JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2004; **47**: 359–371.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.822

Research Article

Investigations into the regioselective *C*-deuteriation of enolates derived from 2-methyl tetralone using piperidine-d_{11}

Gregory S. Coumbarides, Jason Eames* and Michael J. Suggate
Department of Chemistry, Queen Mary, University of London, Mile End Road, London E1 4NS, UK

Summary

Results are reported on the regioselective *C*-deuteriation of 2-methyl tetralone using piperidine-d_{11} as a deuterium source. The results presented further aid the understanding of kinetic deuteriation of amine–enolate complexes. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: ammonium salts; *D*-enols; deuterium; enolates; internal deuterium transfer; 2-methyl tetralone and piperidine-D_{11}

Introduction

The understanding of proton transfer in chemical and biological systems is becoming an increasingly important area.[1] The absolute and relative rates of many individual chemical proton transfer processes have been well documented,[2] but their chemical consequence has been less studied.[3] Over the last decade,[4] numerous research groups have focused their attention on the enantioselective protonation of enol(ate) derivatives with some success.[5] Of these reports, many have used the commercially available racemic ketone, 2-methyl tetralone **1** as their preferred carbonyl substrate.[6] This is primarily due to its predictable enolate chemistry[7] and the ease of which it can be recovered (due to its UV activity and non-volatile nature).

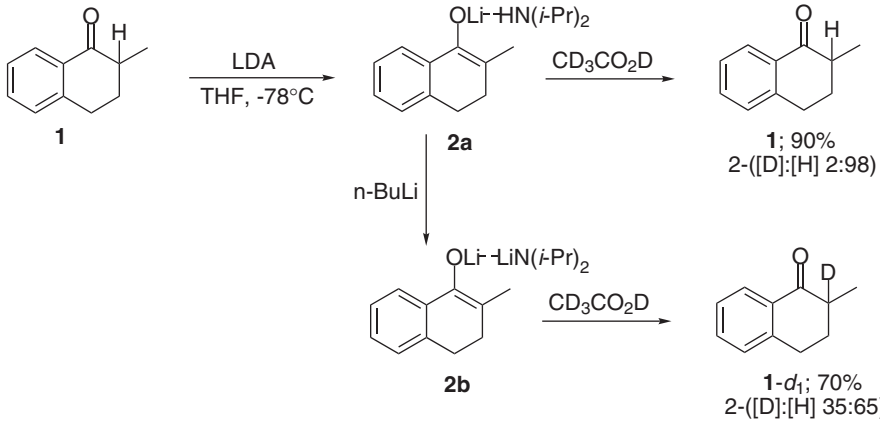
Over the last few years,[8] we have been interested in the mechanistic pathway of such processes, and recently, we have reported[9] the deuteriation of related

*Correspondence to: Dr. J. Eames, Department of Chemistry, Queen Mary, University of London, Mile End Road, London E1 4NS, UK. E-mail: j.eames@qmul.ac.uk

Contract/grant sponsor: London University Central Research Fund
Contract/grant sponsor: Nuffield Foundation; contract/grant number: NUF-NAF 99
Contract/grant sponsor: GOSS Scientific Instruments Ltd
Contract/grant sponsor: Royal Society

Received 6 January 2004
Revised 27 February 2004
Accepted 1 March 2004

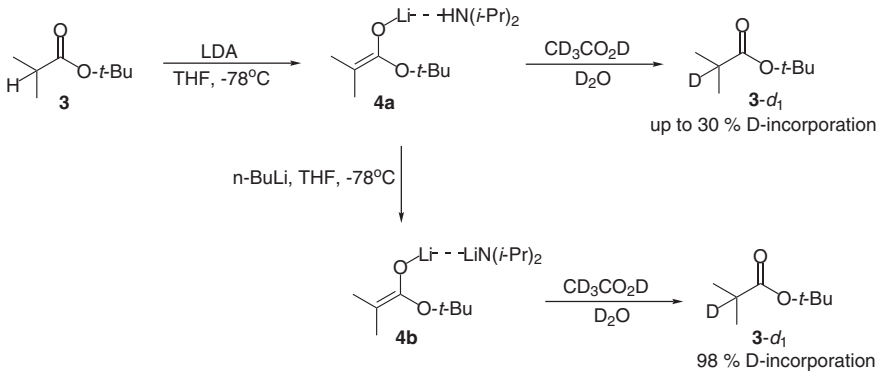
enolates to aid the understanding of these proton transfer processes. For example, deprotonation of 2-methyl tetralone **1** with lithium diisopropylamide (LDA) and attempted deuteriation of the corresponding diisopropylamine–enolate complex **2a** with acetic acid-d_4 gave the recovered tetralone **1** with virtually no *D*-incorporation[9] ([D]:[H] = 2:98) in 90% yield (Scheme 1).[10] This poor level of incorporation was not that unsurprising since in related studies enolate deuteriation has been shown to be problematic in the presence of an amine.[11]



Scheme 1.

