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# Ring-chain tautomerism in 2,2-bis(2-thienyl)-tetrahydrofurans: preparation of [*butene*-$^2H_5$]-tiagabine

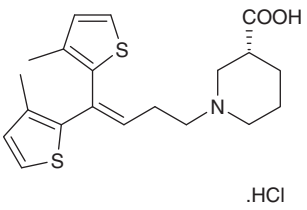
**John M. Herbert[a]* and Trevor W. Mathers[a]**

**A concise preparation of [*butene*-$^2H_5$]-tiagabine hydrochloride starting from [$^2H_6$]-γ-butyrolactone is described. It was necessary to ring-open the labeled γ-butyrolactone precursor before the addition of 2-thienyllithium to avoid cyclisation of the intermediate to a 2,2-bis(2-thienyl)tetrahydrofuran.**

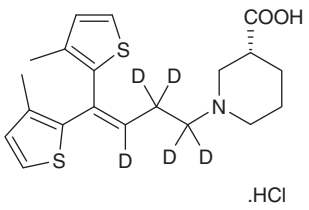
**Keywords:** 2,2-bis(2-thienyl)tetrahydrofuran; [butane-$^2H_5$]-tiagabine; Gabitril; deuterium; piperidines

## Introduction

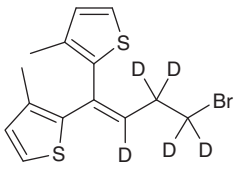
Tiagabine (Gabitril™, **1a**) is an anticonvulsive believed to act by blocking GABA reuptake into presynaptic neurons.[1] In order to facilitate the development of mass spectrometric assays for tiagabine, it was necessary to prepare a stable isotope-labelled mass spectrometric standard for **1a**. In principle, the desired labelled form **1b** could be prepared following the published preparation of **1a**[2]: treatment of labelled methyl 4-bromobutyrate with an excess of 3-methyl-2-thienyllithium followed by acid-catalysed dehydration of the product to afford the homoallylic bromide **2b**, coupling of which with ethyl R(+)-nipecotate (**3**) would give **1b**. However, while no suitably labelled form of 3-bromobutyric acid or an ester was available commercially, [$^2H_6$]-γ-butyrolactone is readily available and was therefore chosen as the starting point.



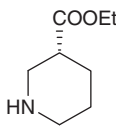

**1a**




**1b**




**2b**




**3**

## Results and discussion

The formation of 2,2-diaryltetrahydrofurans,[3] and of 2,2-bis(2-thienyl)tetrahydrofurans in particular,[4] upon treatment of γ-butyrolactone with an arylmetallic reagent is well known. Generally, treatment of 2,2-bis(2-thienyl)tetrahydrofurans with acid results in ring-opening to give the isomeric homoallylic alcohol (Scheme 1),[4] suggesting that the ring-opened form is thermodynamically favoured.

In trials with unlabelled γ-butyrolactone, addition of excess 3-methyl-2-thienyllithium gave the expected diol **4**, from which acid-promoted elimination of water gave a mixture of the homoallylic alcohol **5** and the tetrahydrofuran **6** (Scheme 2). In contrast to literature precedents, extended treatment of **6** with acid did not result in ring-opening to **5**. Indeed, although **5** appeared to be kinetically favoured, the thermodynamically favoured product proved to be the tetrahydrofuran (**6**), with hydrochloric acid in tetrahydrofuran at room temperature giving principally the homoallylic alcohol whereas heating in toluene in the presence of *p*-toluenesulfonic acid gave **6** almost exclusively after an extended period. Other acid conditions gave mixtures of **5** and **6**, but in all cases slow cyclisation of **5** occurred after its isolation. In the absence of acid, **4** underwent thermal elimination under GC conditions (this is presumed to have occurred in the injector which was maintained at 250°C) to give **6** exclusively. Both **5** and **6** were converted into **2a** by treatment with carbon tetrabromide and triphenylphosphine, and indeed **2a** was formed directly by the treatment of **4** with these reagents, but in each case the yield of **2a** was modest at best. This is not conclusive evidence of a tautomeric equilibrium

