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Unforeseen formation of 2-bromo-3-hydroxybenzaldehyde by bromination of 3-hydroxybenzaldehyde

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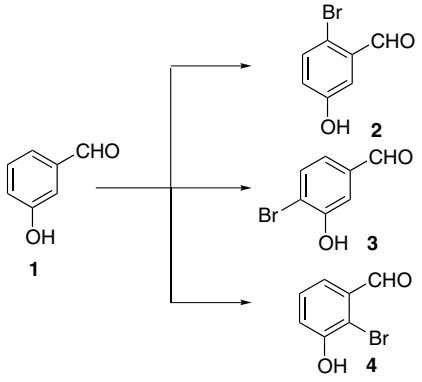
Abstract—Contrary to literature reports, bromination of 3-hydroxybenzaldehyde can afford both 2-bromo-5-hydroxybenzaldehyde and 2-bromo-3-hydroxybenzaldehyde, but 4-bromo-3-hydroxybenzaldehyde was not detected. 2-Bromo-3-hydroxybenzaldehyde was converted into 2-(benzyloxy)-1-bromo-5-methoxy-7-methylnaphthalene. X-ray crystallographic analysis supports the identity of 2-bromo-3-hydroxybenzaldehyde.

As a result of recent debate in the chemistry literature the outcome of the bromination of 3-hydroxybenzaldehyde **1** has been placed in doubt.[1,2] In 1912 Pschorr reported that bromination (Br_2, $CHCl_3$) of 3-hydroxybenzaldehyde **1** afforded 2-bromo-5-hydroxybenzaldehyde **2** (Scheme 1).[3] On the contrary, in 1925, Hodgson and Beard reported that bromination of **1** under the same conditions afforded a mixture of **2** and 4-bromo-3-hydroxybenzaldehyde **3** (Scheme 1), although only **2** was characterized.[4] More than 25 years later, Pandya et al. also reported that bromination of **1**, this time using acetic acid as solvent, afforded only **3** in a 52% yield.[5]



Scheme 1. Bromination of 3-hydroxybenzaldehyde.

More recently, other workers,[6] including ourselves,[7] have used related reaction conditions (e.g., our conditions: Br_2, CCl_4) for the bromination of **1** to afford **2**. In our work this product was used for the synthesis of complex isochromanes and related compounds.[7] At least two other groups of workers[8,9] have repeated the reaction using the conditions published by both Hodgson (Br_2, $CHCl_3$) and Pandya (Br_2, AcOH). These results, including an X-ray crystal structure,[9] indicate that bromination of **1** affords only the Pschorr product **2** and *not* compound **3**.

However, based on the fact that Hodgson's bromination of **1** can also apparently afford **3**, Tatsuta and co-workers have described a synthesis of the natural product medermycin (also known as lactoquinomycin)[10] **5** and its enantiomer using the putative **3** as a starting material.[11] As shown in Figure 1 the phenolic substituent of the starting material is required to be the phenol in position 9 of medermycin. Subsequently, in 2002, Morin and co-workers cast doubt on the product of Tatsuta's synthesis, based on their experimental evidence.[1] They reported that bromination of 3-hydroxybenzaldehyde **1** using Tatsuta's bromination conditions (HBr, AcOH), afforded the Pschorr product **2**. This assignment was supported by an X-ray crystal structure

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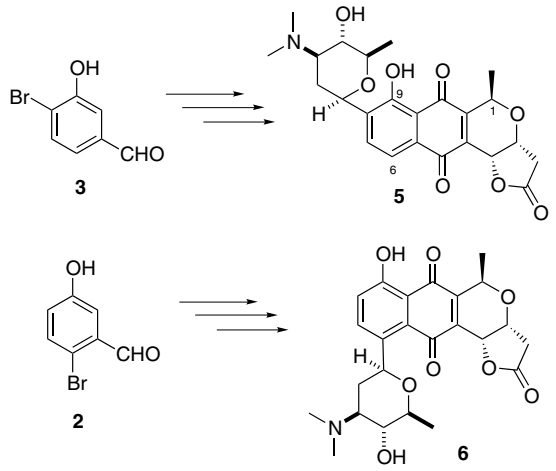


