Investigations on the Efficiency of Regioselective *C*-Deuteration of Endocyclic Enolates

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Regioselective *C*-deuteration of a series of Endocyclic enolates (derived from cyclic aryl ketones) was efficiently achieved by quenching the corresponding "base-free" enolate in the presence of a suitable deuterium source. We discuss the structural nature of the deuterium donor and comment on the use of additives within this deuteration step.

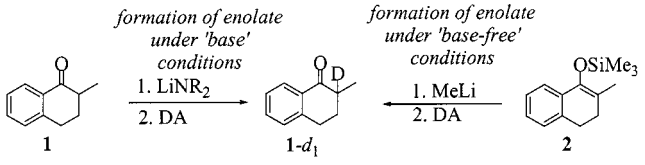
Introduction

The continuing development of novel synthetic methodologies for the direct incorporation of nonradioactive isotopic labels into organic molecules for chemical and biological studies is a major field of research.[1] A great deal of attention has been paid to deuterium incorporation involving simple carbon−hydrogen bond exchange reactions,[2] many of which have relied on a deprotonation-deuteration strategy involving relatively acidic centres,[3] most notably adjacent to a carbonyl group.[4] For synthetic ease, most H−D exchange reactions are generally performed under thermodynamic control[5] by using an excess of the deuterium source to drive the reaction to completion.[6] However, there are problems associated with this protocol, such as overall *D*-efficiency,[7] cost and the difficulty associated with product separation (due to incomplete substitution or over-incorporation).[8] Deuteration under kinetic control[9] could potentially solve many of these problems, but this strategy has been studied far less. In some cases, direct incorporation under kinetic control has also been shown to be problematic due to a number of factors,[10] such as the nature of the enolate complex and the presence of competitive bases that can give rise to internal proton return.[11] This problem has been partially solved by removing the unwanted pro-acidic proton through further deprotonation to form an enolate−amide complex,[4,12,13] or by ensuring the formation of a less basic amine.[4] Of similar importance is the less obvious concept of regioselective *C*-deuteration, which can give the *C*-deuterated carbonyl derivative directly without proceeding via the enol.

Ideally, the best method would involve the use of enolates in the absence of any competitive base using an efficient *C*-deuterating reagent. There have been some reports in this area,[14] but the concept of regioselective *C*-deuteration has largely been ignored. We have previously shown that carbonyl-directing proton donors, such as ethyl acetoacetate and acetic acid, can efficiently form *C*-protonated enolates under "base-free" conditions.[15] We now report[16] our studies into regioselective *C*-deuteration of "base-free" enolates using an analogous carbonyl-chelating deuterium donor ([D_4]acetic acid) under kinetic control. We comment on the effect that reaction parameters such as the presence of base and the structural nature of the deuterium source have on the outcome of the reaction, and discuss the role of such deuterium sources.

Results and Discussion

We first established the need for such a process by attempting to synthesise the deuterated tetralone **1**-d_1 [17] under traditional lithium amide conditions (Scheme 1). Formation of the diisopropylamine-enolate **3a** by addition of LDA to a stirred solution of 2-methyl tetralone **1** at −78 °C and attempted deuteration with a series of *D*-sources (Table 1) gave the partially incorporated tetralone **1**-d_1 (Scheme 2). Those sources that were rather *D*-acidic,[18] such as [D_3]nitromethane and [D_4]acetic acid gave little or no *D*-incorporation. This subsequent proton transfer is presumably due to the presence of the diisopropylamine **4** and must therefore involve the ammonium salt **5**-d_1.[19] Formation of this salt can occur by competitive deuteration invol-



Scheme 1. Deuteration of enol and carbonyl derivatives under two different conditions