*Isotope Chemistry and Metabolite Synthesis Department, Sanof-Aventis, Willowburn Avenue, Alnwick, Northumberland NE66 2JH, UK*

**Correspondence to: John M. Herbert, Isotope Chemistry and Metabolite Synthesis Department, Sanofi-Aventis, Willowburn Avenue, Alnwick, Northumberland NE66 2JH, UK.*
*E-mail: john.herbert@sanofi-aventis.com*

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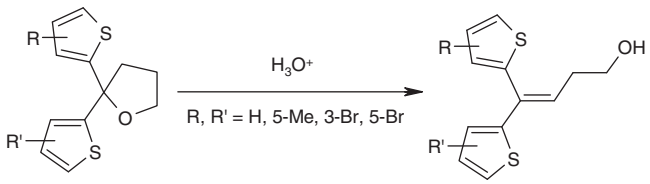
between **5** and **6** since, in principle, **2a** could be formed from **6** as well as from **5**. However, it does appear likely that this tautomerism is occurring and that the equilibrium is displaced very strongly in favour of **6**.

The ease of cyclisation to give **6** is readily attributed to the Thorpe-Ingold effect exerted by the geminal thienyl substituents. However, this effect is clearly present in the previously reported cases also,[4] and the single difference between **5** and previously reported analogues is the presence of the methyl group at C3 of both thiophene units; this is unlikely to have a large effect upon the stability of **6**, but the steric interaction between the methyl groups on the two thienyl substituents, assuming that these are coplanar, could destabilise **5** sufficiently to displace the equilibrium completely in favour of **6**.

