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SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3321–3323

Glucuronide conjugates of Soraprazan (BY359), a new potassium-competitive acid blocker (P-CAB) for the treatment of acid-related diseases

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Received 12 January 2006; revised 21 February 2006; accepted 24 February 2006
Available online 27 March 2006

Abstract—Glucuronide conjugates of Soraprazan (BY359), a potent novel anti-secretory drug (currently in Phase II clinical trials), were not directly accessible synthetically. This was due to the relative instability of Soraprazan under the harsh Lewis acid conditions employed in popular glucuronidation methodologies and a lack of reactivity under alternative, Koenigs–Knorr, coupling conditions. We have now devised a successful synthesis using the novel N-acetylated Soraprazan to access the required glucuronide metabolites on gram scale. Coupling of this novel aglycone with methyl 1-*O*-trichloroacetimidoyl-2,3,5-tri-*O*-isobutyryl-α-D-glucopyran-uronate in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave the protected glucuronide intermediates. A one-pot two-step deprotection involving hydrolysis of the ester functionalities and removal of the *N*-acetyl group with alkaline hydrazine delivered the title compounds in satisfactory yield.

Current treatment of acid-related intestinal diseases focuses on the inhibition of the gastric H^+/K^+-ATPase. This pump is involved in the final step of acid secretion, and therefore, there is no by-passing of stimuli resulting in efficient pH elevation in the stomach. Irreversible inhibitors of this proton pump belong to the largest group of the prescription drugs. Reversible inhibitors of the proton pump have been studied much more recently. Most of these are based on the lead structure SCH28080, an imidazo[1,2-*a*]pyridine derivative.[1] Generally, however, they possess insufficient pharmacokinetics due to rapid metabolization and high clearance rate. Soraprazan (**1**)[2] has been developed to address the rapid clearance issue by introducing both polarity and rigidity to the original structure. The introduction of the polar 8-hydroxy group provides the drug with a site for glucuronidation without the need for phase I metabolization.[3] Studies on the metabolism of Soraprazan (**1**) in humans, involving extensive use of NMR and MS, confirmed that the 8-*O*-glucuronide **2** is indeed the predominant metabolite. Glucuronidation of the side-chain, following O-demethylation, also occurred to give **3** in much lower levels (Fig. 1).

There are a range of glucuronidation methods available and our initial efforts towards the synthesis of **2** involved screening the direct reaction of Soraprazan (**1**) with some of the most commonly used protected glucuronic acid derivatives, to see which was most applicable. After initial investigations the trichloroacetimidate coupling was found to be the most promising method.[4] Major synthetic problems were, however, encountered due to the relative acid instability of Soraprazan (**1**) under the required reaction conditions which resulted in cleavage of the C-7 ether linkage upon treatment with Lewis acids. Previous work in our lab had shown that this lability is greatly reduced by the presence of an acetyl group at N-10, presumably due to the diminished lone-pair availability.[5] Accordingly, the N-acetylated Soraprazan (**4**)[6] was envisaged as a more viable substrate for these Lewis acid catalyzed trichloroacetimidate couplings. The tri-*iso*-butyrate trichloroacetimidate **5** of glucuronic acid was found to be preferable for such a

Keywords: Anti-ulcer; Gastric anti-secretory; Soraprazan; Glucuronidation; Imidazo-naphthyridine.
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† Ultrafine is now part of SAFC Pharma (Sigma–Aldrich Company Limited).

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doi:10.1016/j.tetlet.2006.02.156

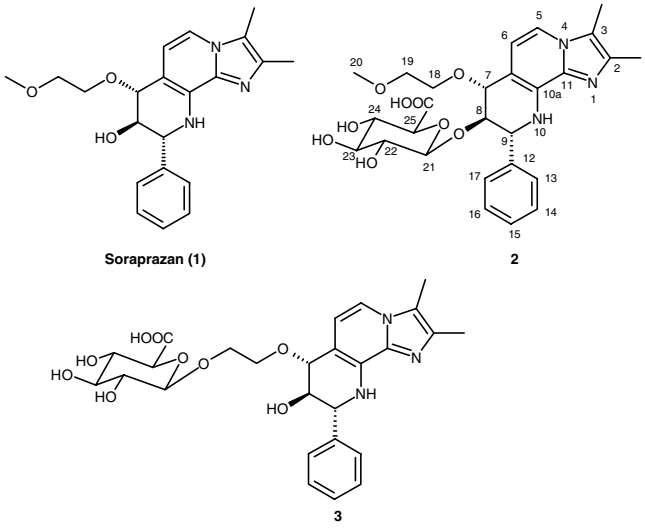
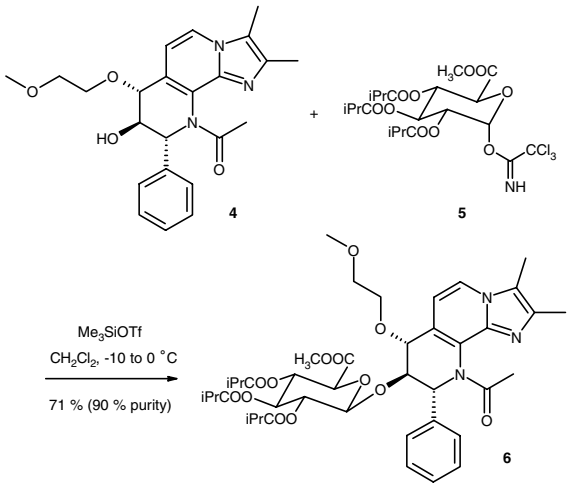


