Note

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A method for the preparation of [$^{13}C_6$]-labelled 2-substituted naphthalenes

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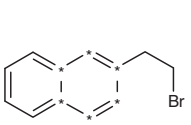
A reliable route is described for the preparation of various 2-substituted derivatives of [1,2,3,4,4a,8a-$^{13}C_6$]-naphthalene *via* the bromide 10. The approach is used to prepare [*naphthalene*-1,2,3,4,4a,8a-$^{13}C_6$]-2-(2-bromoethyl)naphthalene (1), a key intermediate in the synthesis of labelled SR57746A, Xaliproden (2).

Keywords: ^{13}C; [$^{13}C_6$]-naphthalene; [$^{13}C_6$]-2-bromonaphthalene; [$^{13}C_6$]-SR57746A; benzannulation; 7-bromo-1-[4a; 5; 6; 7; 8; 8a-$^{13}C_6$]tetralone

Introduction

A variety of routes to a number of singly and multiply ^{13}C-labelled arenes,[1] and specifically to naphthalenes with defined labelling patterns,[2,3] have been described in the literature in recent years. Many of the methods described are somewhat limited in scope,[2] but there is one convenient and reliable approach that appears consistently in the literature, involving annulation of a second ring onto an existing benzene framework, and has been used for the generation of both singly and multiply labelled naphthalenes.[1,3] In this paper, we report the adaptation of this sequence to the synthesis of 2-substituted [$^{13}C_6$]-naphthalenes, exemplified by [*naphthalene*-1,2,3,4,4a,8a-$^{13}C_6$]-2-(2-bromoethyl)naphthalene (**1**), which was required for the synthesis of the neurotropic and neuroprotective agent Xaliproden,[4] in labelled form ([*naphthalene*-1,2,3,4,4a,8a-$^{13}C_6$]-SR57746A, **2**). As **2** was to be used in human comparative bioavailability studies, it was necessary to develop a route which was robust, and where it would be possible to ensure that any side-products could be removed efficiently. Indeed, the choice of labelling pattern was made following the examination of potential routes to the alternative labelled form **3**, which were abandoned in view of difficulties encountered in separating side-products generated during the introduction of a trifluoromethyl group onto a labelled arene precursor.[4]



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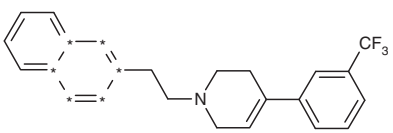

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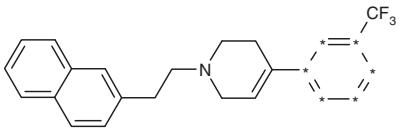

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Results and discussion

The preparation of bromide **1** is outlined in Scheme 1. Generation of naphthalenes with one or two labels in the ring that is being built up is well precedented,[1] and a very similar sequence to that illustrated has been used to prepare 1,4-dilabelled 1-tetralone from 1,4-dilabelled succinic anhydride.[5] In our case, Friedel-Crafts acylation of [$^{13}C_6$]-bromobenzene with succinic anhydride, followed by Huang-Minlon reduction of the keto acid (**4**), gave [*benzene*-$^{13}C_6$]-4-(4-bromophenyl)butanoic acid (**5**). It was necessary to ensure that the formation of the hydrazone derived from **5** was complete before heating the reaction mixture, in order to avoid formation of the pyrazinone **6**; to this end, it was desirable to stir the mixture for an extended period at room temperature and then at 90°C before refluxing. Polyphosphoric acid-promoted intramolecular Friedel-Crafts acylation was carried out on this intermediate to give 7-bromo-1-tetralone (**7**).[6] This in turn was reduced with sodium borohydride, and the intermediate alcohol dehydrated by heating in toluene with *p*-toluenesulfonic acid to give the dihydronaphthalene **8**,[7] from which the fully aromatic system was obtained by dehydrogenation with DDQ in dioxane. [1,2,3,4,4a,8a-$^{13}C_6$]-2-Bromonaphthalene (**9**) was thereby prepared by benzannulation of [$^{13}C_6$]-bromobenzene in an overall yield of 25%. Efficient lithium/halogen exchange occurred on treatment of **9** with *tert*-butyllithium, the lithiated species being quenched in the present case with ethylene oxide[8] to give **10**, accompanied by a small quantity of the parent naphthalene, **11**. Final conversion of **10** into **1** was conveniently carried out using hydrobromic acid at reflux.[8]

