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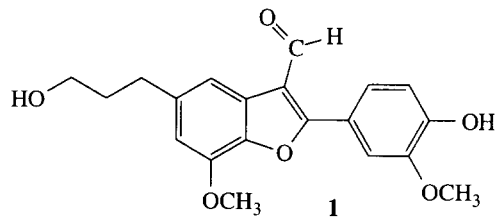
A NEW SYNTHESIS OF THE BENZOFURAN ADENOSINE ANTAGONIST XH-14

Sally A. Hutchinson, Henning Luetjens, and Peter J. Scammells*

School of Biological and Chemical Sciences, Deakin University, Geelong Vic 3217, Australia.

Abstract: 5-(3-Hydroxypropyl)-7-methoxy-2-(3'-methoxy-4'-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (XH-14, **1**) has been reported to be a potent A_1 adenosine antagonist. We have developed an efficient synthesis of this compound that should prove valuable for further structure–activity studies. The synthesis incorporates optimised methodology for the selective protection of a hydroxyl group and the *ortho*-bromination of a phenol.

5-(3-Hydroxypropyl)-7-methoxy-2-(3'-methoxy-4'-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (XH-14, **1**) was isolated from the plant *Salvia miltorrhiza* Bunge (Danshen), which has been widely used in China for the treatment of coronary heart diseases such as myocardial infarction and angina pectoris.[1-3] This benzofuran has been reported to bind the A_1 adenosine receptor[4] with high affinity (IC_{50} = 17 nM in a competitive assay with [^{3}H]-N-(R-2-phenylisopropyl)adenosine. Yang et al. devised a total synthesis of **1**, which involved 8 steps from vanillin.[1-3] We now report an alternative strategy that is shorter and introduces the C-2 substituent later in the synthesis, facilitating SAR studies on the importance of this substituent.



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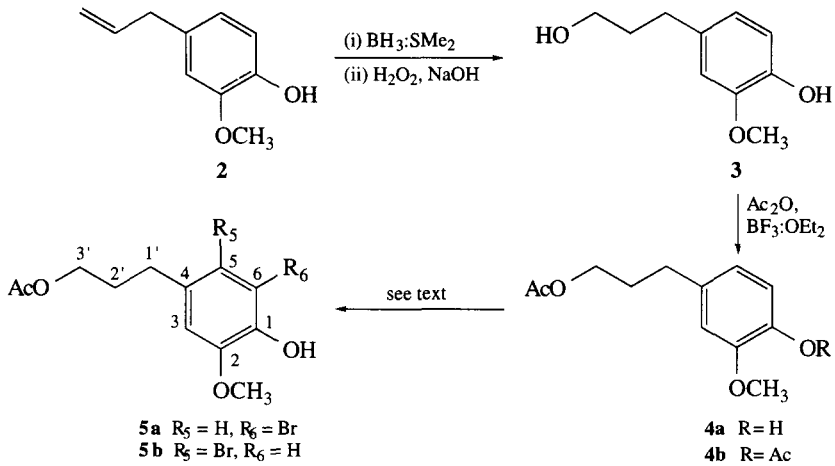
Eugenol (**2**) was chosen as the starting material due to it favourable substitution pattern and ready availability. Hydration, acetylation, and bromination reactions were used to convert eugenol to the key intermediate **5a** (Scheme 1). The *ortho*-bromophenol **5a** was further elaborated to the target benzofuran **1** via cyclisation, debenzylation, and formylation (Scheme 2).

Hydration of the alkene moiety (hydroboration-oxidation) of eugenol (**2**) was initially attempted using borane:THF and later 9-borabicyclo[3.3.1]nonane (9-BBN). In each case negligible amounts of the desired alcohol **3** were isolated. Borane:methyl sulfide proved to be a much more effective reagent, possibly due to its higher concentration (~10 M compared with 0.5 M for 9-BBN).