The mechanism of simple enolate deuteriation has been well documented, most notably by Seebach *et al.*[11] They concluded that the presence of a *residual* base derived from the original lithium diisopropylamide base (e.g. lithium diisopropylamine) was responsible for the poor levels of *D*-incorporation. For example, they reported[11] that deprotonation of the ester **3** with LDA and addition of a solution of acetic acid-d_4 (in D_2O) to the resulting diisopropylamine–enolate complex **4a** gave only moderate *D*-incorporation (of up to 30%) (Scheme 2). However, by removing the NH proton of diisopropylamine by the sequential addition of *n*-BuLi to form the amide–enolate complex **4b**, and repeating the same deuterium quench gave significantly higher levels of *D*-incorporation (98%). This has led to the idea of *internal proton return*,[11] in which the NH proton of the intermediate amine is re-supplied to the enolate in **4a** (during the *D*-quench) to give back the recovered ester **3**. This reaction must proceed *via* an intermediate diisopropylamine-d_1–enolate complex like **4a**, which must evidently allow efficient internal deuterium return (back to the enolate) in the presence of acetic acid.[11]

However, using Seebach's approach[11] the level of *D*-incorporation could be improved by removing the problematic NH proton from the intermediate



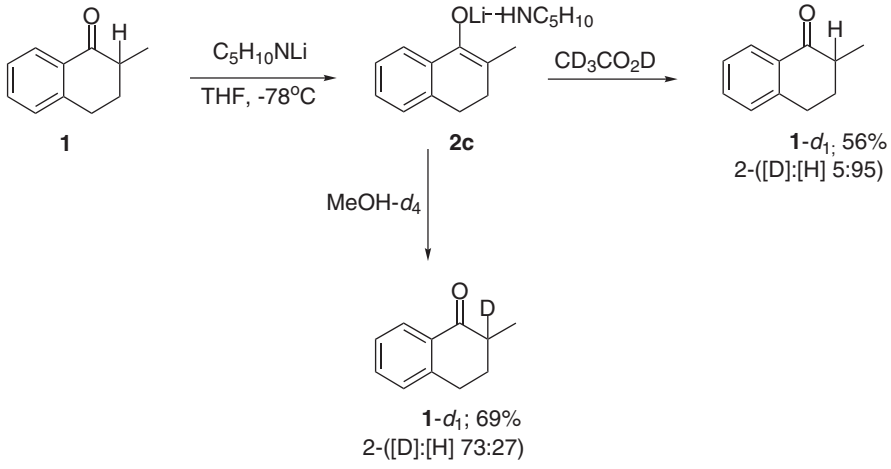
Scheme 2.

diisopropylamine–enolate complex **2a** using *n*-BuLi. Deuteriation of the resulting amide–enolate **2b** with acetic acid-d_4 gave slightly better *D*-incorporation (increasing from 2% to 35%) (Scheme 1). However, this level of *D*-incorporation was significantly lower than expected. This may be attributed to the reduced *C*-basicity of the tetralone enolate **2** thus lowering the amount of *C*-deuteriation than that of the corresponding ester **3** (Scheme 2).[12,13]

In an attempt to gain further insight and comprehension into the mechanism of this amine-mediated deuteriation of enolates, we chose to investigate the use of a commercially available secondary amine, piperidine-d_{11} as a potential deuterium source for enolate deuteriation.