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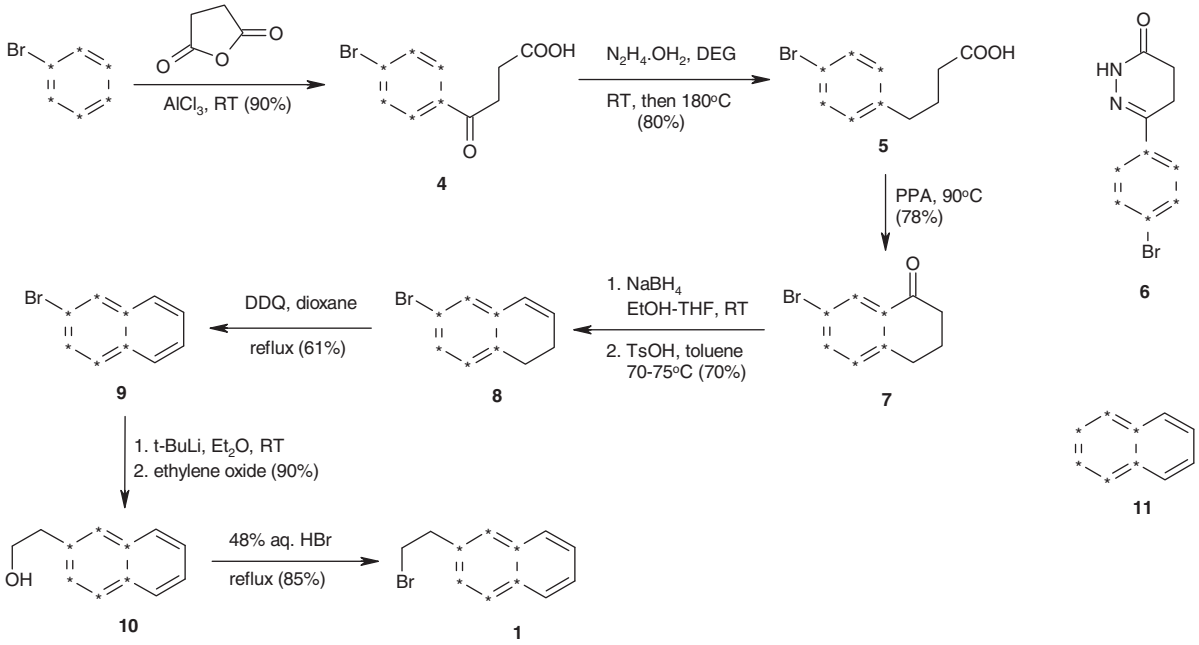

Scheme 1. Preparation of **1** from [$^{13}C_6$]-bromobenzene.

In principle, a range of 2-substituted labelled naphthalenes should be available from intermediate **10** and, given the commercial availability of [$^{13}C_2$]- and [$^{13}C_4$]-succinic acids, the approach is also applicable to the preparation of 2-substituted naphthalenes with a range of substitution patterns.

Experimental

All NMR spectra were recorded using a Jeol GSX-270 instrument, unless otherwise indicated. Low- and high-resolution (electron impact) mass spectra were recorded using a VG Autospec magnetic sector instrument at the University of York. Reagents were obtained commercially; in particular, [$^{13}C_6$]bromobenzene (99 atom %) was purchased from Isotec Ltd. and Cambridge Isotope Laboratories.

[*benzene*-$^{13}C_6$]-4-(4-Bromophenyl)-4-oxobutanoic Acid (4)

Aluminium (III) chloride (21.559 g, 0.162 mol) was added to a stirred suspension of succinic anhydride (7.729 g, 77 mmol) in [$^{13}C_6$]-bromobenzene (12.639 g, 77 mmol). The mixture was stirred at room temperature for 18 h, then poured onto a mixture of ice and concentrated hydrochloric acid (500 ml). The resulting suspension was stirred for 45 min, filtered, and the solid washed with water and air-dried to give **4** (18.304 g, 90%) as a white solid. $\delta_H(CDCl_3)$ 2.84 (2H, *t*), 3.28 (2H, *t*), 7.44 (2H, dm), 8.04 (2H, dm); *m/z* 262, 264 (M^+), 245, 247 (M-.OH), 189, 191 (100%); HRMS 261.9938 (calc. for $C_4^{13}C_6H_9BrO_3$ 261.9948).