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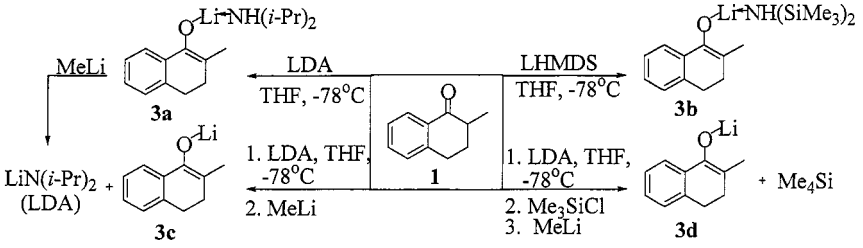
Table 1. Interconversion of 2-methyl tetralone **1** into 2-methyl tetralone **1**-d_1

Entry	1	2	3	4	5	6
Series / base	DA D_2O	MeOH-d_4	malonate-d_2	acetic -d_4	$MeNO_2$-d_3	DCl/D_2O
1 LDA	52:48[a] (72%)[b]	55:45 (67%)	>2:98 (88%)	**>2:98 (90%)**	>2:98 (82%)	**72:28 (78%)**
2 LHMDS	89:11 (78%)	78:22 (81%)	62:38 (79%)	**38:62 (87%)**	16:84 (78%)	**90:10 (72%)**
3 LDA.MeLi	62:38 (62%)	58:42 (66%)	52:48 (58%)	**35:65 (70%)**	41:59 (69%)	**83:17 (63%)**
under 'base-free' conditions						
4 MeLi	**>98:2 (72%)**	**>98:2 (66%)**	>86:14 (69%)	**>95:5 (68%)**	38:62 (74%)	**84:16 (70%)**

[a]isotopic [D]:[H] ratio; [b]yield.



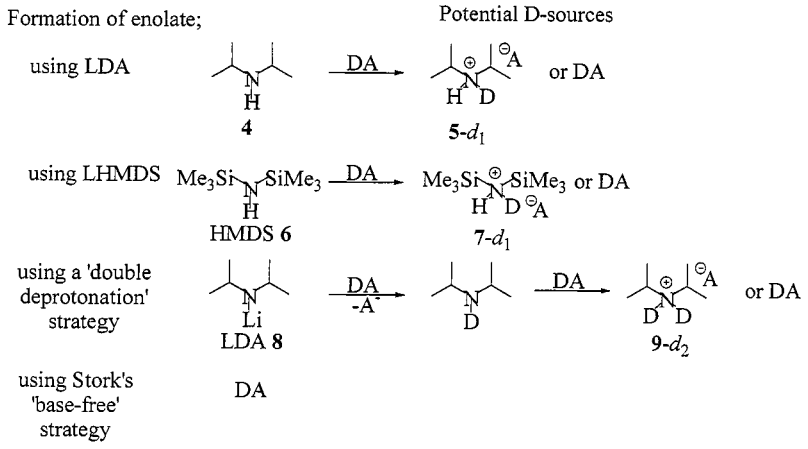
Scheme 2. The formation of four different 2-methyl tetralone enolates **3a**−**d**

ving the residual diisopropylamine **4** and the *D*-source, although the use of a *D*-enol **10** as an additional *D*-source cannot be ruled out. For less *D*-acidic sources, such as D_2O and [D_4]MeOH, where regioselective *O*-deuteration (of the enolate) and amine deuteration were less favourable, overall *D*-incorporation was much higher (Table 1, entry 1 and 2 versus 3, 4 and 5), but was clearly not perfect.[20]

The use of a less basic residual amine can potentially solve this inherent problem. There are limited reports[20] which suggest that a related amine, hexamethyldisilylamine (HMDS) **6**, is significantly less basic than diisopropylamine (Scheme 3) and thus less likely to form an ammonium salt such as **7**-d_1. However, under our standard deuteration conditions, using the corresponding lithium amide, LHMDS gave an increase in *D*-incorporation, which presumably illustrates its reduced basicity. This trend was observed in all cases studied (Table 1). More surprisingly, an increase in *D*-incorporation was evident with more *D*-acidic reagents, such as [D_2]malonate, [D_1]acetic acid and [D_3]nitromethane. The origin of this residual Brönsted base effect appears to be far more complicated than simple competitive deuteration.

