JOC*Note*

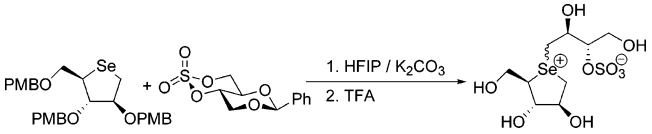
Efficient Synthesis of the Glucosidase Inhibitor Blintol, the Selenium Analogue of the Naturally Occurring Glycosidase Inhibitor Salacinol

Hui Liu and B. Mario Pinto*

Department of Chemistry, Simon Fraser University, Burnaby, B.C., Canada V5A 1S6

bpinto@sfu.ca

Received November 1, 2004



An efficient synthesis of blintol, the selenium congener of the naturally occurring glycosidase inhibitor salacinol, and a potent glucosidase inhibitor itself, is described. Unlike our previously reported synthesis, this improved route makes use of *p*-methoxybenzyl ether protecting groups in the synthesis of one of the two key intermediates, 2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-anhydro-4-seleno-D-arabinitol, from L-xylose. The other key intermediate, 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate, was successfully prepared from D-glucose instead of the expensive L-glucose. All protecting groups in the resulting adducts were removed with trifluoroacetic acid to yield a mixture of stereoisomers, thereby obviating the problematic deprotection of benzyl ethers by hydrogenolysis. The major stereoisomer, blintol, was then obtained by fractional crystallization.

Salacinol (**1**), a potent glycosidase inhibitor isolated from the aqueous extracts of *Salacia reticulata* that are used in Sri Lanka and India for the treatment of diabetes, has generated a lot of attention recently.[1−3] The unique structure of salacinol is a sulfonium ion (1,4-anhydro-4-thio-D-pentitol cation) stabilized by an internal sulfate counterion (1-deoxy-L-erythroxyl-3-sulfate anion). This glycosidase inhibitor is presumably a mimic of the oxacarbenium-ion intermediate in glycosidase-mediated hydrolysis reactions. We and others have previously reported the synthesis of salacinol and its stereoisomers.[2−4]

In the search for novel glycosidase inhibitors, we have also reported the synthesis and glycosidase inhibitory properties of the heteroatom congeners of salacinol in which the ring sulfur atom has been substituted by the cognate atoms nitrogen and selenium.[5,6] The structure−activity studies revealed different inhibitory activities of these compounds against different glycosidase enzymes.[5,6] Significantly, the selenium analogue, blintol, has been shown to be very effective in controlling blood glucose levels in rats after a carbohydrate meal, thus providing a lead candidate for the treatment of Type 2 diabetes.[7] This agent acts by inhibiting the membrane-bound glucosidase enzymes in the small intestine that break down oligosaccharides to glucose.[7] The extended study of the effectiveness and toxicities of these types of compounds in animal models demands more efficient and economical synthetic routes. Toward this end, we have already reported an optimized synthesis of salacinol (**1**).[8] We now report an efficient method for the synthesis of the selenium congener, blintol (**2**). Unlike our previously reported synthesis,[6] the present route makes use of *p*-methoxybenzyl ether protecting groups on the selenium heterocycle and D-glucose instead of L-glucose for the synthesis of the other reacting partner, a cyclic sulfate.

Retrosynthetic analysis indicated that blintol (**2**) could be obtained by alkylation of anhydroseleno-D-arabinitol (**3**) at the ring heteroatom using an appropriately protected cyclic sulfate (**4**) (Scheme 1).[3]

The previously reported synthesis of blintol (**2**) used benzyl ethers as the protecting groups for the hydroxyl groups on the anhydroseleno-D-arabinitol **3**.[6] However, the deprotection of the benzyl-protected blintol (**2**) by hydrogenolysis was problematic due to the poisoning of the palladium catalyst by small amounts of the selenoether **3** formed in the reaction mixture.