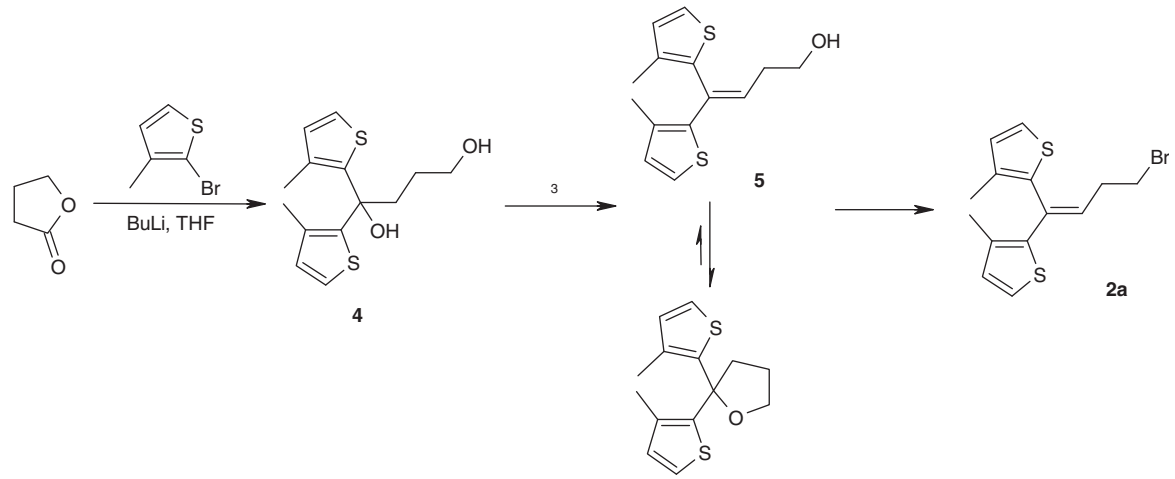



**Scheme 1.** Ring-opening of 2,2-bis(2-thienyl)tetrahydrofurans in acid.[4]

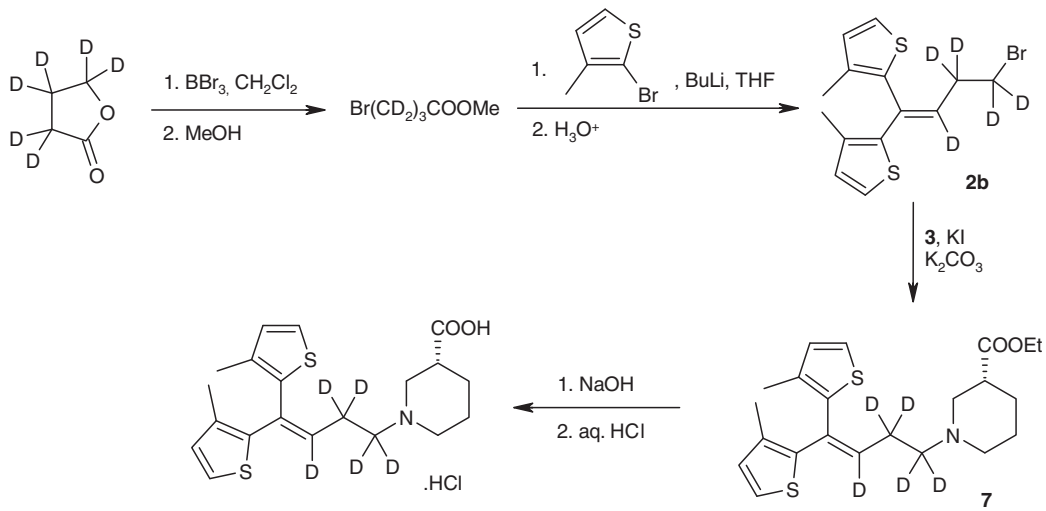
Since the direct preparation of **2a** from γ-butyrolactone was inefficient, and separation of **2a** from **6** following the bromination step was difficult, we reverted to the original route for the preparation of **2b**.[2] The key step in this sequence was the one-pot boron tribromide-mediated ring-opening of [$^2H_6$]-γ-butyrolactone with methanolysis of the intermediate to give methyl [$^2H_6$]-4-bromobutyrate.[5] Subsequent addition of 3-methyl-2-thienyllithium followed by acid-promoted elimination of the intermediate alcohol proceeded smoothly to give **2b**, which was coupled with ethyl R(+)-nipecotate (Scheme 3). Finally, straightforward hydrolysis and salification of the ester intermediate **7** gave [*butene*-$^2H_5$]-tiagabine (**1b**) hydrochloride essentially as described for the unlabelled material in an overall 24% yield.

## Experimental

All n.m.r. spectra were recorded using a Jeol GSX-270 instrument. Low-resolution mass spectra were acquired using a Hewlett-Packard HP5890 GC connected to a Hewlett-Packard HP5972 MSD instrument, while high-resolution mass spectra




**Scheme 2.** Products from the reaction between 3-methyl-2-thienyllithium and γ-butyrolactone.




**Scheme 3.** Preparation of [*butene*-$^2H_5$]-tiagabine hydrochloride, **1b**.

were recorded using a Bruker Micro-TOF instrument. Reagents were obtained commercially, with [$^2H_6$]-γ-butyrolactone being obtained from Isotec Inc. Ethyl R(+)-nipecotate was obtained by resolution of racemic material using L-tartaric acid;[6] the material obtained by these means had an enantiomeric excess of 91% as determined from $^1H$ n.m.r. of the urea formed upon treatment with 1-(1-naphthyl)ethyl isocyanate.[7]

