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A Short and Efficient Synthesis of Bridgehead Mono- and Dideuteriated Tropinones

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Studies of the biosynthesis and degradation of alkaloids of the tropane class require substrates isotopically-labelled at specific positions. To investigate the mechanism of the enzyme reactions involved in the hydroxylation of the bridgehead position(s), compounds deuteriated at this position are needed. An efficient synthesis of 1,5-dideuterio- and racemic 1-deuteriotropinone is described in which high levels of deuterium are incorporated from the corresponding di- and mono-labelled 2,5-dibutoxytetrahydrofuran.

Introduction

The tropane alkaloids, which all have the 8-azabicyclo-[3.2.1]octane core, are found in plants of the *Solanaceae*, *Erythroxylaceae* and *Convolvulaceae* families.[1] A number of these alkaloids, notably hyoscyamine (**1**), scopolamine (**2**) and cocaine (**3**) (Figure 1), have received considerable attention due to their important biological properties and their various medicinal uses. A sub-group, the calystegines [e.g., calystegine A_3 (**4**), Figure 1], are known to be powerful glycosidase inhibitors.[2] These polyhydroxylated nortropane alkaloids, derived from tropinone (**5**) by *N*-demethylation, have been isolated from a number of plant species.[3] They are characterised by a 3-*exo*-hydroxy group [in contrast to the 3-*endo* of, for example, hyoscyamine (**1**)] and all have a hydroxy function at the bridge position of the nortropane skeleton. Indeed, calystegines can also be hydroxylated at the 2-, 4-, 6- or 7-position. To date, the mechanism by which these hydroxy groups are introduced is unknown. The only enzyme that has been reported to hydroxylate a tropane alkaloid is the enzyme that hydroxylates the 7-position of hyoscyamine (**1**) in the first step of the formation of the 6,7-*exo*-epoxide of scopolamine (**2**).[4] This enzyme belongs to the iron ascorbate class and not to the more commonly encountered and better described cytochrome P450 oxidases. Thus, it is of general interest to investigate further the mechanism(s) of the enzymes responsible for the hydroxylation at other positions.

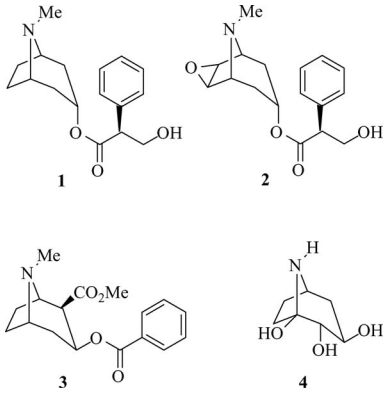

Figure 1. Structures of (–)-hyoscyamine (**1**), (–)-scopolamine (**2**), (–)-cocaine (**3**) and (–)-calystegine A_3 (**4**).

Furthermore, and especially in view of their importance as bioactive compounds, the degradation of tropane alkaloids has received surprisingly little attention. It has been demonstrated in humans that the degradation of these alkaloids involves P450 cytochrome oxidase and is initiated by *N*-demethylation.[5] However, the best-studied system is a *Pseudomonas* bacterium, which exploits tropine alkaloids as the sole source of carbon and nitrogen.[6] In this organism, degradation of tropane bases is also initiated by *N*-demethylation followed by cleavage of the N–C1 or N–C5 bond and then deamination to recover the nitrogen and catabolism of the carbon skeleton. Critically, it is implicit that the cleavage reaction involves hydroxylation of the 1- or 5-position, although this remains to be rigorously proven. Nevertheless, this micro-organism provides a good system in which to carry out mechanistic studies both of the *N*-demethylation and of the hydroxylation/ring-opening steps of tropane alkaloid degradation. This objective requires the

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synthesis of several tracer molecules, including bridge-labelled di- and mono-deuteriated tropinones **6** and (±)-**7**, respectively (Figure 2). Only a few ring-deuteriated tropanone derivatives have been described in the literature[7] and, to the best of our knowledge, none have been labelled at the bridgehead carbon positions.

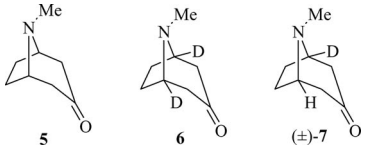


Figure 2. Structures of tropinone (**5**), [1,5-$^2H_2$]tropinone (**6**) and (±)-[1-^{2}H]tropinone (**7**).