To eliminate the problematic hydrogenolysis step, the use of *p*-methoxybenzyl (PMB) protecting groups on the seleno-D-arabinitol, as in our optimized synthesis of salacinol (**1**) and the synthesis of 1,4-anhydro-4-thio-D-ribitol,[8] was considered. Thus, the reaction of the *p*-methoxybenzyl-protected selenoether **4** with the benzylidene-protected L-erythritol-1,3-cyclic sulfate (**5**; R = benzylidene) was envisioned. Since both PMB and benzylidene protecting groups are labile to acidic hydrolysis, the removal of all protecting groups by acid hydrolysis would be facile.[8]

The synthesis of the PMB-protected anhydroseleno-D-arabinitol (**3**) from L-xylose (**6**) required the judicious choice of aglycon. Initial attempts to use the allyl glycosides yielded an inseparable mixture of the desired

* To whom correspondence should be addressed. Tel: (604) 291-4327. Fax: (604) 291-3765.

(1) (a) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J. Tanabe, G.; Muraoka, O. *Tetrahedron Lett*. **1997**, *38*, 8367−8370. (b) Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull*. **1998**, *46*, 1339−1340. (c) Muraoka, O.; Ying, S.; Yoshikai, K.; Matsuura, Y.; Yamada, E.; Minematsu, T.; Tanabe, H.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull*. **2001**, *49*, 1503−1505. (d) Yoshikawa, M.; Morikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioog Med. Chem.* **2002**, *10*, 1547−1554.

(2) Yuasa, H.; Takada, J.; Hashimoto, H. *Tetrahedron Lett*. **2000**, *41*, 6615−6618.

(3) Ghavami, A.; Johnston, B. D.; Pinto, B. M. *J. Org. Chem*. **2001**, *66*, 2312−2317.

(4) Ghavami, A.; Johnston, B. D.; Maddess, M. D. Chinapoo, S. M.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *Can. J. Chem*. **2002**, *80*, 937−942.

(5) Ghavami, A.; Johnston, B. D.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2001**, *123*, 6268−6271.

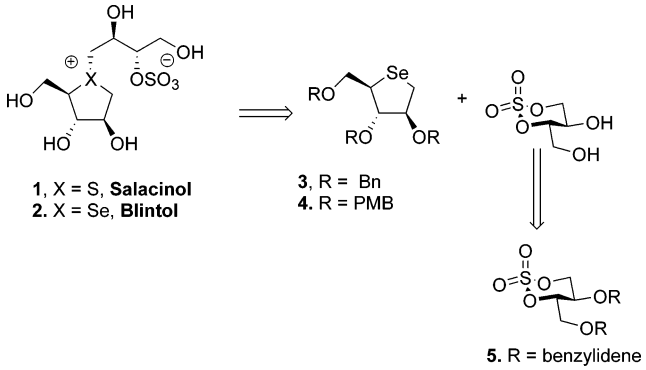
(6) Johnston, B. D.; Ghavami, A.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2002**, *124*, 8245−8250.

(7) (a) Pinto, B. M.; Johnston, B. D.; Ghavami, A.; Szczepina, M. G. US Provisional Patent, filed June 25, 2003. (b) Pinto, B. M.; Johnston, B. D.; Ghavami, A.; Szczepina, M. G.; Liu, H.; Sadalapure, K. US Patent, filed June 25, 2004.

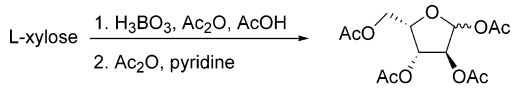
(8) (a) Ghavami, A.; Sadalapure, K. S.; Johnston, B. D.; Lobera, M.; Snider, B. B.; Pinto, B. M. *Synlett* **2003**, 1259−1262. (b) Minakawa, N.; Kato, Y.; Uetake, K.; Kaga, D.; Matsuda, A. *Tetrahedron* **2003**, 1699−1702.