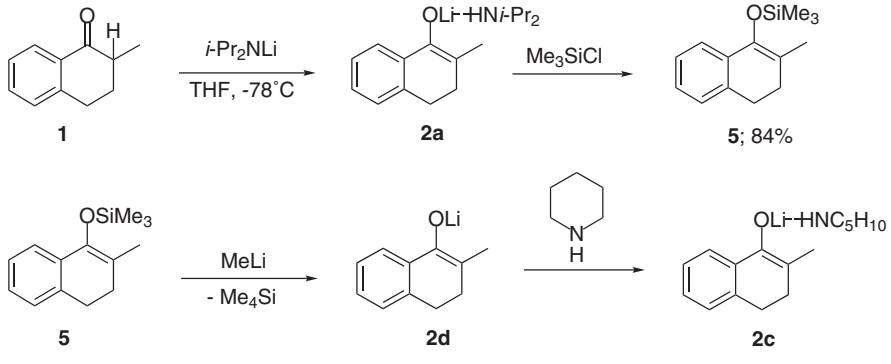
Results and discussion

We first established the need to investigate this process by attempting to deuteriate 2-methyl tetralone **1** through deprotonation with lithium piperidide, followed by addition of acetic acid-d_4 (Scheme 3). Deprotonation of 2-methyl tetralone **1** with lithium piperidide (formed by the addition of *n*-BuLi to a solution of piperidine in THF at -78°C) under our standard conditions[14] gave the corresponding piperidine–enolate complex **2c**. Slow addition of acetic acid-d_4 to **2c** gave the required 2-methyl tetralone **1**-d_1 with low *D*-incorporation ([D]:[H] = 5:95) in 56% yield. However, by using a less *D*-acidic deuterium source, such as MeOH-d_4, gave a further increase in *D*-incorporation ([D]:[H] = 73:27; 69% yield) (Scheme 3). These relative levels of *D*-incorporation are common for these types of *D*-sources.[14] In addition, the amount of proton return which leads to the unlabelled 2-methyl tetralone **1** is the dominant pathway in the case of acetic acid-d_4. However, an obvious problem associated with this approach is that unlabelled 2-methyl tetralone **1** could be derived directly from undeprotonated starting material **1**. In an attempt to get a better understanding of this process, we chose to study these reactions under conditions in which the starting precursors and product(s) were distinct.



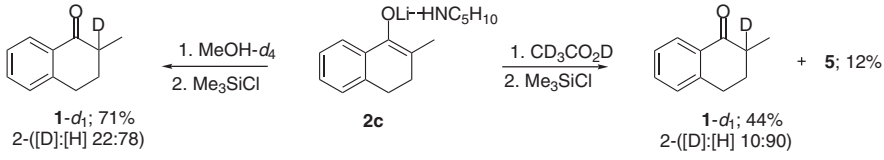
Scheme 3.

We decided to use Stork's silyl enol ether methodology[15] for the formation of the lithium enolate **2d** derived from 2-methyl tetralone **1**; by addition of MeLi to the corresponding silyl enol ether **5** (formed by trapping the diisopropylamine–enolate complex **2a** with Me_3SiCl) (Scheme 4). It is important to note that this enolate **2d** is generated in the absence of diisopropylamine since this was removed during purification of the precursor, silyl enol ether **5**. This methodology is clearly versatile since it allows the construction of a particular enolate complex through the addition of additives to the corresponding parent enolate **2d**. For example, addition of unlabelled piperidine to the 'base-free' enolate **2d** should lead directly to the original base–enolate **2c** (Scheme 4) derived from 2-methyl tetralone **1** and lithium piperidide (Scheme 3). However, by comparison, addition of acetic acid-d_4 and MeOH-d_4 to this constructed piperidine–enolate complex **2c** gave the corresponding 2-deuterio-2-methyl tetralone **1**-d_1



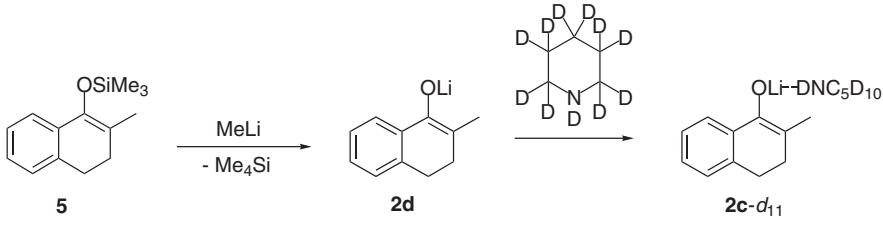
Scheme 4.

in moderate to good yield (Scheme 5). The level of *D*-incorporation for acetic acid-d_4 was similar to that obtained using the original piperidine–enolate complex **2c** (Scheme 3). By comparison, for MeOH-d_4 the level of *D*-incorporation for the constructed enolate **2c** was slightly lower (Schemes 3 and 4).



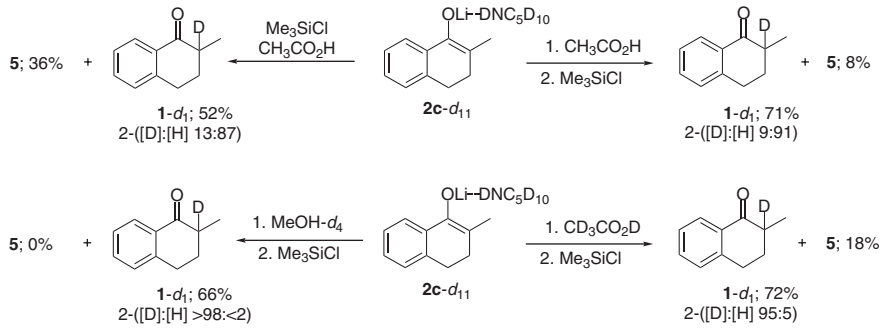
Scheme 5.