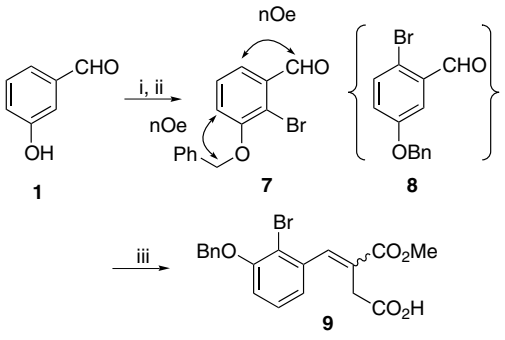
Figure 1. Synthesis of medermycin **5** from the putative 4-bromo-3-hydroxybenzaldehyde **3** or the isomer **6** from **2**.

of a derivative, 2-bromo-5-(*p*-nitrobenzoyl)benzaldehyde.[1] Based on this experimental finding, Morin proposed a structural revision to natural medermycin in which the carbohydrate moiety is now attached to position 6 of the naphthoquinone that is **6**. However, there seems to be little doubt that the natural product itself has structure **5**: Williamson et al. has recently provided extensive NMR spectral evidence to support the original structure assigned to the natural product.[2]

In this paper we wish to report that the bromination of 3-hydroxybenzaldehyde **1** can also afford an alternative regioisomer, 2-bromo-3-hydroxybenzaldehyde **4** (Scheme 1), indicating that another possible regioisomer of medermycin may have been synthesized by Tatsuta and co-workers.[11]

As part of our ongoing programme on the synthesis of substituted naphthalenes,[12] we had previously brominated 3-hydroxybenzaldehyde **1** (Br_2, CCl_4) to afford 2-bromo-5-hydroxybenzaldehyde **2** under rather specific conditions.[13,14] Recently, we isolated the product of this reaction in a different manner. The reaction mixture was stirred for 2 h at room temperature, water was added and the resulting solution placed in a refrigerator. After 16 h an off-white solid had crystallized from the reaction mixture. This was isolated by filtration and subjected to a normal O-benzylation protocol (BnBr, Me_2CO, K_2CO_3). However, we were surprised to isolate the 2-bromo-3-benzyloxy regioisomer **7** as the major product (45%, two steps) after column chromatography,[15] rather than the 2-bromo-5-benzyloxy isomer **8** (yield 1%) isolated previously as the major component in our work (Scheme 2).[7,15] Repeating the reaction a number of times in this manner again gave **7** as the major product.

The structure of the O-benzylated product **7** was supported by NOE NMR spectroscopic studies in which distinctive interactions were evident between the benzyl methylene and 4-H protons, and also between the aldehyde and 6-H protons. In addition, comparison of the spectroscopic data of **7** with the same compound



Scheme 2. Reagents and conditions: (i) Br_2, CCl_4, rt, add H_2O, crystallized at 0 °C; (ii) BnBr, K_2CO_3, DMF, 60 °C (45% over two steps); (iii) NaOMe, dimethyl succinate, MeOH, 50 °C (77%).

synthesized by Nicolaou et al.[16] using an alternative route indicated that **7** was the product obtained and *not* **8**. The ^{13}C NMR spectrum of **7** proved to be substantially different to that of **8**.[15]

Further investigation of this reaction showed in fact that a mixture of the regioisomers **2** and **4** (ratio 1:2) was obtained in the bromination of **1** and we were able to obtain predominantly 2-bromo-3-hydroxybenzaldehyde **4** by crystallization at 0 °C from CCl_4.[17] Most importantly, a single crystal X-ray structure (Fig. 2) confirmed that the bromine atom of intermediate **4** was placed between the aldehyde and the phenol substituents as suggested by the NOE NMR spectroscopic studies and comparison of spectral data.[18]

Pursuing our interests in the synthesis of substituted naphthalenes, we converted the aldehyde **7** into the conjugated half-ester **9** (77% yield) by using modified Stobbe conditions.[19] We used sodium methoxide generated in situ as base instead of the usual potassium *tert*-butoxide because the benzyl-protecting group of **7** proved to be unstable when using the latter. Subsequent cyclization of **9** with sodium acetate in acetic anhydride afforded naphthalene derivative **10** in acceptable yields (Scheme 3).