10.1021/jo048058+ CCC: $30.25
Published on Web 12/23/2004

SCHEME 1



SCHEME 2

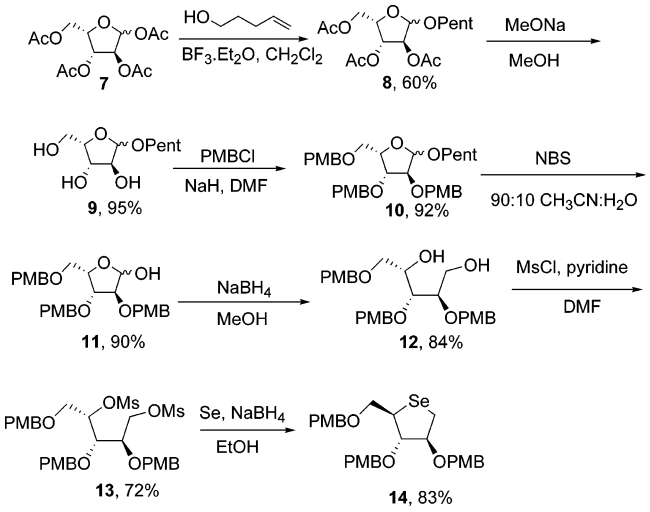


allyl xylofuranosides and undesired allyl xylopyranosides.[7a] Furthermore, the cleavage of the allyl group was judged to be too expensive a process for large-scale synthesis. Nevertheless, the mixture of furanosides and pyranosides was used in the successful synthesis of blintol (**2**), their separation being effected at a later stage in the synthetic scheme.[8]

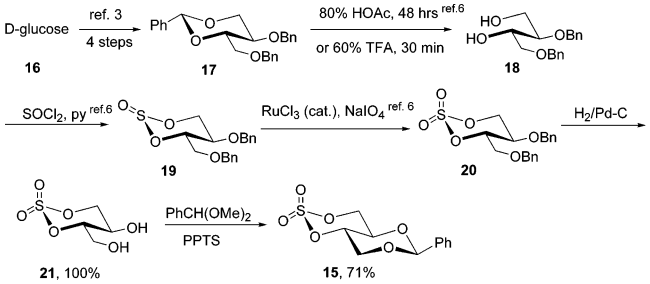
These concerns led us to explore the following strategy: (1) The use of *n*-pentenyl glycosides, first exploited by Fraser-Reid and co-workers:[9] this group was also reported to be cleaved by NBS without affecting the PMB groups.[10] (2) The use of boric acid in the acid-catalyzed acetylation of L-xylose (**6**) to improve the furanoside-to-pyranoside ratio.[11] The latter procedure led to the conversion of L-xylose (**6**) to 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (**7**) in a two-step, one-pot procedure. Analysis of the ^{1}H and ^{13}C NMR spectra indicated that the furanosides **7** were formed exclusively without formation of the undesired pyranoside side products (Scheme 2).

Compound **7** was then treated with 4-penten-1-ol and $BF_3{\cdot}OEt_2$ to give the 4-pentenyl 2,3,5-tri-*O*-acetyl-L-xylofuranosides (**8**).[12] This compound underwent acidic hydrolysis to cleave the acetyl groups, followed by the reprotection of the three hydroxyl groups with PMB groups, to afford the 4-pentenyl 2,3,5-tri-*O*-*p*-methoxybenzyl-L-xylofuranosides (**10**). The anomeric hydroxyl group of **10** was then released using NBS in acetonitrile−water to yield the corresponding 2,3,5-tri-*O*-*p*-methoxybenzyl-L-xylofuranose (**11**). The 2,3,5-tri-*O*-*p*-methoxybenzyl-L-xylofuranose **11** was reduced to the corresponding xylitol **12** by $NaBH_4$; mesylation of the hydroxyl groups then gave the dimesylate **13**. Compound **13** was then converted to the 1,4-anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-seleno-D-arabinitol (**14**) in 83% yield, using sodium selenide, generated in situ, from selenium metal and sodium borohydride in ethanol (Scheme 3).

SCHEME 3



SCHEME 4



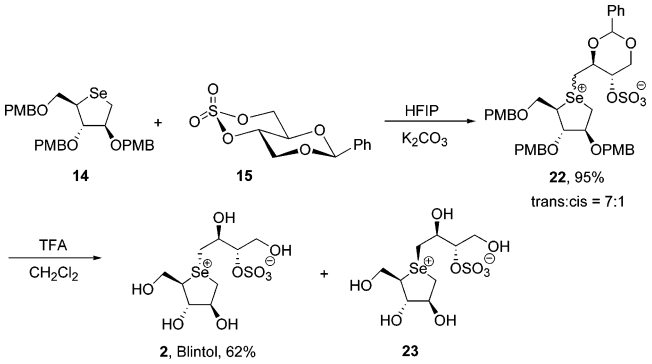
Another problem in the synthesis of blintol (**2**) (and the optimized synthesis of salacinol[7]) is the availability of 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**15**). This compound was previously prepared from L-glucose.[3] However, due to the high cost of L-glucose and the fact that it was the starting material in a six-step synthetic route, it was critical to prepare the cyclic sulfate **15** from a less expensive material. We report here the preparation of compound **15** from D-glucose (**16**).