*1,1-Bis(3-methyl-2-thienyl)butane-1,4-diol* (**4**). 2-Bromo-3-methyl thiophene (1.932 g, 11 mmol) in ether (15 ml) was added under nitrogen at 5–10°C to a stirred solution of butyllithium (1.6 M in hexanes: 7.5 ml, 12 mmol) in ether (7.5 ml). The mixture was stirred for 15 min, cooled to −60°C, and γ-butyrolactone (0.330 ml, 4.3 mmol) was added. After a further 2.5 h, water (15 ml) was added followed by 1 M hydrochloric acid (15 ml). The organic phase was separated and the aqueous phase re-extracted with ether. The combined ethereal phases were washed with water and brine, and dried ($MgSO_4$). Solvent was removed under reduced pressure to leave **4** (1.025 g, 84%) as a white solid. $\delta_H(CDCl_3)$ 1.59 (2H, m), 1.85 (6H, s), 2.45 (2H, t), 3.54 (2H, t), 6.76 (2H, d), 7.12 (2H, d); *m/z* 282 ($M^+$), 264 (M-$H_2O^+$), 233, 223, 125 (100%).

*Example Procedure: 4,4-bis(3-methyl-2-thienyl)-3-buten-1-ol* (**5**), and *2,2-bis(3-methyl-2-thienyl)tetrahydrofuran* (**6**). A solution of **4** (304 mg, 1.1 mmol) in toluene (30 ml) containing 4-toluenesulfonic acid (22 mg) was heated at reflux for 45 min, cooled, and washed with aqueous sodium hydrogencarbonate. The organic phase was dried ($MgSO_4$) and solvent was removed under reduced pressure. Column chromatography of the residue in ethyl acetate–hexane (1:3) on silica gel gave **6** (130 mg, 45%). $\delta_H(CDCl_3)$ 1.97 (6H, s), 2.07 (2H, pentet), 2.60 (2H, t), 4.05 (2H, t), 6.75 (2H, d), 7.04 (2H, d); *m/z* 264 ($M^{+\cdot}$), 249, 207 (100%), 167, 125 (100%); HRMS (esi-TOF) 265.0753 (calc. for $C_{14}H_{17}OS_2$ 265.0715). Further elution gave **5** (91 mg, 32%). $\delta_H(CDCl_3)$ 2.00 (3H, s), 2.05 (3H, s), 2.41 (2H, appears as q), 3.71 (2H, t), 6.09 (1H, t), 6.74 (1H, d), 6.84 (1H, d), 7.05 (1H, d), 7.20 (1H, d); *m/z* 264 ($M^{+\cdot}$), 233, 111 (100%); HRMS (esi-TOF) 265.0730 (calc. for $C_{14}H_{17}OS_2$ 265.0715).

*Methyl [butyric acid-$^2H_6$]-4-bromobutyrate*. Boron tribromide in dichloromethane (1 M; 65 ml) was added to a stirred solution of [$^2H_6$]-γ-butyrolactone (5.0 g, 54 mmol) in dichloromethane (60 ml) under nitrogen at room temperature. The mixture was stirred for 18 h, following which additional boron tribromide in dichloromethane (1 M; 15 ml) was added. After a further 3 h, anhydrous methanol (200 ml) and additional dichloromethane (125 ml) were added. The mixture was stirred for a further 10 min, and then washed with aqueous sodium carbonate, aqueous sodium thiosulfate, and water (200 ml each). The organic phase was dried ($MgSO_4$) and solvents were removed under reduced pressure to leave methyl [*butyric acid*-$^2H_6$]-4-bromobutyrate (6.636 g, 66%) as a colourless liquid. $\delta_H(CDCl_3)$ 3.68 (s); $\delta_H(CHCl_3)$ 2.14, 2.49, 3.44; *m/z* 186, 188 ($M^{+\cdot}$), 155, 157 (M-$^{\cdot}$OMe), 127/129 (155-CO), 77 ($CD_3COOMe^{+\cdot}$, 100%); HRMS($NH_3$-$CI^+$) Found: 204.0505 (calc. for $C_5H_3{}^2H_6BrO_2.NH_4^+$ 204.0506).