In view of the unique core unit of these natural products, it is not surprising that they have emerged as a crucial scaffold in a wide variety of analogues with various pharmacological properties.[8] The tropanes and their congeners have been the target of many syntheses since Willstätter's synthesis of tropinone (**5**; see Figure 2) in 1903.[9] Robinson's landmark synthesis of tropinone (**5**) by a double-Mannich three-component reaction from succinaldehyde, methylamine and the calcium salt of acetone-1,3-dicarboxylic acid, published in 1917, can be regarded as one of the first multi-component reactions and is still one of the most effective ways to synthesise the tropane core structure.[10] A major improvement in this procedure was the use of 2,5-dimethoxytetrahydrofuran (**8**) as a precursor of succinaldehyde.[11] Since this pioneering work of Robinson, a variety of synthetic approaches for the preparation of tropine derivatives have been described in the literature. Tropinone (**5**) can be prepared by the simple addition of methylamine to cycloheptadienone[12] or by [4+3] cycloaddition[13] of *N*-protected pyrroles and tetrabromoacetone. An efficient one-pot synthesis of the tropane alkaloid based on tandem (domino) ene-type reactions of siloxyallylsilane with *N*-methoxycarbonyl-2,5-dimethoxypyrrolidine (**9**) without acidification and decarboxylation was published by Mikami and Ohmura.[14]

The selective introduction of a labelled atom into organic structures offers a continuing challenge to organic chemists due in part to the relatively small number of enriched starting materials and/or reagents that are commercially available, placing considerable limitations on the choice of strategy. An examination of the published syntheses of tropinone (**5**) showed many of them not to be compatible with an efficient and selective introduction of deuterium into the desired positions. For example, to follow the work of Mikami and Ohmura,[14] the preparation of the required deuteriated *N*-methoxycarbonyl-2,5-dimethoxypyrrolidine derivatives by anodic dimethoxylation of the corresponding carbamate of pyrrolidine was not obvious.[15] In this context, we felt that Robinson's synthesis offered the most attractive access to our targets. It was clear that the success of this approach would be dependent on the preparation of the corresponding di- and mono-labelled 2,5-dialkoxytetrahydrofurans **A** and **B** (Figure 3). Even though the 2,5-dialkoxytetrahydrofurans are an important class of intermediates, mainly for the preparation of various pyrrole derivatives,[16] to the best of our knowledge only two different routes to these compounds have been reported in the literature. In both approaches from furans in alcoholic solution, the unstable 2,5-dialkoxy-2,5-dihydrofurans are hydrogenated after being obtained either by the electrochemical method of Clausson–Kass[17] or by oxidative alkoxylation[18] with bromine or chloride. The key elements to our success in generating deuteriated 2,5-dialkoxytetrahydrofurans **A** and **B** were, first, the introduction of deuterium from a low-cost commercially available deuteriated reagent and, secondly, the use of higher-mass alkyl groups to decrease their volatility, thus facilitating their work-up and purification.

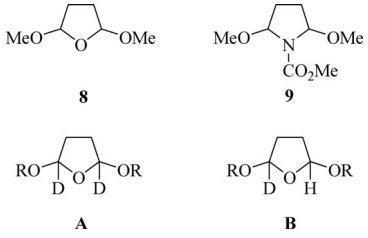
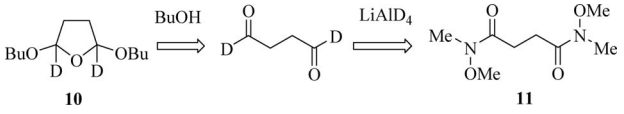


Figure 3. Intermediates of the Robinson (**8**) and Mikami and Ohmura (**9**) syntheses and the deuteriated 2,5-dialkoxytetrahydrofurans **A** and **B** corresponding to **8**.