Selective protection of the primary alcohol in the presence of the phenolic moiety also proved to be problematic. Attempts to benzylate the primary alcohol of **3** under a range of conditions showed poor selectivity. Selective acetylation was attempted using a method developed by Nagao et al.[5] which involved the use of acetic anhydride (3 M equiv) and boron trifluoride diethyerate (0.25 equiv). In our case, this method

afforded the desired mono-acylated product **4a** along with a considerable amount of bis-acetylated material **4b** (~23% by ^{1}H NMR). This by-product proved difficult to remove; base extraction of **4a** resulted in a significant amount of hydrolysis (reconversion to **3**) while distillation and chromatography were unsuccessful due to the similar polarity of the two compounds. Reduction of the amount of acetic anhydride used (to 2.5 M equiv) gave a ratio of mono- to bis-acetylation of 80:20, while further reduction (to 2.0 equiv) improved this ratio to 86:14. An further improvement was achieved by shortening the reaction time. These changes resulted in a slightly lower conversion, but unlike the bis-acylated compound **4b** the starting material **3** could be readily separated by column chromatography. The reaction was scaled up using 2.0 equiv of acetic anhydride and 0.25 equiv of boron trifluoride diethyerate at 0 °C for 5 h.[6] Following purification by chromatography a yield of 77% and a ratio of mono to bis-acetylation of 92:8 was obtained.

Scheme 1



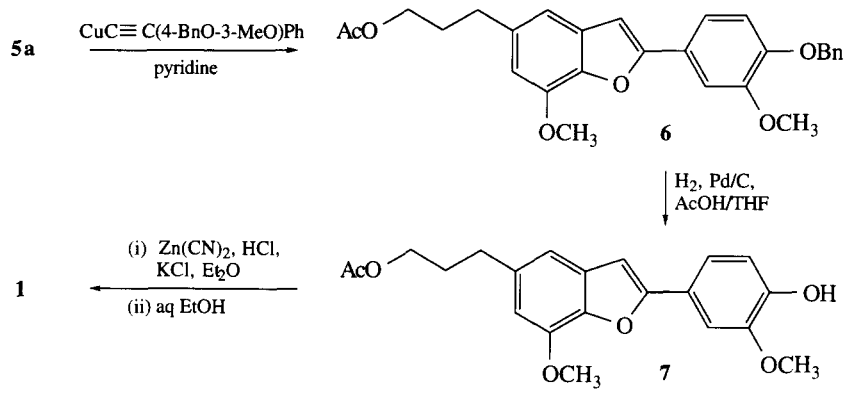
The next step involved bromination of 4-(3'-acetoxypropyl)-2-methoxyphenol (**4a**). The regiochemistry of this reaction was the major concern since substitution was possible at the 5- or 6-positions. Although the methoxy and alkyl groups direct to the 5-position it was hoped that the strong activation of the 6-position by the phenolic OH would result in formation of the desired *ortho*-bromophenol **5a**. Compounds with similar substitution patterns [eugenol and eugenol with the alkene protected by $C_5H_5Fe(CO)_2^+$] have been reported to undergo *ortho*-bromination upon treatment with bromine at 0 °C.[7,8] Initially, bromination of **4** was attempted with bromine in dichloromethane. This was found to produce only the isomer in which the bromine was *meta* to the phenolic OH (**5b**) in 71% yield. The structure of this regioisomer was elucidated using NMR spectroscopy. The long-range HETCOR showed that H-2 (δ 2.6) was coupled to carbons up to three bonds away; C-1', C-3', ArC and C-4' (δ 32.1, 63.8, 112.4 and 131.6, respectively). These couplings would be expected for both possible regioisomers (**5a** or **5b**). However, H-2 was also coupled to the carbon bearing the bromine (C-5) which would only be expected for the 5-bromo compound **5b**. The assignment of C-5 was based on the DEPT spectrum, which indicated that it was a quartenary carbon as well as the chemical shift which was consistent with

a brominated carbon.[9] Further evidence that the undesired isomer had been produced came from the fact that this compound failed to couple with cuprous phenylacetylide to form a benzo[*b*]furan.

The use of *N*-bromosuccinimide (NBS) in the presence of diisopropylamine has been reported to favour *ortho* over *para*-bromination of phenols.[10] It is believed that the NBS reacts with the diisopropylamine to form *N*-bromodiisopropylamine which hydrogen bonds strongly to the phenolic OH resulting in the preference for *ortho*-bromination. After reaction with the phenol the amine is regenerated hence a catalytic amount only is required. Whilst *para*-bromination was not a possibility in our case it was thought that this approach may also overcome the unwanted directing effects of the alkyl and methoxy substituents to give the desired *ortho*-bromophenol **5a**. Compound **4** was treated with NBS and diisopropylamine in dichloromethane at ambient temperature.[11] The ^{1}H NMR spectrum of the purified product showed different chemical shifts for the aromatic and a crystal structure[12] proved conclusively that *ortho*-bromination had occurred.