With this information in hand, we were now able to investigate the use of piperidine-d_{11} as a potential *D*-source for enolate deuteriation. Formation of the required base–enolate complex **2c**-d_{11} was easily achieved by addition of piperidine-d_{11} to the 'base-free' enolate **2d** (derived from the corresponding silyl enol ether **5** and MeLi) (Scheme 6).



Scheme 6.

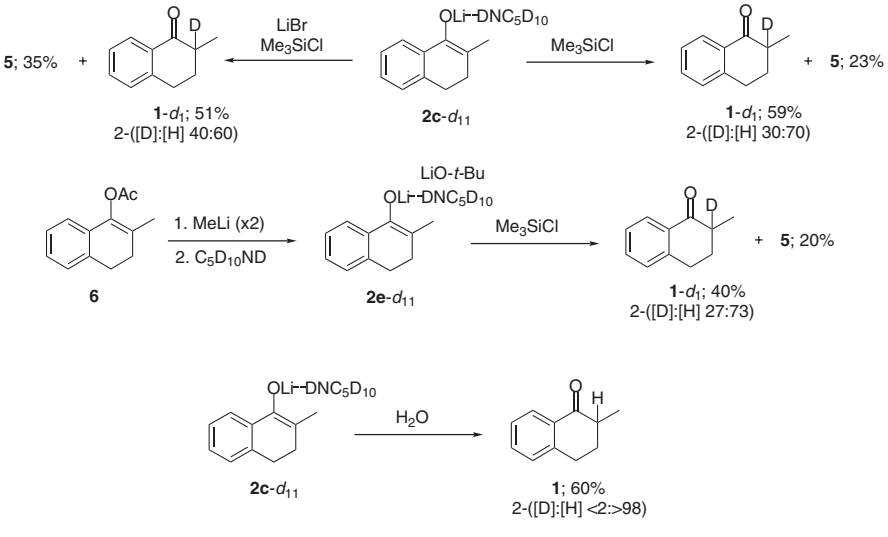
We first investigated the addition of unlabelled acetic acid to this piperidine-d_{11}–enolate complex **2c**-d_{11}. Slow addition of acetic acid to this piperidine-d_{11}–enolate, followed by the addition of Me_3SiCl after 30 min (to remove any unreacted enolate in the form of its silyl enol ether **5**) gave the required 2-deuterio-2-methyl tetralone **1**-d_1 but with low *D*-incorporation ([D]:[H] = 9:91) in 71% yield (Scheme 7). As an alternative strategy, addition of a pre-mixed solution of acetic acid and Me_3SiCl to this piperidine-d_{11}–enolate complex **2c**-d_{11} gave 2-deuterio-2-methyl tetralone **1**-d_1 with similar levels of *D*-incorporation ([D]:[H] = 13:87) but in lower chemical yield; this was primarily due to an increase in silyl enol ether **5** formation (36% yield) (Scheme 7). By comparison, addition of *D*-labelled acetic acid-d_4 and MeOH-d_4, followed by the addition of Me_3SiCl (after 30 min) gave the corresponding 2-deuterio-2-methyl tetralone **1**-d_1 with near perfect *D*-incorporation in 72% and 66% yield respectively (Scheme 7). The higher levels of *D*-incorporation are not that surprising since both the



Scheme 7.

internal (piperidine-d_{11}) and external deuteriation source (acetic acid-d_4 or MeOH-d_4) were fully deuteriated.

However, the role of Me_3SiCl in these deuterium transfer processes was rather intriguing. Simple addition of Me_3SiCl to the piperidine-d_{11}–enolate complex **2c**-d_{11} enabled *D*-transfer to occur from the piperidine-d_{11} to the enolate **2** to give 2-deuterio-2-methyl-tetralone **1**-d_1 with moderate *D*-incorporation ([D]:[H] = 30:70; 59% yield). This level of *D*-transfer can be increased slightly to 40% ([D]:[H] = 40:60) by use of a LiBr additive (Scheme 8).



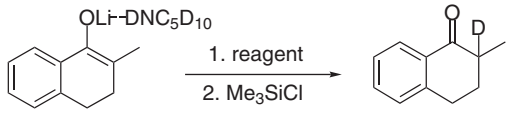
Scheme 8.

The formation of this LiBr-enolate complex was achieved by the addition of a solution of MeLi-LiBr to the original silyl enol ether **5**.[16] The structural nature of the lithium enolate appears to be unimportant as far as the outcome of this deuteriation process. Addition of Me_3SiCl to a preformed solution of House and Trost's[17] lithium *t*-butoxide-piperidine–

enolate complex **2e**-d_{11} [formed by addition of MeLi (two equivalents) to the enolacetate **6**][18] gave the required 2-deuterio-2-methyl tetralone **1**-d_1 with a moderate level of *D*-incorporation ([D]:[H] = 27:73; 40% yield).