Results and Discussion

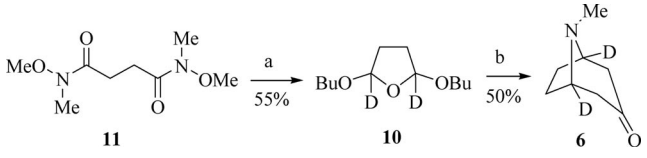
On the basis of these requirements, an obvious synthetic strategy (Scheme 1) to reach our first labelled target **10** was to exploit the well-described chemistry of the Weinreb diamides.[19] Thus, reducing the Weinreb diamide **11** with $LiAlD_4$ (98 atom-% D) and treatment of the reaction mixture directly with an acidic aqueous solution of BuOH should afford the di-deuteriated 2,5-dibutoxytetrahydrofuran (**10**),[20] which is less volatile than the dimethoxy derivative **8**.



Scheme 1. Retrosynthetic scheme for the preparation of 2,5-dibutoxytetrahydrofuran (**10**).

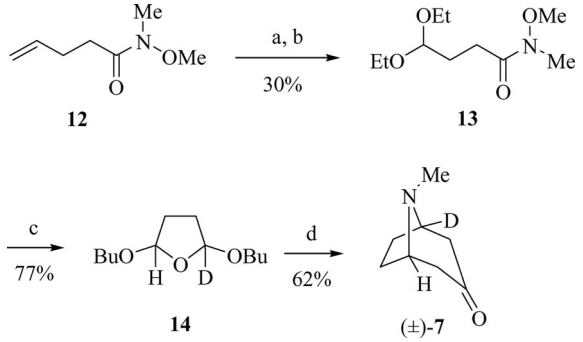
The Weinreb diamide **11** was prepared from succinyl chloride as described previously in the literature.[21] With this substrate in hand, reduction with $LiAlD_4$ followed by treatment with BuOH was then investigated under various conditions. The best result was obtained when the Weinreb diamide **11** was treated at 0 °C in THF with a slight excess of $LiAlD_4$ followed by the slow addition of an aqueous solution of BuOH (Scheme 2). Under these conditions, the desired labelled 2,5-dibutoxytetrahydrofuran (**10**) was isolated in 55% crude yield for this one-pot two-step process. This material was suitable for use in the Robinson synthesis without further purification. Note that, although with both

2,5-dibutoxytetrahydrofurans **10** and **14** the *trans* and *cis* isomers could be isolated in pure form after purification on silica gel chromatography, a slow isomerisation occurred to afford a *cis*/*trans* mixture (see the NMR spectra in the Supporting Information). Careful monitoring of the hydrolysis of 2,5-dibutoxytetrahydrofuran (**10**) by TLC ensured that the formation of succinaldehyde[22] was complete before the addition of this solution to a mixture of methylamine and acetone-1,3-dicarboxylic acid following the Robinson protocol. The pure, doubly labelled tropinone **6** was isolated in 50% crude yield. The absence of proton signals from the C-1 and C-5 bridge positions is immediately apparent by inspection of the ^{1}H NMR spectrum (see the Supporting Information), which indicates a high level of deuteriation ([^{2}H]/[^{1}H] ≥ 95:5).[23] In contrast, no other positions are deuteriated, as evidenced by a comparison of the calculated (142.1201) and measured HRMS values (142.1200). In all other respects, the ^{1}H NMR spectrum is identical to that of authentic tropinone, taking into account the altered coupling pattern due to the presence of the bridgehead deuterium atoms.



Scheme 2. Reagents and conditions: (a) $LiAlD_4$, THF, 0 °C, 30 min, then BuOH/H_2O (25:1) followed by 6 M HCl, 55% (crude); (b) 0.3 M HCl, H_2O, 100 °C, 2 h, then addition to a solution of $MeNH_2$, acetone-1,3-dicarboxylic acid, AcONa, concentrated aqueous HCl, H_2O, 2 h, 50 °C, 50%.

