$, CH; Ar), 7.30-7.18 (2 H, m, 2 × CH; Ar), 3.10-2.87 (2 H, m, CH_2), 2.78 (1 H, t, $^3J_{H,H} = 6.6$, CHMe), 2.15-2.02 (1 H, m, CH_AH$_B$), 1.95-1.86 (2 H, m, CH_2) and 1.77-1.56 (3 H, m, CH_2 and CH_ACH_B); δ_C (100.6 MHz, $CDCl_3$) 207.9, 141.8, 139.8, 131.3, 129.7, 128.5, 126.4, 44.0, 33.7, 31.8, and 25.5 (Found MH^+, 178.1303. $C_{12}H_{12}D_3O$ requires MH, 178.1311). The absence of the septet [1:3:6:7:6:3:1] around 15 ppm for the CD_3 substituent in the ^{13}C NMR spectrum is common due to the long T_1 relaxation time associated with this substituent.[16]

2-Methyl-[^{13}C]-benzosuberone **12b**

In the same way as 2-trideuteriomethylindanone **5a**, benzosuberone **11** (0.36 g, 2.25 mmol), LDA (1.5 ml, 1.5 M in THF, 2.25 mmol) and methyl-[^{13}C]-iodide (0.32 g, 0.14 ml, 2.25 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), *2-methyl-[^{13}C]-benzosuberone* **12b** (0.24 g, 61%) as an oil; R_F

[light petroleum (40–60°C): ether (9:1)] 0.31; ν_{max} (film)/cm^{-1} 1680 (CO); δ_H (600 MHz, $CDCl_3$) 7.66 (1 H, d, $^3J_{H,H}$ = 7.6, CH; Ar), 7.36 (1 H, t, $^3J_{H,H}$ = 7.6, CH; Ar), 7.28 (1 H, m, CH; Ar), 7.21 (1 H, m, CH; Ar), 3.04-2.91 (1 H, m, $^{13}CH_3CH$), 2.92-2.89 (2 H, m, CH_2), 2.09-2.04 (1 H, m, CH_AH_B), 1.94-1.88 (1 H, m, CH_ACH_B), 1.74-1.67 (1 H, m, CH_ACH_B), 1.63-1.56 (1 H, m, CH_ACH_B) and 1.24 (3 H, dd, $^1J_{C,H}$=127.5 and $^3J_{H,H}$ = 6.7, $^{13}CH_3$); δ_C (150.9 MHz, $CDCl_3$) 207.7, 141.7, 139.6, 131.2, 129.7, 128.3, 126.2, 44.2 (1 C, doublet [1:1], $^1J_{C,C}$ = 36.2, $C^{13}CH_3$), 33.6, 31.9, 25.5 and 16.4 ($^{13}CH_3$) (Found MH^+, 176.1162. $C_{11}^{13}CH_{15}O$ requires M, 176.1156).

1-Trimethylsilyoxy-2-trideuteriomethylbenzosuber-1-ene **13a**-d_3

In the same way as silyl enol ether **6a**, 2-trideuteriomethylbenzosuberone **12a** (0.4 g, 2.29 mmol), LDA (1.5 ml, 1.5 M in THF, 2.29 mmol) and Me_3SiCl (0.25 g, 0.29 ml, 2.29 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), *1-trimethylsilyoxy-2-trideuteriomethyl benzosuber-1-ene* **13a**-d_3 (0.43 g, 76%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.8; ν_{max} (film)/cm^{-1} 2111 (CD) and 1600 (C = C); δ_H (270 MHz, $CDCl_3$) 7.52-7.25 (4 H, m, 4 × CH; Ar), 2.67 (2 H, t, $^3J_{H,H}$ = 7.1, CH_2), 2.21 (2 H, quintet, $^3J_{H,H}$ = 7.1, CH_2), 1.95-1.91 (2 H, t, $^3J_{H,H}$ = 7.1, CH_2) and 0.18 (9 H, s, Me_3Si); δ_C (100.6 MHz, $CDCl_3$) 141.9, 138.9, 138.7, 127.5, 126.8, 125.8, 124.6, 116.6, 32.6, 31.6, 28.7 and 0.52 (Found M^+, 249.1439. $C_{15}H_{19}D_3OSi$ requires M, 249.1442). The absence of the septet [1:3:6:7:6:3:1] around 15 ppm for the CD_3 substituent in the ^{13}C NMR spectrum is common due to the long T_1 relaxation time associated with this substituent.[16]