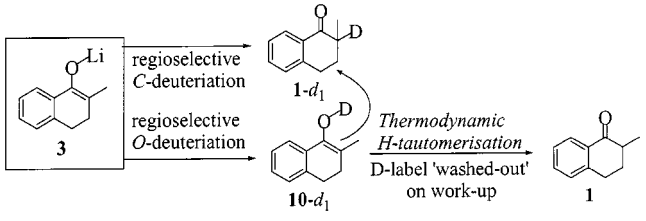
As an alternative, addition of MeLi to the preformed "base-enolate" **3a** using a double-deprotonation strategy would ensure removal of the residual proton of the amine by reforming the original amide (LDA) to give the amide-enolate complex **3c** (Scheme 2). Subsequent deuteration with a variety of *D*-sources (Table 1) gave the partially deuterated 2-methyl tetralone **1**-d_1 in good yield (Table 1). This combination of reagents (LDA, followed by MeLi) is certainly better than LDA itself, although the use of LHMDS does appear to be better (Table 1). This competitive basic amine can be removed from the reaction mixture by proceeding via the silyl enol ether **2** — the enolate **3d** is easily re-formed by the addition of MeLi to the silyl enol ether using Stork's original procedure (Scheme 2).[22] The required silyl enol ether **2** was readily formed by the consecutive addition of LDA and Me_3SiCl to the ketone, 2-methyltetralone.[23] Slow addition of MeLi to this silyl enol ether **2** rapidly liberates methane, tetramethylsilane and the base-free enolate **3d**. This solution was cooled to −78 °C, before being quenched with a series of *D*-sources (Table 1). In virtually all cases studied, there was an improvement in *D*-incorporation, the better *D*-sources (D_2O, [D_4]MeOH and [D_4]acetic acid) giving near perfect exchange. It is not that surprising for weakly *D*-acidic sources (like D_2O and [D_4]MeOH) that efficient *C*-deuteration occurs since *O*-deuteration is no longer kinetically favourable. Whereas, for more *D*-acidic sources (e.g. [D_4]acetic acid), competitive *C*- and *O*-deuteration can occur.

It is clear that the presence of a residual base (diisopropylamine **4** or hexamethyldisilylamine **6**) (Table 1; series 1−3) does have a detrimental effect on kinetic D-incorporation. It is rather intriguing that in the case of a double-deprotonation strategy (series 2) where attention had been paid to removing the unwanted proton from the residual amine, the incorporation was still quite low. In these cases, where fully or partially deuterated ammonium salts **5**-d_1, **7**-d_1 and **9**-d_2 have the potential to form, these may subsequently be responsible for some competitive *O*-protonation/deutera-



Scheme 3. The possible D-sources **5**, **7**, **10** and **DA** under each different reaction condition

tion (to give an H/D-enol), which under aqueous workup can result in the loss of the deuterium label through isotopic *H*-tautomerisation (Scheme 4). This type of behaviour may be responsible for the low incorporation when using carbon-based deuterium sources such as [D_2]malonate or [D_3]nitromethane under base-free conditions (Table 1, series 4: entry 3 and 5).