For the preparation of the mono-deuteriated derivative (±)-**7** from the unsaturated Weinreb **12**, the idea was to use ozonolysis followed by protection of the resulting aldehyde as the corresponding acetal in order to differentiate the two potential aldehyde functions, leading to the reduction of the amide with $LiAlD_4$, as outlined in Scheme 3. Ozonolysis of the unsaturated Weinreb amide **12**, prepared from the commercially available carboxylic acid, was carried out in CH_2Cl_2 solution at –78 °C followed by reduction of the intermediate ozonide with Me_2S. After work-up, the crude aldehyde intermediate was treated with triethyl orthoformate[24] in ethanol in the presence of a catalytic amount of APTS to afford the desired acetal[25] **13** in 30% yield for the two steps after purification. This material **13** was reduced with $LiAlD_4$ and treated as described previously for **10** to afford the mono-deuteriated dibutoxytetrahydrofuran **14** in 77% crude yield. This material was sufficiently pure to be used directly in the Robinson synthesis under the same conditions as those used for **6**. The pure mono-labelled tropinone (±)-**7** was isolated in 62% yield. As previously, there was no evidence for either loss of deuterium or of deuterium being introduced elsewhere into the molecule. Thus, integration of the C-1/C-5 protons in the ^{1}H NMR spectrum gives [^{2}H]/[^{1}H] ≥ 98:2 (see the Supporting Information), as would be predicted for a high level of monodeuteriation at the C-1 position. Similarly, the excellent correlation between the HRMS values, 141.1138 and 141.1137, calculated and found, respectively, confirms that the deuterium is only present at the bridge carbon position. In all other respects, the ^{1}H NMR spectrum is identical to that of authentic tropinone taking into account the altered coupling pattern due to the presence of the bridgehead deuterium.



Scheme 3. Reagents and conditions: (a) O_3, CH_2Cl_2, –78 °C, then Me_2S; (b) $(EtO)_3CH$, EtOH, cat. APTS, 6 h, room temp., 30% for the two steps; (c) $LiAlD_4$, THF, 0 °C, 30 min, then BuOH/H_2O (25:1) followed by 6 M HCl, 3 h, room temp., 77% (crude); (d) 0.3 M HCl, H_2O, 100 °C, 2 h, then addition to a solution of $MeNH_2$, acetone-1,3-dicarboxylic acid, AcONa, concentrated aqueous HCl, H_2O, 2 h, 50 °C, 62%.

Conclusions

We have reported herein a short practical synthesis of labelled tropinone in which deuterium is incorporated in a specific manner at the bridgehead carbons C-1 and C-5. Deuterium can be introduced at one position, or simultaneously at both. The key to the approach is the preparation of appropriately labelled deuteriated 2,5-dibutoxytetrahydrofurans **10** and **14** in which the introduction of the heavier alkyl substituent markedly improves the overall yield while diminishing volatility. This approach is scalable and avoids the use of costly deuteriated reagents. Furthermore, modifications such as their reduction to tropine[26] and the synthesis of the corresponding biologically active esters[27] can be achieved by using standard procedures. We can anticipate that these deuteriotropinones will find application in a wide range of studies of the metabolism of tropane alkaloids, notably the calystegines, in studies of biologically active tropane derivatives, and as substrates for probing the mechanisms of tropine-metabolising enzymes.

Experimental Section

Lithium aluminium deuteride (98 atom-% ^{2}H) was purchased from Acros Organics (www.acros.com).

***N*,*N*′-Dimethoxy-*N*,*N*′-dimethylsuccinimide (11):** Triethylamine (18.1 mL, 129.9 mmol) was added slowly to a suspension of *N*,*O*-dimethylhydroxylamine (6.3 g, 64.5 mmol) and succinyl chloride (5.0 g, 32.3 mmol) in CH_2Cl_2 (80 mL) at 0 °C under nitrogen. After stirring for 2 h the solution was warmed to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution. The lay-

ers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine, dried with $MgSO_4$ and evaporated under reduced pressure. The crude material (6.4 g) was used directly in the next step. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.72 (s, 4 H), 3.13 (s, 6 H), 3.69 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 32.0, 61.0, 173.2 ppm.

[2,5-$^2H_2$]2,5-Dibutoxytetrahydrofuran (10): $LiAlD_4$ (1.37 g, 36.3 mmol) was added to a solution of *N*,*N*′-dimethoxy-*N*,*N*′-dimethylsuccinimide (**11**; 2.50 g, 12.3 mmol) in THF (90 mL) at 0 °C. After stirring for 30 min at 0 °C, a mixture of *n*-butanol (300 mL) and water (11.3 mL) was added slowly, followed by aqueous 6 M HCl (37.7 mL). After stirring at room temperature for 4 h, the mixture was washed with saturated $NaHCO_3$ solution and brine, and dried with $MgSO_4$. The organic layer was filtered and the solvents evaporated. The crude material as a *cis*/*trans* mixture (1.49 g, 55%) was used directly in the next step without further purification. An analytical sample containing *trans*-[2,5-$^2H_2$]2,5-dibutoxytetrahydrofuran (**10**) as the major isomer was obtained by column chromatography on silica gel (pure petroleum ether to 96:4 petroleum ether/diethyl ether as eluent). Evaporation of the appropriate fractions gave [2,5-$^2H_2$]2,5-dibutoxytetrahydrofuran (**10**) as a colourless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 6 H), 1.26–1.40 (m, 4 H), 1.45–1.57 (m, 4 H), 1.70–1.82 (m, 2 H), 2.04–2.10 (m, 2 H), 3.40 (td, *J* = 6.7, *J* = 9.4 Hz, 2 H), 3.65 (td, *J* = 6.7, *J* = 9.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 19.3, 30.1, 31.8, 67.4, 103.8 ($J_{C\text{-}D}$ = 34.4 Hz) ppm.