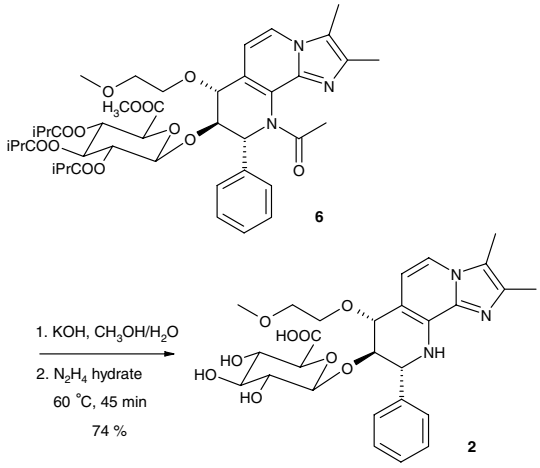
Figure 1.



Scheme 1. Glucuronidation of N-acetylated Soraprazan **4**. $^{i}Pr = 2$-propyl.

coupling,[7] as reactions with the analogous acetate protected trichloroacetimidate had resulted in the formation of orthoesters.[8] The conditions for glucuronidation of **4** were eventually optimized using 2 equivalents of tri-*iso*-butyrate trichloroacetimidate sugar **5** and 3 equiv trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane at −10 °C to yield 71% of the β-glucuronide coupled product **6** with approximately 90% purity (HPLC analysis). Addition of the first equivalent of TMSOTf was clearly exothermic, presumably due to acid–base interactions with the imidazo moiety of the bicyclic system of **4**. In fact, running the reaction with only 1 equiv of TMSOTf gave predominantly starting materials alongside some unidentified decomposition products (Scheme 1).

To obtain the final glucuronide **2** we were faced with the removal of the two different esters as well as the *N*-acetyl group. Acidic conditions were not possible as both the glucuronide linkage and the ether side chain would be compromised. The removal of the *N*-acetyl group had been investigated previously for N-acetylated Soraprazan **4** and its analogues and could be performed using either sodium methoxide in methanol or hydrazine hydrate with heating. Both of these sets of conditions could, however, be incompatible with the protected glucuronide. Reaction of the fully protected compound **6** with methoxide indeed gave unwanted side reactions, with elimination occurring in the sugar ring to give the 4′,5′-dehydro compound. Direct reaction of **6** with hydrazine would also be highly likely to give the undesired carboxylic hydrazide. This possibility was avoided by employing a two-stage deprotection approach where initial treatment of **6** with aqueous potassium hydroxide was followed by TLC to ensure complete hydrolysis of all esters. Hydrazine hydrate was then added and the mixture heated to 60 °C to remove the *N*-acetyl group (Scheme 2). Work-up conditions for this reaction also needed careful consideration to facilitate isolation of the crude glucuronide **2**. Final purification of compound **2** was carried out by preparative HPLC, with fractions being treated with an excess of ammonium hydroxide



Scheme 2. Removal of protecting groups of **6**.

prior to lyophilisation to facilitate the removal of trifluoroacetic acid present in the mobile-phase as the volatile ammonium salt.

The identity of the synthetic β-glucuronide **2** compared with the isolated metabolite from human blood plasma has been confirmed using NMR-spectroscopic data and HPLC-MS analysis.[9] The minor glucuronide metabolite **3** could also be synthesized using this approach.

Acknowledgements

We are grateful to Professor R. R. Schmidt for useful discussions regarding the glucuronidation and isolation difficulties encountered during this work.