1-Trimethylsilyoxy-2-methyl-[^{13}C]-benzosuber-1-ene **13b**

In the same way as silyl enol ether **6a**, 2-methyl-[^{13}C]-benzosuberone **12b** (0.23 g, 1.31 mmol), LDA (0.9 ml, 1.5 M in THF, 1.31 mmol) and Me_3SiCl (0.14 g, 0.2 ml, 1.31 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), the *1-trimethylsilyoxy-2-methyl-[^{13}C]-benzosuber-1-ene* **13b** (0.26 g, 81%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.8; ν_{max} (film)/cm^{-1} 1598 (C = C); δ_H (250 MHz, $CDCl_3$) 7.38 (1 H, d, $^3J_{H,H}$ = 7.1, CH; Ar), 7.24-7.07 (3 H, m, 3 × CH; Ar), 2.57 (2 H, t, $^3J_{H,H}$ = 7.0, CH_2), 2.12 (2 H, quintet, $^3J_{H,H}$ = 7.0, CH_2), 1.89 (3 H, d, $^1J_{C,H}$ = 126.3, $^{13}CH_3$),

1.85 (2 H, m, CH_2) and 0.80 (9 H, s, Me_3Si); δ_C (62.5 MHz, $CDCl_3$) 141.3, 140.1, 137.2, 130.6, 128.5, 126.9, 125.7, 116.7, 45.8, 33.7, 32.6, 29.8, 17.7, and 0.50 (Found M^+, 247.1770. $C_{14}^{13}CH_{22}OSi$ requires M, 247.1773).

1-Deuterio-2-trideuteriomethylbenzosuberone **14a**-d_4

In the same way as 2-trideuteriomethylindanone **7a**-d_4, silyl enol ether **13a** (0.1 g, 0.4 mmol), MeLi (0.25 ml, 1.6 M in ether, 0.4 mmol) and acetic acid-d_4 (51 mg, 45 µl, 0.8 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1), the *2-deuterio-2-trideutereiomethylbenzosuberone* **14a**-d_4 (52 mg, 73%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.8; ν_{max} (film)/cm^{-1} 2140 (CD) and 1679 (CO); δ_H (250 MHz, $CDCl_3$) 7.67 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.40-7.18 (3 H, m, 3 × CH; Ar), 3.06-2.87 (2 H, m, CH_2), 2.11-2.02 (1 H, m, CH_AH_B), 1.94-1.82 (1 H, m, CH_AH_B) and 1.73-1.54 (2 H, m, CH_2); δ_C(67.5 MHz, $CDCl_3$) 211.1, 139.5, 138.6, 132.3, 130.4, 129.3, 127.3, 41.7 (1 C, triplet [1:1:1], $^1J_{C,D} = 19.5$, *C*DCO), 36.2, 29.6 and 25.6 (Found MH^+, 179.1185. $C_{12}H_{11}D_4O$ requires M, 179.1189). The absence of the septet [1:3:6:7:6:3:1] around 15 ppm for the CD_3 substituent in the ^{13}C NMR spectrum is common due to the long T_1 relaxation time associated with this substituent.[16] The negative isotopic shift was 0.2 ppm (29.5 Hz at 150.9 MHz).

2-Deuterio-2-methyl-[^{13}C]-benzosuberone **14b**-d_1

In the same way as 2-trideuteriomethylindanone **7a**-d_4, silyl enol ether **13b** (0.14 g, 0.57 mmol), MeLi (0.36 ml, 1.6 M in ether, 0.57 mmol) and acetic acid-d_4 (73 mg, 65 µl, 1.14 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether–ether (9:1) *2-deuterio-2-methyl-[^{13}C]-benzosuberone* **14b**-d_1 (77 mg, 77%) as an oil; R_F [light petroleum (40–60°C): ether (9:1)] 0.8; ν_{max} (film)/cm^{-1} 2105 (CD) and 1679 (CO); δ_H (250 MHz, $CDCl_3$) 7.60 (1 H, d, $^3J_{H,H} = 7.6$, CH; Ar), 7.42 (1 H, t, $^3J_{H,H} = 7.6$, CH; Ar), 7.28-7.18 (2 H, m, 2 × CH; Ar), 3.05-2.87 (2 H, m, CH_2), 2.17-2.01 (1 H, m, CH_AH_B), 1.98-1.83 (1 H, m, CH_AH_B), 1.76-1.69 (2 H, m, CH_2) and 1.20 (3 H, d, $^1J_{C,H} = 127.3$, $^{13}CH_3$); δ_C (62.5 MHz, $CDCl_3$) 207.9, 137.6, 131.3, 129.8, 128.4, 126.4, 123.4, 43.9 (1 C, m, *C*D^{13}CH$_3$), 33.7, 32.0, 25.6 and 16.5 ($^{13}CH_3$) (Found M^+, 176.1077. $C_{11}^{13}CH_{13}DO$ requires M,

176.1079). The negative isotopic shift could not be determined due to the multiplicity of the ^{13}C NMR signal at 43.9 ppm.

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