[1,5-$^2H_2$]Tropinone (6): Aqueous 0.3 M HCl (1.8 mL) was added to the previous crude [2,5-$^2H_2$]2,5-dibutoxytetrahydrofuran (**10**; 500 mg, 2.3 mmol) and the solution was heated at 100 °C for 2 h. After cooling to 10 °C this mixture was added to a solution containing water (2.2 mL), NaOAc (1.06 g, 12.9 mmol), $MeNH_2$ (322 μL, 40% aqueous solution, 3.6 mmol), conc. HCl (308 μL, 3.6 mmol) and acetone-1,3-dicarboxylic acid (540 mg, 3.6 mmol). The mixture was warmed at 50 °C for 2 h and then cooled to ambient temperature. A 2 M NaOH solution was added to give pH 10. After the addition and complete dissolution of NaCl (600 mg), the solution was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were acidified with aqueous 0.1 M HCl to give pH 2. The acidified aqueous layer was extracted three times with CH_2Cl_2. The aqueous phase was basified with a 0.1 M NaOH solution to give pH 13 and then extracted with CH_2Cl_2. The combined organic layer was concentrated under reduced pressure to give pure [1,5-$^2H_2$]tropinone (**6**; 160 mg, 50%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.62 (m, 2 H), 2.09 (d, *J* = 7.8 Hz, 2 H), 2.17 (d, *J* = 16.4 Hz, 2 H), 2.47 (s, 3 H), 2.67 (d, *J* = 15.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 38.2, 47.4, 60.4 ($J_{C\text{-}D}$ = 22.3 Hz), 209.5 ppm. HRMS (ESI): calcd. for $C_{12}H_{23}D_2NO$ $[M + H]^+$ 142.1201; found 142.1200.

***N*-Methoxy-*N*-methylpent-4-enamide (12):** 4-Pentenoic acid (3 g, 30.0 mmol) and $SOCl_2$ (3.2 mL, 44.9 mmol) were heated at 60 °C for 5 h. Once cooled, the corresponding acid chloride was added at 0 °C to a solution of *N*,*O*-dimethylhydroxylamine (4.38 g, 44.9 mmol) in CH_2Cl_2 (150 mL). Then triethylamine (13 mL, 89.9 mmol) was added dropwise over 15 min. After stirring for 30 min at 0 °C, the solution was warmed to room temperature over 2 h. The mixture was quenched with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and washed with brine, dried with $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by column chromatography (silica gel; 100 to 50:50 petroleum ether/diethyl ether as eluent). Evaporation of the appropriate fractions gave *N*-methoxy-*N*-methylpent-4-enamide (3.54 g, 83% over two steps). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33–2.39 (m, 2 H), 2.40–2.53 (m, 2 H), 3.16 (s, 3 H), 3.66 (s, 3 H), 4.91–5.11 (m, 2 H), 5.80–5.89 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 30.9, 31.9, 60.9, 114.8, 137.2, 173.5 ppm. HRMS (ESI): calcd. for $C_7H_{13}NO_2$ $[M + H]^+$ 144.1025; found 144.1024.