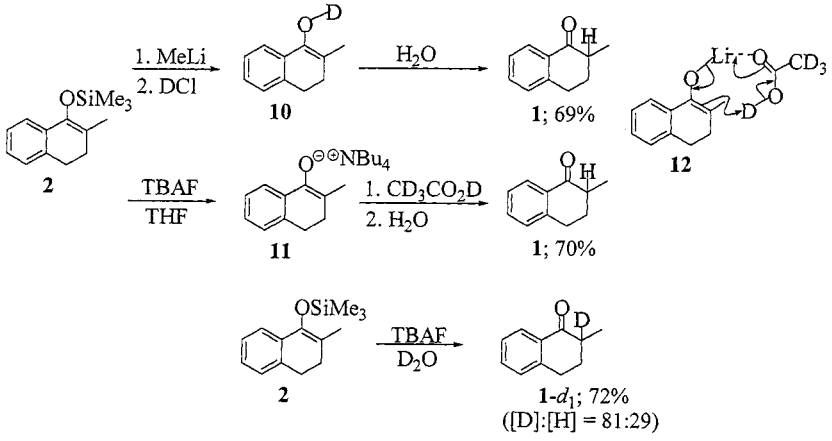


Scheme 4. Different products and pathways resulting from enolate deuteration

Whereas quenching the corresponding enolates **3a**−**d** with DCl (three equivalents, 37% in D_2O) under thermodynamic control[24] gave moderate *D*-incorporation (Scheme 4). This thermodynamic pathway must occur by initial *O*-deuteration to give the D-enol **10**-d_1, followed by DCl-catalysed thermodynamic tautomerisation.[24] When a single equivalent of DCl was used; no incorporation occurred, presumably due to the label being "washed out" during the workup procedure. This type of behaviour has also been observed previously.[25]

The presence of a lithium cation was found to be important: when quenching with a carbonyl-directing deuterium donor, in the presence of a non-coordinating tetrabutylammonium counter ion, the naked enolate **11** (formed by the addition of TBAF to the silyl enol ether **2**) gave no incorporation. However, if a solution of TBAF in D_2O was added to the silyl enol ether **2**, partial *D*-incorporation was observed ([D]:[H] = 81:19; 72%) (Scheme 5). Further evidence of regioselective *C*-protonation/deuteration has come from quenching the base-free enolate **3d** with an equimolar mixture of [D_0]- and [D_4]acetic acid giving a primary kinetic effect of 4 (from [D]:[H] = 20:80; 71%). This has led us to propose that protonation and deuteration of base-free enolates occur via a chelated intermediate such as **12** (Scheme 5).

For the remainder of this study we chose to use [D_4]acetic acid as our deuterating reagent primarily due to the forma-



Scheme 5. Attempted regioselective deuteration of 2-methyl tetralone **1**

Table 2. The synthesis of 2-substituted aryl ketones **1**, **14**, **16**, **17**, **19** and **21**

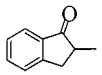
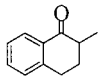
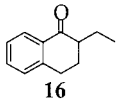
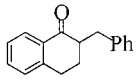
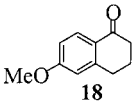
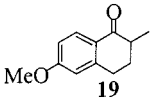
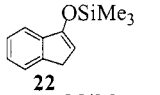
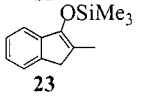
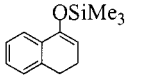
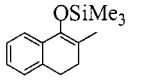
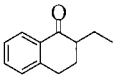
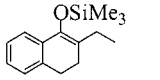
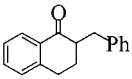
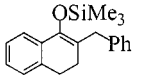
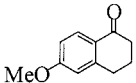
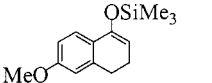
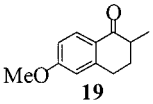
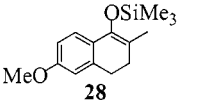
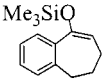
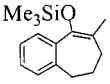
entry	starting material	product	yield
1	 **13**	 **14**	76%
2	 **15**	 **1**	76%
3	 **15**	 **16**	65%
4	 **15**	 **17**	62%
5	 **18**	 **19**	54%
6	 **20**	 **21**	61%

Table 3. The synthesis of silyl enol ethers **1** and **22**−**29**

entry	starting material	product	yield
1	 **13**	 **22**	73%
2	 **14**	 **23**	70%
3	 **15**	 **24**	81%
4	 **1**	 **2**	69%
5	 **16**	 **25**	69%
6	 **17**	 **26**	53%
7	 **18**	 **27**	71%
8	 **19**	 **28**	62%
9	 **20**	 **29**	70%
10	 **21**	 **30**	90%

tion of a non-basic acetate counterion.[26] The required silyl enol ethers **2**,[27] **22**,[28] **23**, **24**,[29] **25**−**27**,[30] **28**, **29** and **30** were derived from the corresponding ketones **1** and **13**−**21** using LDA and Me_3SiCl.[31] The corresponding 2-alkyl-substituted ketones **1**,[32] **14**,[33] **16**, **17**,[34] **19**,[35] and **21** required for this study were synthesised from the commercially available[36] ketones **13**, **15**, **18** and **20** using traditional S_N2 alkylation methodology (Table 2 and 3).