Using our previously reported method,[3,6] the benzyl-protected cyclic sulfate **20** was prepared from D-glucose (**16**). It is interesting to note that cleavage of the benzylidene protecting group in compound **17** was achieved with 60% TFA at room temperature for 30 min to afford the corresponding diol **18** in a comparable yield to that obtained with aqueous acetic acid. Since the original method involved refluxing compound **17** in 80% HOAc for 48 h, this modification proved to be more efficient. Compound **20** underwent hydrogenolysis to afford the unprotected cyclic sulfate **21**. Installation of the benzylidene acetal using pyridinium *p*-toluenesulfonate (PPTS) as the catalyst was the critical step since, under these conditions, the cyclic sulfate was not cleaved. The desired benzylidene-protected cyclic sulfate **15** was obtained in 71% yield (Scheme 4).

The coupling reaction of the anhydroseleno-D-arabinitol **14** with the cyclic sulfate **15** in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 60−65 °C proceeded smoothly in 7 h to give a mixture of the 2,3,5-tri-*O*-*p*-methoxybenzylselenonium salts **22** in 95% yield (Scheme 5). The choice of HFIP as a solvent was based on our previous work.[6,8a] Analysis of the ^{1}H and ^{13}C NMR spectra indicated that

(9) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun*. **1987**, 1462−1463.
(10) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc*. **1988**, *110*, 2662−2663.
(11) Furneaux, R. H.; Rendle, P. M.; Sims, I. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2011−2014.
(12) Gurjar, M. K.; Reddy, L. K.; Hotha, S. *J. Org. Chem*. **2001**, *66*, 4657−4660.

SCHEME 5



compound **22** was a 7:1 mixture of isomers at the stereogenic selenium center. The major isomer was assigned to that with a *trans* relationship between C-5 and C-1′, as described previously.[6]

The selenonium salts **22** were subsequently deprotected by treatment with trifluoroacetic acid (TFA) and purified by recrystallization to afford pure blintol (**2**) in 62% yield (Scheme 5). The isomers were configurationally stable.[6]

In conclusion, an improved synthesis of *p*-methoxybenzyl-protected 1,4-anhydro-4-seleno-D-arabinitol (**14**) was achieved. Another key intermediate in the synthesis of blintol (**2**), namely 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**15**), was successfully prepared from D-glucose instead of expensive L-glucose. The coupling of **14** and **15** in HFIP was extremely efficient and amenable to the large-scale synthesis of blintol (**2**).