4,4-Diethoxy-*N*-methoxy-*N*-methylbutanamide (13): Ozone was bubbled through a solution of *N*-methoxy-*N*-methyl-4-pentanamide (**12**; 1.7 g, 11.9 mmol) in CH_2Cl_2 (90 mL) at –78 °C until a blue colour persisted. Then Me_2S (8.7 mL, 118 mmol) was added and the reaction mixture was stirred and warmed to room temperature overnight. The resulting crude product was washed with brine and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde was used in the next step without further purification. Triethyl orthoformate (1.7 mL, 10.1 mmol) and a catalytic amount of APTS (133 mg, 0.7 mmol) was added to a solution of the aldehyde (1.02 g, 7.0 mmol) in ethanol (30 mL). After stirring for 6 h at room temperature the reaction mixture was quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The crude material (1.30 g) was purified by column chromatography on silica gel (80:20 to 35:65 petroleum ether/diethyl ether as eluent). Evaporation of the appropriate fractions gave 4,4-diethoxy-*N*-methoxy-*N*-methylbutanamide (**13**; 840 mg, 30% over two steps) as a colourless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.0 Hz, 6 H), 1.91 (dt, *J* = 5.6, *J* = 7.5 Hz, 2 H), 2.48 (t, *J* = 7.4 Hz, 2 H), 3.14 (s, 3 H), 3.39–3.52 (m, 2 H), 3.60–3.72 (m, 2 H), 3.65 (s, 3 H), 4.52 (t, *J* = 5.5 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 26.7, 28.3, 32.1, 61.1, 61.3, 102.9, 174.0 ppm.

[2-^{2}H]2,5-Dibutoxytetrahydrofuran (14): $LiAlD_4$ (206 mg, 4.9 mmol) was added to a solution of 4,4-diethoxy-*N*-methoxy-*N*-methylbutanamide (**13**; 863 mg, 3.9 mmol) in THF (45 mL) at 0 °C. After stirring for 30 min at 0 °C a solution of *n*-butanol (80 mL) and water (2.9 mL) was added slowly followed by aqueous 6 M HCl (10.1 mL). The resulting mixture was stirred at room temperature for 3 h and then washed with a solution of K_2CO_3 until pH 7. The organic layer was evaporated under reduced pressure to give crude [2-^{2}H]2,5-dibutoxytetrahydrofuran (**14**; 655 mg, 77%) as a *cis*/*trans* mixture, which was used directly in the next step without further purification. An analytic sample containing *trans*-**14** as the major isomer was obtained by column chromatography on silica gel (pure petroleum ether to 50:50 petroleum ether/diethyl ether as eluent). Evaporation of the appropriate fractions gave [2-^{2}H]2,5-dibutoxytetrahydrofuran (**14**) as a colourless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 6 H), 1.28–1.38 (m, 4 H), 1.47–1.58 (m, 4 H), 1.73–1.81 (m, 2 H), 2.06–2.12 (m, 2 H), 3.32–3.44 (m, 2 H), 3.62–3.71 (m, 2 H), 5.15–5.19 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 19.2, 29.6, 31.0, 67.5, 103.8 ($J_{C\text{-}D}$ = 34.4 Hz), 104.1 ppm.

[1-^{2}H]Tropinone (7): Aqueous 0.3 M HCl (1.8 mL) was added to the crude [2-^{2}H]2,5-dibutoxytetrahydrofuran (**14**; 250 mg, 1.15 mmol) and heated at 100 °C for 2 h. After cooling to 10 °C, this mixture was added to a solution containing water (1.1 mL), NaOAc (528 mg, 6.44 mmol), $MeNH_2$ (160 μL, 40% aqueous solution, 1.84 mmol), conc. HCl (153 μL, 1.84 mol) and acetone-1,3-dicarboxylic acid (268 mg, 1.84 mmol). The mixture was warmed at 50 °C for 2 h, cooled to ambient temperature and worked up as described for [1,5-$^2H_2$]tropinone (**6**) to give [1-^{2}H]tropinone (**7**;

100 mg, 62%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52–1.62 (m, 2 H), 2.07 (dd, J = 3.1, J = 7.9 Hz, 2 H), 2.16 (d, J = 16.4 Hz, 2 H), 2.45 (s, 3 H), 2.65 (d, J = 15.8 Hz, 2 H), 3.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 38.2, 47.5, 60.3 ($J_{C\text{-}D}$ = 22.3 Hz), 60.7, 209.5 ppm. HRMS (ESI): calcd. for $C_{12}H_{21}DNO$ $[M + H]^+$ 141.1138; found 141.1137.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of **6**, **7**, **10**–**14**.

Acknowledgments

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[24] Note that direct treatment of the crude aldehyde in *n*BuOH in the presence of APTS to yield the corresponding acetal is less efficient.
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