[*benzene*-$^{13}C_6$]-4-(4-Bromophenyl)butanoic Acid (5)

4 (18.304 g, 70 mmol.) was redissolved in diethylene glycol (180 ml) at 60°C, potassium hydroxide (9.853 g) in water (15 ml) was added, and the deep yellow solution was stirred for a further 30 min while cooling to room temperature. A nitrogen atmosphere was established and hydrazine hydrate (5.9 ml, 0.105 mol) was added. The mixture was stirred for 12 h, then heated at 90°C for 30 min, and then at 180°C for 9 h, cooled, and added to 2 M hydrochloric acid (1400 ml) and extracted four times with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel (400 g) in hexane: ethyl acetate (3:1) containing glacial acetic acid (0.5%), followed by azeotropic removal of traces of acetic acid using toluene, to give **5** (14.567 g, 84%) as a white solid, $\delta_H(CDCl_3)$ 1.96 (2H, *m*), 2.38 (2H, dd), 2.62 (2H, *m*), 6.92 (2H, dm), 7.54 (2H, dm); *m/z* 248, 250 (M^+), 188, 190 (100%, M-CH_3COOH), 175, 177 ($C_7H_6Br^+$); HRMS 248.0145 (calc. for $C_4^{13}C_6H_{11}BrO_2$ 248.0156).

[4a,5,6,7,8,8a-$^{13}C_6$]-7-Bromo-3,4-dihydro-2H-naphthalen-1-one (7)

A mixture of **5** (14.567 g, 58 mmol.) and 85% polyphosphoric acid (84 g) was heated at 90°C for 90 min, and then diluted with water. The mixture was extracted three times with ethyl acetate, and the combined extracts were washed with aqueous sodium hydrogencarbonate and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel in with hexane: ethyl acetate (95:5) to give **7** (10.498 g, 78%) as a white solid, m.p. 69–71°C. $\delta_H(CDCl_3)$ 2.13 (2H, *tt*), 2.66 (2H, *t*), 2.93 (2H, br), 7.17 (1H, dm, $^1J_{CH}$ *ca.* 160 Hz), 7.56 (1H, dm, $^1J_{CH}$ *ca.* 165 Hz), 8.18 (1H, dm, $^1J_{CH}$ *ca.* 165 Hz); $\delta_C(CDCl_3)$ 120.6 (ddd), 129.7 (ddd), 130.85 (ddd), 134.05 (ddd, C4a), 136.1 (ddd), 143.1 (ddd, C8a); *m/z* 230, 232 (100%, M^+), 202, 204 (M-CO), 174, 176 (202-C_2H_2); HRMS 230.0036 (calc. for $C_4^{13}C_6H_9BrO$ = 230.0038).

[4a,5,6,7,8,8a-$^{13}C_6$]-7-Bromo-1,2-dihydronaphthalene (8)

Sodium borohydride (1.201 g, 32 mmol) was added to **7** (10.498 g, 45 mmol.) in ethanol: tetrahydrofuran (1:1, 120 ml) at room temperature. After stirring for 1 h, volatile materials were removed under reduced pressure and 1 M hydrochloric acid (100 ml) was added to the residue. The mixture was extracted three times with ether and the combined extracts were washed with aqueous sodium hydrogencarbonate, dried ($MgSO_4$), and

concentrated to dryness. The residue was redissolved in toluene (200 ml), 4-toluenesulfonic acid (1.071 g, 6 mmol.) was added, and the mixture was stirred for 75 min at 70–75°C. On cooling, the mixture was washed with aqueous sodium hydrogencarbonate and diluted with hexane to 1000 ml. The solution was filtered through silica gel and eluted further with hexane. The filtrates were evaporated to give **8** (6.666 g, 70%) as a pale yellow oil. $\delta_H(CDCl_3)$ 2.33 (2H, m), 2.76 (2H, m), 6.10 (1H, m), 6.40 (1H, m), 6.6–7.6 (3H, m); $\delta_C(CDCl_3)$ 120.6 (ddd), 129.9 (ddd), 130.5 (ddd), 134.05 (ddd), 136.1 (ddd), 143.1 (ddd); *m/z* 214, 216 (M^+), 135 (100%); HRMS 214.0090 (calc. for $C_4^{13}C_6H_9Br = 214.0089$).

[1,2,3,4,4a,8a-$^{13}C_6$]-2-Bromonaphthalene (9)

DDQ (21.450 g, 94 mmol.) was added to a stirred solution of **8** (6.666 g, 31 mmol.) in dioxane (100 ml) and the resulting deep green suspension was heated at 100°C for 75 min. After cooling, the mixture was diluted with 2 M aqueous sodium hydroxide, hexane, and methyl *tert*-butyl ether. The phases were separated and the organic phase was washed five times with 2 M aqueous sodium hydroxide, water, and dried ($MgSO_4$). Solvent was evaporated and the residue was chromatographed on silica gel in hexane to give **9** (4.029 g, 61%) as a white solid, m.p. 56–57°C. $\delta_H(CDCl_3)$ 7.2–8.4 (*m*); *m/z* 212, 214 (M^+), 133 (100%); HRMS 211.9933 (calc. for $C_4^{13}C_6H_7Br$ 211.9932).