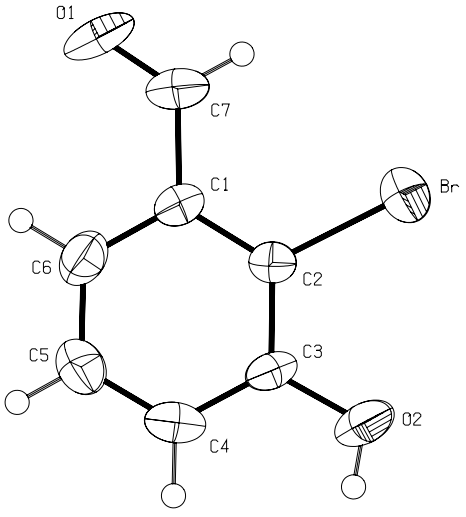
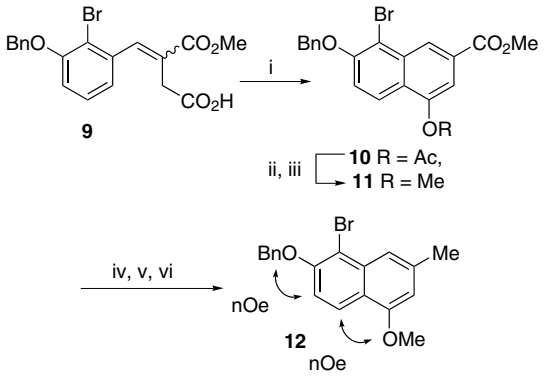


Figure 2. X-ray crystal structure of 2-bromo-3-hydroxybenzaldehyde **4**.



Scheme 3. Reagents and conditions: (i) NaOAc, Ac_2O, reflux, 61%; (ii) KOH, MeOH, rt, 100%; (iii) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux, 98%; (iv) $LiAlH_4$, THF, 0 °C, 99%; (v) $(Cl_2BrC)_2$, PPh_3, CH_2Cl_2, rt, 81%; (vi) L-Selectride, CH_2Cl_2, 0 °C, 93%.

Acetate **10** was successfully hydrolyzed with sodium or potassium hydroxide to give the crystalline naphthol in quantitative yield. The intermediate was methylated under standard conditions to afford the substituted naphthalene **11** in excellent yield. The ester substituent of **11** was then converted into a methyl group using conditions optimized by Bringmann et al.[20] to afford **12**, characterized by rigorous NMR spectroscopy, which included NOE and a three bond HMBC ^1H–^{13}C NMR spectroscopy experiment. Comparison of the spectroscopic data of **12** with those obtained by using **8** as a starting material by other researchers, which led to 4-(benzyloxy)-1-bromo-5-methoxy-7-methyl-naphthalene proved to be substantially different.[21]

In conclusion, it is clear that the bromination of **1** gives mixtures of monobrominated products. In our case we were able to detect both the 2-bromo-5-hydroxybenzaldehyde and 2-bromo-3-hydroxybenzaldehyde isomers **2** and **4** in the reaction mixture, but not **3**. We were also successful in synthesizing the substituted naphthalene **12** from isomer **4**. It is unlikely that the structure of the natural medermycin is incorrect, as extensive spectroscopic data have been produced to verify the structure.[2] On the basis of the bromination experiments conducted in our laboratories, 2-bromo-5-hydroxybenzaldehyde **2** and 2-bromo-3-hydroxy-benzaldehyde **4** were the *only* isomers that we were able to isolate in appreciable quantities. An extensive literature search shows no claims, apart from the work of Hodgson and Beard,[4] Tatsuta and co-workers[11] and Pandya et al.,[5] for the formation of the alternative regioisomer **3** from **1**. Therefore, in addition to the regioisomer of medermycin suggested by Morin and co-workers[1] it is also possible that Tatsuta may have synthesized regiosiomer **13** from 2-bromo-3-hydroxybenzaldehyde **4** as depicted in Figure 3.

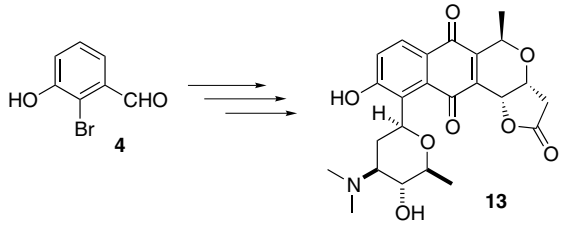


Figure 3. Regioisomer **13** of medermycin, which could be synthesized from 2-bromo-3-hydroxybenzaldehyde **4**.