The key intermediate **5a** was converted to the natural product **1** using the methodology developed by Yang et al.[1-3] (Scheme 2). Briefly, this involved coupling with cuprous (4-benzyloxy-3-methoxy)phenyl acetylide, debenzylation and formylation using a Gatterman–Adams reaction.[13]

Scheme 2



In summary, XH-14 (**1**) was prepared in 6 steps from eugenol and proved to be spectroscopically identical to the natural product. The synthetic approach reported here is currently being used for a structure–activity evaluation of the influence of the C-2 substituent of adenosine receptor binding.

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6. 4-(3-Acetoxypropyl)-2-methoxyphenol (**4a**): A solution of 4-(3-hydroxypropyl)-2-methoxyphenol (10.59 g, 58 mmol) in dry THF (90 mL) was cooled to 0 °C. A mixture of boron trifluride etherate (1.8 mL, 14

mmol) and acetic anhydride (13.1 mL, 14 mmol) was also cooled to 0 °C then added to the solution of **3**. The reaction was stirred for 5 h at 0 °C. Sodium acetate (6 g) was added and the reaction was heated gently on a warm water bath. Water (100 mL) was added and the solution was extracted with chloroform (3 x 30 mL). The chloroform layer was then dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification using column chromatography (hexane:ethyl acetate, 2:1) afforded the product (10.01 g, 77%) as a translucent oil. ^{1}H NMR ($CDCl_3$) δ 1.93 (m, *J* = 6.6, 7.9 Hz, 2H, H-2'), 2.06 (s, 3H, CO_2CH_3), 2.62 (t, *J* = 7.9 Hz, 2H, H-1'), 3.86 (s, 3H, OCH_3), 4.09 (t, *J* = 6.6 Hz, 2H, H-3'), 5.59 (br s, 1H, OH), 6.67 (d, *J* = 8.8 Hz, 1H, H-5/H-6), 6.68 (s, 1H, H-3), 6.83 (d, *J* = 8.6 Hz, H1, H-5/H-6); ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3), 30.5 (C-2'), 31.8 (C-1'), 55.8 (OCH_3), 63.8 (C-3'), 110.9 (C-3), 114.3 (C-6), 120.9 (C-5), 133.1 (C-4), 143.8 (C-1/C-2), 146.4 (C-1/C-2), 171.2 (C=O); MS *m/e* 224 (M^+).

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11. 4-(3-Acetoxypropyl)-2-methoxy-6-bromophenol (**5a**): A solution of **4** (0.71 g, 3.1 mmol) in dry DCM (10 mL) was stirred with a solution of $NHEt_2$ (0.04 g, 0.4 mmol) in dry DCM (1 mL) under an atmosphere of nitrogen. A solution of NBS (0.61 g, 3.4 mmol) in dry DCM (20 mL) was added over 30 min and the reaction was stirred at room temperature for 16 h. The reaction was acidified to pH 1 with concentrated sulpuric acid. Water (50 mL) was added and the solution was extracted with DCM (3 x 20 mL) and washed with water (50 mL). The organic layer was then ($MgSO_4$) and evaporated under reduced pressure to give a purple oil. This oil was purified by column chromatography (hexane/ethyl acetate, 1:1 with 1% acetic acid) and recrystallisation (ethyl acetate/hexane) afforded a pure crystalline solid (0.37 g, 39%). mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (m, *J* = 6.6, 7.8 Hz, 2H, H-2'), 2.05 (s, 3H, $COCH_3$), 2.58 (t, *J* = 7.8 Hz, 2H, H-1'), 3.87 (s, 3H, OCH_3), 4.07 (t, *J* = 6.6 Hz, 2H, H-3'), 5.83 (br s, 1H, OH), 6.61 (s, 1H, H-3/H-5), 6.91 (s, 1H, H-3/H-5); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 30.2 (C-2'), 31.6 (C-1'), 56.3 (OCH_3), 63.6 (C-3'), 110.3 (C-3), 124.1 (C-5), 133.9 (C-4), 141.3 (C-1/C-2), 147.1 (C-1/C-2), 171.1 (C=O); MS *m/e* 224 (M^+).

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13. In our hands, the Gattermann-Adam reaction proved to be quite temperamental. The HCl gas required for this reaction was generated from concentrated sulphuric acid and solid ammonium chloride. Attempts using HCl from a commercial cyclinder (>99%) or generated from concentrated sulphuric acid and concentrated hydrochloric acid resulted in only deacetylation of **7**.

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