### [butene-$^2H_5$]-1,1-Bis(3-methyl-2-thienyl)-4-bromo-1-butene (2b)

Butyllithium in hexanes (1.6 M; 20 ml) was added under nitrogen at 5–10°C to a stirred solution of 2-bromo-3-methylthiophene (5.66 g, 32 mmol) in ether (30 ml). The mixture was stirred for 15 min, and then cooled to −70°C and methyl [*butyric acid*-$^2H_6$]-4-bromobutyrate (2.504 g, 13 mmol) was added. After stirring for a further 3 h at the same temperature, the mixture was quenched by addition of aqueous ammonium chloride and allowed to warm to room temperature. The phases were separated, the aqueous phase was re-extracted twice with ether, and the combined organic phases were washed with brine and evaporated to leave an oil, which was redissolved in 2-propanol (15 ml). Aqueous sulfuric acid (20%, 1.5 ml) was added, and the mixture was stored for 3 h at room temperature. Volatiles were removed under reduced pressure and the residue was diluted with water and extracted three times with dichloromethane. The combined extracts were washed with saturated aqueous sodium hydrogencarbonate, dried ($Na_2SO_4$) and evaporated to leave [*butene*-$^2H_5$]-1,1-bis(3-methyl-2-thienyl)-4-bromo-1-butene as an oil (4.39 g; 70% pure by GC), which was used directly in the next step.

### [butene-$^2H_5$]-Ethyl (R)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate (7)

A suspension of potassium iodide (0.23 g, 1.4 mmol) and potassium carbonate (2.24 g, 16.2 mmol) in acetone containing **2b** (4.394 g, 13.4 mmol) and ethyl R(+)-nipecotate (2.18 g, 13.8 mmol) was stirred at room temperature for 46 h, then filtered. The filtrate was evaporated and the residue was chromatographed in 9:1 hexane-THF on silica gel to give ethyl [*butene*-$^2H_5$]-(R)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate (3.367 g, 62% from methyl [*butyric acid*-$^2H_5$]-4-bromobutyrate). $\delta_H(CDCl_3)$ 1.22 (3H, t), 1.3–1.6 (2H, m), 1.68 (1H, m), 1.92 (1H, m), 2.01 (3H, s), 2.02 (3H, s), 2.12 (1H, t), 2.52 (1H, m), 2.71 (1H, m), 2.93 (1H, m), 3.10 (1H, m), 4.19 (2H, q), 6.74 (1H, d), 6.82 (1H, d), 7.02 (1H, d), 7.18 (1H, d). *m/z* 408 ($M^{+\cdot}$), 172 (100%).

*[butene-$^2H_5$]-Tiagabine hydrochloride* (**1b**). Aqueous sodium hydroxide (12 M, 1.5 ml) was added to a solution of **7** (3.367 g, 8.25 mmol) in ethanol (20 ml). The mixture was stirred for 4 h at room temperature, cooled to 5°C, and acidified to pH 1 with 4 M hydrochloric acid. The mixture was extracted with dichloromethane (400 ml) and the extract washed with water (5 ml). Solvent was removed under reduced pressure and the residue was recrystallised from isopropanol to give [*butene*-$^2H_5$]-tiagabine hydrochloride (2.056 g, 60%), m.p. 182–185°C (lit.[2] 183.5–185.5°C). $[\alpha]_D$ −20° (C 1, $H_2O$). $\delta_H(CD_3OD)$ 1.5–2.3 (4H, m), 1.99 (3H, s), 2.06 (3H, s), 2.7–3.3 (3H, m), 3.3–3.8 (2H, m), 6.80 (1H, d), 6.95 (1H, d), 7.19 (1H, d), 7.39 (1H, d); $\delta_H(CH_3OH$-$CDCl_3)$ 1.99 (2D), 2.60 (2D), 5.40 (1D); *m/z* (esi-TOF) 381 ($MH^+$, 100%), 282, 252; HRMS found: 381.1718 (calc. for $C_{20}H_{21}{}^2H_5NO_2S_2$ 381.1719).

## Acknowledgements

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