Acknowledgements

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13. Br_2 (2.1 cm^3, 6.5 g, 41 mmol) was added dropwise over 15 min under N_2 to a solution of 3-hydroxybenzaldehyde **1** (5.0 g, 41 mmol) in CCl_4 (150 cm^3) kept at 25 °C. The reaction mixture was stirred under N_2 for 2 h at rt, after which H_2O (250 cm^3) and CH_2Cl_2 (250 cm^3) were added. The organic layer was separated, dried and removed in vacuo to afford compound **2** as a white solid (4.2 g, 51%).
14. Most of this work is taken from the PhD thesis of W.A.L. van Otterlo, University of the Witwatersrand, 1999.
15. Compound **7**: Pale pale yellow solid (mp 131.5–132.5 °C, sublimes above 120 °C, recrystallized from EtOH/H_2O). Spectroscopic data for **7**: ^1H NMR (400 MHz; $CDCl_3$) δ_H 10.44 (1H, s, CHO), 7.55–7.29 (7H, m, 5-H, 6-H and 5×PhH), 7.15 (1H, dd, *J* 8.1 and 1.6, 4-H), 5.20 (2H, s, OCH_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 192.2 (CHO), 155.4, 135.9, 134.9, 128.7, 128.2, 128.2, 127.0, 121.8, 118.8, 117.9, 71.3 (OCH_2); IR (KBr pellet) ν_{max}/cm^{-1} 1682s (C=O st), 1567m (ArC=C st), 698s (C–Br st); CHN C, 57.48; H, 3.68; ($C_{14}H_{11}O_2Br$ requires C, 57.75; H, 3.80%). Compound **8**: Pale yellow solid (mp 43–45 °C, recrystallized from CH_2Cl_2/hexane; lit. 52–54 °C); Keserű, G. M.; Mezey-Vándor, G.; Nógrádi, M.; Vermes, B.; Katjár-Peredy, M. *Tetrahedron* **1992**, *48*, 913–922. Spectroscopic data for **8**: ^1H NMR (200 MHz; $CDCl_3$) δ_H 10.28 (1H, s, CHO), 7.51–7.31 (7H, m, 5×PhH, 3- and 6-H), 7.07 (1H, dd, *J* 8.8 and 3.2, 4-H), 5.06 (2H, s, OCH_2); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 191.5 (CHO), 158.3, 135.8, 134.6, 133.9, 128.6, 128.2, 127.5, 123.6, 118.1, 113.8, 70.4 (OCH_2); IR (KBr) ν_{max}/cm^{-1} 1694vs (C=O st), 1590m (ArC=C st).
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18. Crystal data for **4**: $C_7H_5BrO_2$, crystal size 0.50×0.09×0.06 mm, crystal system monoclinic, space group $P2_1$, $Z = 2$, unit cell dimensions: $a = 4.8625(8)$ Å, $b = 12.987(2)$ Å, $c = 5.6842(9)$ Å, $\beta = 101.873(3)°$, $V = 351.28(10)$ $Å^3$, $D_c = 1.900$ Mg/m^3, intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA), wavelength 0.71073 Å, collection temperature 293(2) K; $\theta_{max} = 26.48$; 2113 reflections collected with 1167 independent reflections ($R_{int} = 0.0365$); 91 parameters; maximum residual electron density 0.278 and −0.209 e $Å^{-3}$; data reduction was carried out using the program SAINT+ [Bruker, **1999**, SAINT+. Version 6.02 (includes XPREP and SADABS). Bruker AXS Inc., Madison, Wisconsin, USA] and face indexed absorption corrections were made using the program XPREP, final *R* indices: $R_1 = 0.0275$, $wR_2 = 0.0522$. The crystal structure was solved by direct methods using SHELXTL. Nonhydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on F^2 using SHELXTL [Bruker, **1999**, SHELXTL. Version 5.1. (includes XS, XL, XP, XSHELL) Bruker AXS Inc., Madison, Wisconsin, USA]. Hydrogen atoms were first located in the difference map, positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON (Spek, A. L. *Acta Cryst.* **1990**, *A46*, C34). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 234067. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk).
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