Experimental Section

Procedure for the Synthesis of 2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*S*,3*S*)-2,4-benzylidenedioxy-3-(sulfooxy)butyl]episelenoniumylidene]-D-arabinitol Inner Salt (22). The seleno-D-arabinitol **14** (3.11 g, 5.59 mmol), the cyclic sulfate **15** (1.33 g, 4.88 mmol), and K_2CO_3 (160 mg, 1.16 mmol) were added to 1,1,1,3,3,3-hexafluoro-2-propanol (8.0 mL), and the mixture was stirred in a sealed tube with heating at 60−65 °C for 7 h. Periodic analysis by TLC (EtOAc/MeOH, 10:1) showed that the reaction proceeded smoothly until the selenoether had been consumed leaving some cyclic sulfate unreacted. The mixture was cooled and filtered through Celite with the aid of CH_2Cl_2. The solvents were removed, and the residue was purified by column chromatography (gradient of EtOAc to EtOAc/MeOH, 10:1). The selenonium salt **22** (3.85 g, 95% based on selenoether **14**) was obtained as a colorless foam. Analysis of the ^{1}H and ^{13}C NMR spectra indicated that compound **22** was produced as a 7:1 mixture of isomers at the stereogenic selenium center. The major isomer was assigned to be the isomer with a trans relationship between C-5 and C-1′ by analogy to the results obtained previously for the corresponding benzyl-protected selenonium salt. For *trans*-**22**: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.45−6.80 (17H, m, Ar), 5.58 (1H, s, C_6H_5CH), 4.51 (1H, dd, $J_{2',3} = J_{3',4'ax} = 9.7$, $J_{3',4'eq} = 5.3$ Hz, H-3′), 4.48 (1H, br s, H-2), 4.46 (1H, dd, $J_{4'ax,4'eq} = 10.5$ Hz, H-4′eq), 4.41, 4.33 (2H, 2d, $J_{A,B} = 11.1$ Hz, CH_2Ph), 4.57 (2H, 2d, $J_{A,B} = 11.3$ Hz, CH_2Ph), 4.43 and 4.40 (2H, 2d, $J_{A,B} = 12.0$ Hz, CH_2-Ph), 4.39 and 4.26 (2H, 2d, $J_{A,B} = 11.4$ Hz, CH_2Ph), 4.32 (1H, dd, $J_{1'a,2} = 2.2$ Hz, H-1′a), 4.27 (1H, br d, $J_{2,3} = 2.0$ Hz, H-3), 4.25 and 4.19 (2H, 2d, $J_{A,B} = 10.8$ Hz, CH_2Ph), 4.21 (1H, ddd, H-2′), 4.04 (1H, br d, $J_{1,2} < 1$ Hz, H-1a), 4.03 (1H, br dd, $J_{3,4} < 1$ Hz, H-4), 3.90 (1H, dd, $J_{1'a,1'} = 12.2$, $J_{1'b,2} = 3.6$ Hz, H-4), 3.78 (3H, s, OCH_3), 3.77 (1H, dd, H-4′ax), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.55 (1H, dd, $J_{1a,1b} = 12.8$, $J_{1b,2} = 2.9$ Hz, H-1b), 3.54(1H, dd, $J_{5a,5b} = 9.7$, $J_{4,5a} = 6.7$ Hz, H-5a), 3.48 (1H, dd, $J_{4,5b} = 9.4$ Hz, H-5b); ^{13}C NMR (150 MHz, $CDCl_2$): δ 160.34, 160.09, 136.58 and 130.14−126.51 (21 C_{Ar}), 114.56, 114.47 and 114.70 (3 × C_{ipso}, OMBn), 102.17 (PHCH), 84.31 (C-3), 83.00 (C-2), 77.30 (C-2), 73.37, 72.49, and 72.10 (3 × CH_2Ph), 69.67 (C-4′), 67.75 (C-3′), 66.80 (2 × C, C-4, C-5), 55.67 (3 × C, 3 × OCH_3), 48.73 (C-1′), 46.69 (C-1). Anal. Calcd for $C_{40}H_{46}O_{12}SSe$: C, 57.90; H, 5.59. Found: C, 57.87; H, 5.57.

Procedure for the Synthesis of 1,4-Dideoxy-1,4-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]episelenoniumylidene]-D-arabinitol Inner Salt (Blintol, 2). The selenonium salts **22** (3.80 g, 4.58 mmol) were dissolved in cold trifluoroacetic acid (40 mL) to give a purple solution. Water (4.0 mL) was added, and the reaction mixture was kept at room temperature for 0.5 h. The solvents were removed on a rotary evaporator, and the residue was triturated with CH_2Cl_2 (4 × 50 mL), with each portion of solvent being decanted from the insoluble gummy product. The crude product was dissolved in water (50 mL) and filtered to remove a small amount of insoluble material. The aqueous filtrate was concentrated to a syrupy residue (1.84 g). Analysis by NMR spectroscopy indicated that the product was an isomeric mixture (7:1) of **2** with its stereoisomer at the selenium center. Recrystallization from MeOH gave pure **2** (1.09 g, 62%) in two crops. This material was identical in all respects to that obtained previously[6] using hydrogenolysis to remove the benzyl protecting groups. Purification of the mother liquor fractions by column chromatography (EtOAc/MeOH/H_2O, 6:3:1) gave a 3:2 mixture of **2** with its isomer (0.25 g, 14%) as a syrup.

Acknowledgment. We are grateful to University Medical Discoveries, Inc., for financial support.

Supporting Information Available: Complete experimental details for the synthesis of **14** from **6** and of **15** from **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048058+