The presence of Me_3SiCl is crucial in mediating some of these deuteriation processes. Without it, no *D*-transfer from the deuterium source, piperidine-d_{11} to the enolate can occur. For example, addition of H_2O to the piperidine-d_{11}–enolate complex **2c**-d_{11} gave exclusively 2-methyl tetralone **1** with no *D*-incorporation ([D]:[H] = ⟨2:⟩98; 60% yield). From this study, it appears that the Me_3SiCl directly assists the *D*-transfer process, presumably by enhancing the *D*-acidicity of the *D*-amine *via* nucleophilic addition of the amine, piperidine-d_{11} to Me_3SiCl. This type of electrophile-mediated process has previously been reported in the enantioselective protonation of 2-methyl tetralone (using a Lewis acid, $SnCl_4$, and BINOL combination)[19] and, also a substituted amide (using a Lewis acid, BF_3, and amine combination).[20]

We next turned our attention to screening a variety of different electrophiles in an attempt to increase the level of *D*-incorporation (Scheme 9). Addition of BBr_3, *t*-BuCOCl and 2-methyl tetralone **1** to the piperidine-d_{11}–enolate complex **2c**-d_{11} gave moderately low levels of *D*-incorporation. It is particularly worthy of note, that some deuterium transfer occurs ([D]:[H] = 19:82) even when 2-methyl tetralone **1** was used as a mediator but not as much as in its absence (Schemes 9 and 10).



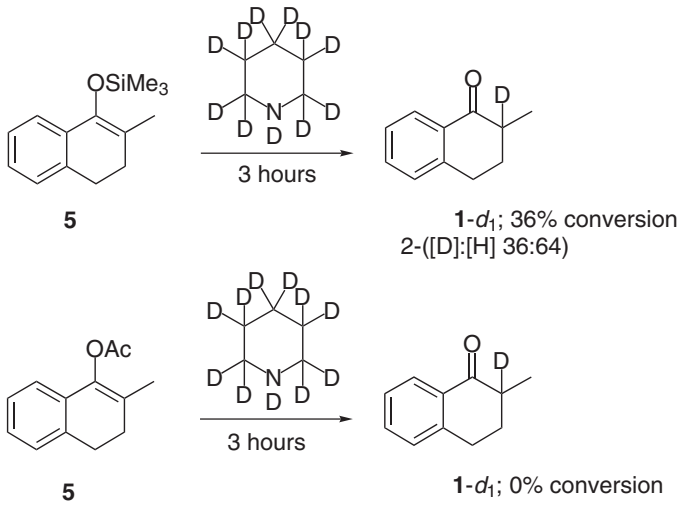
2c-d_{11} **1**-d_1

reagent	none	LiBr	BBr_3	*t*-BuCOCl	2-methyl tetralone **1**
2-([D]:[H])	30:70; 59%	40:60; 51%	7:93; 94%	32:68; 66%	19:82; 41%[a]

[a]49% of silyl enol ether **5** was formed/recovered

Scheme 9.

In light of Me_3SiCl being a mediator for deuterium transfer from an amine to an enolate, we next chose to investigate the use of the silyl enol ether **5** as a mediator itself. Addition of piperidine-d_{11} to the silyl enol ether **5** at room temperature, and stirring the resulting solution for 3 h resulted in 40% conversion of the silyl enol ether **5** into the required 2-deuterio-2-methyl tetralone **1**-d_1 with 36% *D*-incorporation ([D]:[H] = 36:64). This silyl enol ether **5** appears to be more electrophilic than the related enol acetate **6** since under identical reaction conditions no reaction appears to occur with the enolacetate **6**.



Scheme 10.

In conclusion, we have shown that *C*-deuteriation of 2-methyl tetralone **1** can occur efficiently in the presence of both a labelled secondary amine, piperidine-d_{11} and an external *D*-source, such as acetic acid-d_4 or MeOH-d_4. The external deuterium donor must naturally favour *C*-deuteriation[13,14] to give directly the required 2-deuterio-carbonyl derivative rather than *O*-deuteriation to give the related *D*-enol. For the synthesis of related *H*-enols see Reference 21. *O*-Deuteriation can be avoided by ensuring analogous non-isotopic acids have a $pK_a > 10$.[14] For a related ketone, e.g. acetophenone; pK_a (enol OH) = 7.9 and pK_a (carbonyl CH) = 18.2. This can be partially controlled by ensuring that the deuterium donor is weakly *D*-acidic (to prevent *D*-enol formation) and by using a *C*-directing deuterium donor,[13,14] whereas, for a *D*-labelled amine, *C*-deuteriation can occur in the presence of a mediating electrophile (e.g. Me_3SiCl) which assists the internal deuterium return to give moderate levels of *D*-incorporation. Presumably, incomplete *C*-deuteriation is due to competitive *O*-deuteriation to give the corresponding *D*-enol, which is known to lead to the label being lost as a result of tautomerisation under aqueous work-up.[13,14,22]