The required base-free enolates were formed by direct addition of MeLi (1.6 M in ether, 1.0 equivalent) to the corresponding silyl enol ether at room temperature. After stirring for an initial five-minute period, THF was added and the solution was cooled to −78 °C. Three equivalents of deuterium donor was then added to give the corresponding deuterated ketones **1**-d_1, **13**−**21**-d_1, **32**-d_1 and **34**-d_1 in good yield (Table 4).

There was little or no effect on changing the carbocyclic ring adjacent to the aryl ring: a five-membered ring (e.g., **13**-d_1) behaved similarly to a six- (e.g. **15**-d_1) or seven-membered ring (e.g. **20**-d_1), and all gave near identical *D*-incorporation ([D]:[H] = 85:15) (Table 4, entries 1, 2 and 3). Whereas, 2-methyl tetralone **1**-d_1 behaved slightly better ([D]:[H] = >95:5; 62%) than the corresponding tetralone **15**-d_1 ([D]:[H] = 87:13; 87%). Other similarly 2-alkyl-substituted tetralones like **16**-d_1 and **17**-d_1 (Table 5, entries 1 and 2) behaved similarly to the 2-methyl tetralone **1**. It was also found that the substitution pattern within the adjacent aryl ring had a surprising effect on the overall incorporation: the introduction of a 6-methoxy substituent into the silyl enol ethers **27** and **28** lowered the overall *D*-incorporation (Table 5, entries 3 and 4). This is presumably due to the presence of an additional coordinating methoxy substituent changing the enolate aggregate enough to prevent efficient regioselective *C*-deuteration. The position of the carbonyl group within this cyclic framework had little effect on the overall *D*-incorporation. Treatment of the silyl enol ether **31** (derived from tetral-2-one) with MeLi and addition of [D_4]acetic acid gave the tetra-2-one **32**-d_1 in good yield with near perfect incorporation ([D]:[H] = >95:5; 79%) (Table 5, entry 5).

To probe the effect of stereochemistry, we chose to quench the chiral base-free enolate of 4-*tert*-butylcyclohexanone derived from silyl enol ether **33**[37] with [D_4]acetic acid, to give the 4-*tert*-butylcyclohexanone *anti*-**34**-d_1 as a single diastereoisomer in a moderate 52% yield.[38] The diastereoselectivity here was particularly good due to the complementarity of both reagent[15,39] and substrate control. During the course of this study, we noticed a number of characteristic features due to the presence of the deuterium atom within these ketones-d_1: a) the presence of an

Table 4. The synthesis of aryl ketones **1**, **13**, **14**, **15**, **20** and **21**-d_1 under base-free conditions

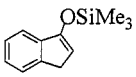
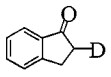
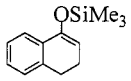
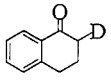
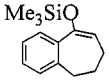
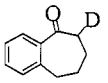
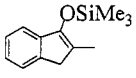
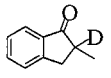
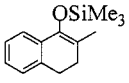
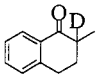
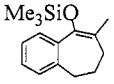
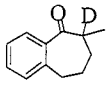
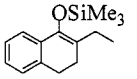
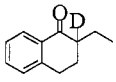
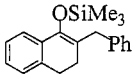
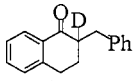
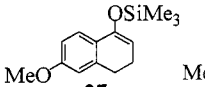
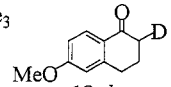
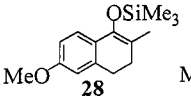
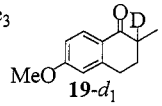
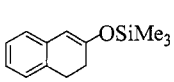
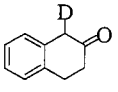
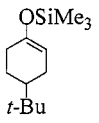
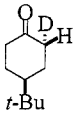
entry	starting material	product	[D]:[H]	yield	$^1J_{C\text{-}D}$ (Hz)	isotopic shift (Hz)
1	 **22**	 **13**-d_1	[84:16]	80%	19.8	20.3
2	 **24**	 **15**-d_1	[87:13]	87%	19.6	34.9
3	 **29**	 **20**-d_1	[86:14]	85%	19.6	19.6
4	 **23**	 **14**-d_1	[84:16]	80%	19.3	27.3
5	 **2**	 **1**-d_1	[>95:5]	62%	19.0	75.4
6	 **30**	 **21**-d_1	[86:14]	85%	19.3	26.8