[*naphthalene*-1,2,3,4,4a,8a-$^{13}C_6$]Naphthalene-2-ethanol (10)

tert-Butyllithium (1.7 M in pentane; 22.2 ml, 38 mmol.) was added to **9** (4.029 g, 19 mmol.) in ether (100 ml) under nitrogen. After 5 min, a solution of ethylene oxide (approx. 5 ml) in ice-cooled ether (50 ml) was added, and the suspension was stirred for further 30 min. The mixture was quenched by addition of aqueous ammonium chloride and, after further 15 min, the phases were separated. The aqueous phase was re-extracted twice with ether and the combined organic phases were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel in ethyl acetate: hexane (1:4) gave [*1,2,3,4,4a,8a*-$^{13}C_6$]naphthalene (**11**; 0.237 g, 10%), m.p. 80–82°C. δ_H(500 MHz, $CDCl_3$) 7.47 (2H, dm, $^1J_{CH}$ 163 Hz), 7.47 (2H, ddd), 7.84 (2H, dm, $^1J_{CH}$ 157 Hz), 7.84 (2H, m); *m/z* 134, 84, 49 (100%); HRMS 134.0830 (calc. for $C_4^{13}C_6H_8 = 134.0827$). Further elution gave **10** (2.280 g, 67%) as a white solid. m.p. 64°C; $\delta_H(CDCl_3)$ 3.04 (2H, m), 3.95 (2H, td), 7.0–8.2 (7H, m); *m/z* 178 (M^+), 147 (100%).

[*naphthalene*-4a,5,6,7,8,8a-$^{13}C_6$]-2-(2-Bromoethyl)naphthalene (1)

A suspension of **10** (1.913 g, 11 mmol.) in 48% hydrobromic acid (27 ml) was stirred at reflux for 18.5 h, cooled, and extracted three times with toluene. The combined extracts were washed with aqueous sodium hydrogencarbonate, evaporated, and the residue redissolved in hexane (25 ml) and filtered through silica gel (100 g), washing with additional hexane until all of the product had been eluted. Evaporation of the eluate gave **1** (2.187 g, 82.5%) as a white solid. m.p. 61–62°C. $\delta_H(CDCl_3)$ 3.33 (2H, *m*), 3.66 (2H, td), 7.0-8.2 (7H, *m*); *m/z* 240, 242 (M^+), 147 (100%); HRMS 240.0247 (calc. for $C_6^{13}C_6H_{11}^{79}Br = 240.0245$).

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References

[1] T. J. Gregson, J. M. Herbert, E. Row, *J. Label. Compd. Radiopharm.* **2010**.
[2] a) K. Ichinose, Y. Ebizuka, U. Sankawa, *Chem. Pharm. Bull.* **1989**, *37*, 2873; b) W. V. Dower, K. P. C. Vollhardt, *Angew. Chem.* **1982**, *94*, 712; c) H. Budzikiewicz, R. Stolze, *Monatsh. Chem.* **1977**, *108*, 869.
[3] a) P. Auger, M. Malaiyandi, R. H. Wightman, D. T. Williams, *J. Label. Compd. Radiopharm.* **1993**, *33*, 263; b) G. H. Walker, D. H. Hathway, *J. Label. Compd. Radiopharm.* **1976**, *12*, 199; c) C. Wright, G. V. Ullas, *J. Label. Compd. Radiopharm.* **2002**, *45*, 1265.
[4] a) L. Cervo, C. Bendotti, G. Tarizzo, A. Cagnotto, M. Skorupska, T. Mennini, R. Samanin, *Eur. J. Pharmacol.* **1994**, *253*, 139; b) N. Robic, J. P. Noel, *J. Label. Compd. Radiopharm.* **1999**, *42*, 109.
[5] R. Gretler, E. Askitoglu, H. Kühne, M. Hesse, *Helv. Chim. Acta* **1978**, *61*, 1730.
[6] M. S. Newman, S. Seshadri, *J. Org. Chem.* **1962**, *76*, 27.
[7] L. M. Jackman, D. T. Thompson, *J. Chem. Soc.* **1961**, 4794.
[8] P. Cagniant, G. Jecko, D. Cagniant, *Bull. Soc. Chim. Fr.* **1961**, 1934.