Experimental

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

60F254 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. 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 spectrometer using a DS503 data system for high-resolution analysis. The levels of *D*-incorporation were determined by a combination of mass and proton NMR spectra.

Synthesis of 2-methyl-tetralone 1[14]

Tetralone (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 min. MeI (0.83 g, 1.9 ml, 13.7 mmol) was 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 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-methyl tetralone **1** (1.67 g, 76%) as a colourless oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.4; ν_{max} (film)/cm^{-1} 1686 (C═O) δ_H(250 MHz, $CDCl_3$) 1.28 (3 H, d, *J* 7.3, MeCH), 1.87 (1 H, m, CH_AH_B), 2.20 (1 H, dt, *J* 13.2 and 4.4, CH_AH_B), 2.60 (1 H, m, CHMe), 3.00 (2 H, m, $CH_2C{=}C$), 7.22 (1 H, d, *J* 7.6, CH; Ar), 7.25 (1 H, t, *J* 7.6, CH; Ar), 7.47 (1 H, dd, *J* 7.7 and 7.6, CH; Ar) and 8.00 (1 H, d, *J* 7.7, CH; Ar); δ_C(62.5 MHz, $CDCl_3$) 15.3, 28.8, 31.3, 42.0, 126.6, 127.4, 128.7, 132.4, 133.1, 144.2 and 200.8 (Found M+, 160.0882. $C_{11}H_{12}O$ requires MH, 160.0882); *m*/*z* 160.1 (100%, M).

Synthesis of silyl enol ether 5[14]

2-Methyl tetralone **1** (1.0 g, 6.24 mmol) was 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 min. Me_3SiCl (0.68 g, 0.8 ml, 6.24 mmol) was added and this solution was stirred for 3 h. 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 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 trimethylsiloxy-2-methyl-tetral-1-ene **5** (1.22 g, 84%) as a colourless oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.9; ν_{max} (film)/cm^{-1} 1657 (C═CO) δ_H(250 MHz, $CDCl_3$) 0.20 (9 H, s, *t*-Bu), 1.80 (3 H, s, CH_3), 2.24 (2 H, t, *J* 7.8, CH_2), 2.72 (2 H, t,

J 7.8, CH_2), 7.18-7.06 (3 H, m, 3 × CH; Ar) and 7.31 (1 H, d, *J* 7.3, CH; Ar); δ_C(62.5 MHz, $CDCl_3$) 1.2, 17.9, 28.9, 29.7, 117.5, 122.1, 126.8, 127.3, 135.0, 136.6 and 143.1 (Found M+, 232.1274. $C_{14}H_{20}OSi$ requires M, 232.1283); *m*/*z* 232.1 (100%, M).

Synthesis of 2-deuterio-2-methyl-tetralone 1-d_1[14]

A solution of MeLi (0.6 ml, 1.6 M in ether, 0.61 mmol) was added dropwise to the silyl enol ether **5** (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. Acetic acid-d_4 (43 mg, 42 µl, 0.68 mmol) in THF (1 ml) was added dropwise, and the solution was stirred for a further 30 min. The reaction was quenched by the addition of water (10 ml), 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-methyl-1-tetralone **1**-d_1 (67 mg, 68%) as an oil; R_F [light petroleum (40–60°C):ether (9:1)] 0.4; ν_{max} (film)/cm^{-1} 2106 (C–D) and 1683 (CO); δ_H(250 MHz, $CDCl_3$) 1.28 (3 H, s, MeCD), 1.87 (1 H, m, CH_AH_B), 2.20 (1 H, dt, *J* 13.2 and 4.4, CH_AH_B), 3.00 (2 H, m, $CH_2C{=}C$), 7.22 (1 H, d, *J* 7.6, CH; Ar), 7.25 (1 H, t, *J* 7.6, CH; Ar), 7.47 (1 H, dd, *J* 7.7 and 7.6, CH; Ar) and 8.00 (1 H, d, *J* 7.7, CH; Ar); δ_C(62.5 MHz, $CDCl_3$) 15.3, 28.8, 31.3, 42.0 (1 C, t, $^1J_{C-D}$ 19.0, CDMe), 126.6, 127.4, 128.7, 132.4, 133.1, 144.2 and 200.8 (Found MH+, 162.1034. $C_{11}H_{12}DO$ requires MH, 162.1029); *m*/*z* 162 (100%, M). The isotopic shift was 0.5 ppm (75.4. Hz at 150 MHz).