Table 5. The synthesis of ketones **16**−**19**, **32** and **34**-d_1 under 'base-free' conditions

entry	starting material	product	[D]:[H]	yield	$^1J_{C\text{-}D}$ (Hz)	isotopic shift (Hz)
1	 **25**	 **16**-d_1	[95:5]	81%	19.1	23.9
2	 **26**	 **17**-d_1	[>95:5]	62%	19.4	35.2
3	 **27**	 **18**-d_1	[67:33]	82%	19.6	34.8
4	 **28**	 **19**-d_1	[73:27]	79%	19.2	30.9
5	 **31**	 **32**-d_1	[>95:5]	79%	19.5	39.5
6	 **33**	 *anti*-**34**-d_1	[>95:5]	52%	19.6	56.3

infrared C−D stretching frequency[40] at approximately 2100 cm^{-1}; b) the presence of a 1:1:1 C−D triplet (J_{C-D} = 19.5 Hz) in the ^{13}C NMR spectra;[25,41] c) a negative isotope shift[42] for the C−D bond (versus the corresponding C−H bond) in the ^{13}C NMR spectra between 23−75 Hz.

Conclusion

In conclusion, we have shown that efficient regioselective *C*-deuteration of enolates can occur under kinetic control using either D_2O, [D_4]MeOH or [D_4]acetic acid as the deuterium donor under "base-free" conditions. Furthermore, we believe there are three factors that are responsible for such efficient *C*-deuteration: a) the absence of diisopropylamine to prevent internal proton return; b) for nonchelating *D*-sources, *O*-deuteration[43] can be avoided by ensuring the analogous nonisotopic acid has a $pK_a > 10$,[43] (e.g., D_2O and [D_4]MeOH); and c) for chelating proton donors, the presence of a Lewis acidic lithium cation is essential to aid regioselective *C*-deuteration.

Experimental Section

General Remarks: All solvents were distilled before use. Tetrahydrofuran (THF) and ether were freshly distilled from sodium wire. Benzophenone 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 Bruker AM 250 Fourier transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield from tetramethylsilane and coupling constants in Hertz. Carbon NMR spectra were recorded with broad-band proton decoupling. Infrared spectra were recorded on a Shimadzu 8300 FTIR machine and mass spectra were recorded on a Kratos 50MSTC machine with a DS503 data system for high-resolution analysis. The levels of D-incorporation were determined by a combination of mass, proton and carbon NMR spectra.

2-Methyltetralone (1): Tetralone **15** (2.0 g, 1.8 mL, 13.7 mmol) was slowly added dropwise to a stirred solution of LDA (9 mL, 1.5 M in THF, 13.7 mmol) in THF (50 mL) at −78 °C and stirred for 20 minutes. MeI (0.83 g, 1.9 mL, 13.7 mmol) was then added and this solution was stirred for 12 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 the solvents evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum ether (b.p. 40−60 °C)/diethyl ether (19:1) to give 2-methyltetralone (**1**)[32] (1.67 g, 76%) as a colourless oil. R_f [light petroleum ether (40−60 °C)/diethyl ether (9:1)] 0.5. IR (film): $\tilde{\nu}_{max}$ = 1686 cm^{-1} (CO). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.28 (d, ^3J = 7.3, 3 H, MeCH), 1.87 (m, 1 H, CH_AH_B), 2.20 (dt, ^3J = 13.2 and 4.4, 1 H, CH_AH_B), 2.60 (m, 1 H, CHMe), 3.00 (m, 2 H, $CH_2CH{=}C$), 7.22 (d, ^3J = 7.6, 1 H, CH-Ar), 7.25 (t, ^3J = 7.7, 1 H, CH-Ar), 7.47 (dd, ^3J = 7.7 and 7.6, 1 H, CH-Ar), 8.00 (d, ^3J = 7.7 Hz, 1 H, CH-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.3, 28.8, 31.3, 42.0, 126.6, 127.4, 128.7, 132.4, 133.1, 144.2, 200.8. HRMS calculated for $C_{11}H_{12}O$ [M + H]: 160.0882; found 160.0882. MS: *m/z* (%) = 160.1 (100) [M^+].