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9. Compound **6**: To a stirred solution of **4** (50 g, 122 mmol) and methyl 1-*O*-trichloroacetimidoyl-2,3,5-tri-*O*-isobutyryl-α-D-glucopyran-uronate **5** (136.5 g, 243 mmol) in dichloromethane (1 l), under an atmosphere of N_2 and cooled to between −10 °C and 0 °C (ice–methanol bath), was added dropwise TMSOTf (67 ml, 365 mmol). The addition was kept slow during the addition of the first equivalent to avoid temperature rises, but thereafter the addition rate could be increased. The solution was then left stirring for a further 2 h, after which time the solution had turned pink and was carefully quenched with sat. $NaHCO_3$ (aq) (500 ml). The mixture was further diluted with dichloromethane (1 l) and the organic extracts were washed with further satd $NaHCO_3$ (aq) (2 × 500 ml), brine (1 l) before drying ($MgSO_4$) and concentrating in vacuo. The resultant brown oil was then purified by silica gel column chromatography [EtOAc/hexane (1:1) to EtOAc (100%) as eluent] to yield compound **6** as a yellow foam in approximately 90% purity (70.25 g, 71%). Higher purity could be obtained, at the expense of yield, by using Et_2O as column eluent. $R_f = 0.35$ [Et_2O as eluent]; ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 1.04–1.15 [m, 18H, ^{i}Pr (6CH_3)], 2.17 [s, 3H, $CH_3C(O)$], 2.38, 2.39 (2 s, 6H, $CH_3C{=}CCH_3$), 2.47 [septet, 1H, $J = 7.0$ Hz, ^{i}Pr ($CHMe_2$)], 2.48 [septet, 1H, $J = 7.0$ Hz, ^{i}Pr ($CHMe_2$)], 2.61 [septet, 1H, $J = 7.0$ Hz, ^{i}Pr ($CHMe_2$)], 3.44 (s, 3H, $OCH_2CH_2OCH_3$), 3.61 (ddd, 1H, $J = 2.9$ Hz, 5.1 Hz, 10.8 Hz, H-14), 3.67 (ddd, 1H, $J = 2.6$ Hz, 7.1 Hz, 10.8 Hz, H-14), 3.93 (d, 1H, $J = 9.6$ Hz, H-5′), 3.95 (ddd, 1H, $J = 2.9$ Hz, 7.1 Hz, 10.5 Hz, H-15), 4.17 (ddd, 1H, $J = 2.6$ Hz, 5.1 Hz, 10.5 Hz, H-15), 4.50 (s, 2H, 2 of H-10, H-11 and H-12), 4.79 (d, 1H, $J = 8.0$ Hz, H-1′), 5.12 (dd, 1H, $J = 8.0$ Hz, 9.5 Hz, H-2′), 5.22 (bt, 1H, $J = 9.5$ Hz, H-4′), 5.28 (bt, 1H, $J = 9.5$ Hz, H-3′), 6.00 (s, 1H, 1 of H-10, H-11 or H-12), 6.90–7.20 (m, 6H, C_6H_5 and H-8), 7.70 (d, 1H, $J = 7.0$ Hz, H-9); *m*/*z* (ES^+) 810.71 (MH^+, 100%).
Compound **2**: A stirred solution of **6** (20 g, 25 mmol) in methanol (124 ml) was treated with 3 M KOH (aq) (68 ml, 204 mmol) and left for at least 2 h. The mixture was then treated with hydrazine hydrate (124 ml) and heated to 60 °C for a further 45 min. Once complete, the reaction mixture was partially acidified by adding enough acetic acid (12 ml) to neutralize the KOH only. The mixture was then concentrated in vacuo before being re-dissolved in water (1 l) and washed with dichloromethane (2 × 500 ml). The resulting aqueous extracts were acidified with more acetic acid to pH 6, concentrated to ~50 ml and loaded onto a reverse phase silica gel pad (250 g). The silica gel was first washed with water (3 × 250 m) to desalt, then eluted with methanol (3 × 250 ml) to collect the product as a yellow oil. Some products existed in the aqueous fractions, which were recolumned to eventually give compound **2** (9.9 g, 74%). Selected spectroscopic data for **2**: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 2.32 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 2.87 (m, 1H, H-19), 2.92 (m, 1H, H-22), 2.99 (s, 1H, H-20), 3.17–3.33 (m, 4H, H-18′,18″,23,24), 3.73 (d, 1H, $J = 9.8$ Hz, H-25), 4.36 (br d, 1H, H-7), 4.44 (bdd, 1H, H-8), 4.62 (d, 1H, $J = 7.8$ Hz, H-21), 4.88 (bdd, 1H, H-9), 6.64 (d, 1H, $J = 6.8$ Hz, H-6), 6.73 (d, 1H, $J = 3.6$ Hz, H-10), 7.15–7.31 (m, 5H, H-13,14,15,16,17), 7.43 (d, 1H, $J = 6.8$ Hz, H-5); ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 7.96 (3-CH_3), 12.60 (2-CH_3), 55.70 (C-9), 57.86 (C-20), 66.42 (C-18), 70.76 (C-19), 71.39 (C-24), 72.95 (C-22), 74.84 (C-7), 75.41 (C-8), 75.55 (C-25), 76.19 (C-23), 102.59 (C-21), 105.17 (C-6a), 110.84 (C-5), 115.50 (C-6), 116.71 (C-3), 126.04 (C-15), 126.55 (C-13, C-17), 127.42 (C-14, C-16), 131.58 (C-10a), 135.08 (C-11), 135.60 (C-2), 141.10 (C-12), 170.35 (COOH).