Typical experimental procedure for deuteriation of a silylenol ether 5. A solution of MeLi (0.66 ml, 1.6 M in ether, 1.06 mmol) was added dropwise to the silyl enol ether **5** (0.25 g, 1.06 mmol) at room temperature. This resulting solution was stirred for 30 min at room temperature and then cooled to −78°C. Piperidine-d_{11} (0.10 g, 0.12 ml, 1.06 mmol) was slowly added and the resulting solution was stirred for 30 min. Acetic acid-d_4 (0.19 g, 0.18 ml, 3.18 mmol) in THF (1 ml) was added dropwise to this solution and the mixture stirred for a further 30 min. Me_3SiCl (0.23 g, 0.17 ml, 2.12 mmol) was added and the resulting solution was stirred for a further 30 min. The reaction was quenched by the addition of H_2O (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-methyl-tetralone **1**-d_1 (0.12 g, 72%) ([D]:[H] = 95:5) as an oil and identical spectroscopically to that previously synthesized.

Typical experimental procedure for deuteriation of an enolacetate 6. A solution of MeLi (0.59 ml, 1.6 M in ether, 0.15 mmol) was added dropwise to the enol acetate **6**[19] (0.19 g, 0.95 mmol) at room temperature. This resulting solution was stirred for 30 min at room temperature and then cooled to −78°C. Piperidine-d_{11} (90 mg, 0.11 ml, 0.95 mmol) was slowly added and the resulting solution was stirred for 30 min. Me_3SiCl (0.17 g, 0.16 ml, 2.85 mmol) in THF (1 ml) was added dropwise to this solution and the mixture stirred for a further 30 min. 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-methyl-tetralone **1**-d_1 (60 mg, 40%) ([D]:[H] = 27:73) as an oil and identical spectroscopically to that previously synthesized.

Typical deprotonation–deuteriation procedure using lithium piperidide. A solution of piperidide (0.82 mmol in 2 ml THF) was added dropwise to a stirred solution of 2-methyl tetralone **1** (0.11 g, 0.68 mmol) in THF (2 ml) at –78°C. The resulting solution was stirred for 30 min. Acetic acid-d_4 (0.12 g, 0.12 ml, 2.04 mmol) was added and the solution stirred for 30 min. A solution of NH_4Cl (10 ml) was added and the mixture was extracted with ether (3 × 20 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-methyl-tetralone **1**-d_1 (21 mg, 56%) ([D]:[H] = 5:95) as an oil and identical spectroscopically to that previously synthesized.

Acknowledgements

We thank the London University Central Research Fund, The Nuffield Foundation (NUF-NAF 99), GOSS Scientific Instruments Ltd and The Royal Society for their generous financial assistance. We are also grateful to the EPRSC National Mass Spectrometry Service (Swansea) for mass determination.

References

1. Kirby AJ. *Acc Chem Res* 1997; **30**: 290.
2. (a) Eigen M. *Angew Chem Int Ed Engl* 1964; **3**: 1; (b) Bell RP. *J Chem Soc Faraday Trans 1* 1983; **79**: 2229; (c) Koch HF. *Acc Chem Res* 1984; **17**: 137; (d) Bagno A, Scorrano G. *Acc Chem Res* 2000; **33**: 609.
3. Eames J. *Eur J Org Chem* 2002; 393.
4. (a) Eames J, Weerasooriya N. *Tetrahedron: Asymmetry* 2001; **12**: 1; Fehr C. *Angew Chem Int Ed Engl* 1996; **35**: 2566.