2-Methyl-1-trimethylsilyoxytetral-1-ene (2): 2-Methyl tetralone **1** (1.0 g, 6.24 mmol) was slowly added dropwise to a stirred solution of LDA (4.2 mL, 1.5 M in THF, 6.24 mmol) in THF (50 mL) at −78 °C and stirred for 20 minutes. Me_3SiCl (0.68 g, 0.8 mL, 6.24 mmol) was then added and this solution was stirred for 3 hours. A solution of NH_4Cl (50 mL) was added and the mixture was extracted with ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvents evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum ether (b.p. 40−60 °C)/diethyl ether (19:1) to give the trimethylsiloxy-2-methyltetral-1-ene **2**[27] (1.22 g, 84%) as a colourless oil; R_f [light petroleum ether (40−60 °C)/diethyl ether (9:1)] 0.9. IR (film): $\tilde{\nu}_{max}$ = 1657 cm^{-1} (C=CO). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.2 (s, 9 H, *t*Bu), 1.80 (s, 3 H, CH_3), 2.24 (t, ^3J = 7.8, 2 H, CH_2), 2.72 (t, ^3J = 8.0, 2 H, CH_2), 7.18−7.06 (m, 3 H, 3 × CH-Ar), 7.31 (d, ^3J = 7.3, 1 H, CH-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 1.2, 17.9, 28.9, 29.7, 117.5, 122.1, 126.8, 127.3, 135.0, 136.6, 143.1. HRMS calculated for $C_{14}H_{20}OSi$ [M^+]: 232.1283; found 232.1274. MS: *m/z* (%) = 232.1 (100) [M^+].

2-Deuterio-2-methyltetralone (1-d_1): A solution of MeLi (0.6 mL, 1.6 M in ether, 0.61 mmol) was added dropwise to the silyl enol ether **2** (0.14 g, 0.60 mmol) at room temperature. The resulting solution was stirred for 1 hour at room temperature and then cooled to −78 °C. [D_4]acetic acid (43 mg, 0.68 mmol) in THF (1 mL) was added dropwise 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 the solvents evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum ether (40−60 °C)/diethyl ether (9:1) to give the 2-deuterio-2-methyl-1-tetralone-d_1 (**1**)[18] (67 mg, 68%) as an oil; R_f [light petroleum ether (40−60 °C)/diethyl ether (9:1)] 0.5. IR (film): $\tilde{\nu}_{max}$ = 2106 (C−D) and 1683 cm^{-1} (CO). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, MeCD), 1.87 (m, 1 H, CH_AH_B), 2.20 (dt, ^3J = 13.2 and 4.4, 1 H, CH_AH_B), 3.00 (m, 2 H, $CH_2CH{=}C$), 7.22 (d, ^3J = 7.6, 1 H, CH-Ar), 7.25 (t, ^3J = 7.7, 1 H, CH-Ar), 7.47 (dd, ^3J = 7.7 and 7.6, 1 H, CH-Ar), 8.00 (d, ^3J = 7.7, 1 H, CH-Ar). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.3, 28.8, 31.3, 42.0 (t, ^2J = 19.0, 1 C, CDMe), 126.6, 127.4, 128.7, 132.4, 133.1, 144.2, 200.8. HRMS calculated for $C_{11}H_{12}DO$ [M + H]: 162.1029; found 162.1034. MS: *m/z* (%) = 162 (100) [M]. The isotopic shift was 75.4 Hz.

Acknowledgments

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