5. (a) Fehr C, Galindo J. *Angew Chem Int Ed Engl* 1994; **33**: 1888; (b) Haubenreich T, Hünigs S, Schulz H-J. *Angew Chem Int Ed Engl* 1993; **32**: 398; (c) Yangagisawa A, Kikuchi T, Kuribayashi T, Yamamoto H. *Tetrahedron* 1998; **54**: 10253; (d) Asensio G, Gavina P, Cuenca A, de Arellano MCR, Domingo LR, Medio-Simón M. *Tetrahedron: Asymmetry* 2000; **11**: 3481; (e) Takahashi T, Nakao N, Koizumi T, *Tetrahedron: Asymmetry* 1997; **8**: 3293; (f) Nakamura Y, Takeuchi S, Ohgo Y, Yamaoka M, Yoshida A, Mikami K. *Tetrahedron Lett* 1997; **38**: 2709; (g) Fuji K, Tanaka K, Miyamoto H. *Tetrahedron: Asymmetry* 1993; **4**: 247; (h) Vedejs E, Kruger AW, Lee N, Sakata ST, Stec M, Suna E. *J Am Chem Soc* 2000; **122**: 4602; (i) Aboulhoda SJ, Reiners I, Wilken J, Henin F, Martens J, Muzart J. *Tetrahedron: Asymmetry* 1998; **9**: 1847; (j) Takahashi M, Ogasawara K. *Tetrahedron: Asymmetry* 1997; **8**: 3125; (k) Takahashi M, Ogasawara K. *Tetrahedron Lett* 1997; **38**: 6429; (l) Henze R, Duhamel L, Lasne MC. *Tetrahedron: Asymmetry* 1997; **8**: 3363; (m) Yamashita Y, Emura Y, Odashima K, Koga K. *Tetrahedron Lett* 2000; **41**: 209.
6. (a) Kosugi H, Hoshino K, Uga H. *Tetrahedron Lett* 1997; **38**: 6861; (b) Asensio G, Cuenca A, Gavina P, Medio-Simón M. *Tetrahedron Lett* 1999; **40**: 3939; (c) Nakamura Y, Takeuchi S, Ohgo Y, Yamaoka M, Yoshida A, Mikami K. *Tetrahedron* 1999; **55**: 4595; (d) Fuji K, Kawabata T, Kuroda A. *J Org Chem* 1995; **60**: 1914; (e) Sugiura M, Nakai T. *Angew Chem Int Ed Engl* 1997; **36**: 2366. (f) Riviere P, Koga K. *Tetrahedron Lett* 1997; **38**: 7859.
7. (a) Coumbarides GS, Eames J, Weerasooriya N. *Bull Chem Soc Jpn* 2002; **75** 1163; (b) Coumbarides GS, Eames J, Weerasooriya N. J *Label Compd Radiopharm* 2002; **45**: 917; (c) Asensio G, Gil J, Aleman P, Medio-Simon M. *Tetrahedron: Asymmetry* 2001; **12**: 1359; (d) Cuenca A, Medio-Simon M, Weibel D, Beck AK, Seebach D. *Helv Chim Acta* 2000; **83**: 3162; (e) Goto M, Akimoto K, Aoki K, Shindo M, Koga K. *Tetrahedron Lett* 1999; **40**: 8129; (f) Yangagisawa A, Kikuchi T, Kuribayashi T, Yamamoto H. *Tetrahedron* 1998; **54**: 10253.
8. (a) Eames J, Weerasooriya N. *Tetrahedron Lett* 2000; **41**: 521; (b) Eames J, Weerasooriya N. *Chirality* 1999; 787.
9. Eames J, Coumbarides GS, Weerasooriya N. *Tetrahedron Lett* 2000; **41**: 5753.
10. Determined by integration of the ^{1}H NMR spectrum of the corresponding methyl doublet at 1.28 ppm in **1** versus the methyl singlet at 1.28 ppm in **1**-d_1.
11. Laube T, Dunitz JD, Seebach D. *Helv Chim Acta* 1985; **68**: 1373.
12. Eames J, Coumbarides GS, Weerasooriya N. *J Label Compd Radiopharm* 2002; **75**: 965.
13. Eames J, Coumbarides GS, Suggate MJ, Weerasooriya N. *Eur J Org Chem* 2003; **634**; and references therein.
14. Eames J, Coumbarides GS, Weerasooriya N. *Eur J Org Chem* 2002; 181.
15. (a) Stork G, Hudrlik P. *J Am Chem Soc* 1968; **90**: 4462; (b) Stork G, Hudrlik PF. *J Am Chem Soc* 1968; **90**: 4464.
16. Koga K. *Pure & Appl Chem* 1994; **66**: 1487; and references therein.
17. (a) House HO, Gall M, Olmstead H. *J Org Chem Soc* 1971; **36**: 2361; (b) House HO, Trost BM. *J Org Chem* 1965; **30**: 2502; (c) House HO, Czuba LJ, Gall M, Olmstead HD. *J Org Chem* 1969; **34**: 2324.

18. Eames J, Coumbarides GS, Weerasooriya N. *J Label Compd Radiopharm* 2001; **44**: 871.
19. Fuji K, Kawabata T, Kuroda A. *J Org Chem* 1995; **60**: 1914.
20. Vedejs E, Lee N. *J Am Chem Soc* 1995; **117**: 891.
21. Rappoport Z, Nugiel DA. *J Am Chem Soc* 1985; **107**: 3669.
22. Bodepudi VR, Noble le WJ. *J Org Chem* 1994; **59**: 3265.

