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The design of efficient and selective routes to pyridyl analogues of 2,3-dihydro-1,4-benzodioxin-6-carbaldehyde

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ABSTRACT

This Letter describes the synthetic routes to challenging pyridyl analogues of 2,3-dihydro-1,4-benzodioxin-6-carbaldehyde which were key intermediates for our antibacterial medicinal chemistry programme. All routes described started from kojic acid (**8**) and have been used to give multigram quantities of each aldehyde.

As part of an antibacterial medicinal chemistry research programme we used commercially available 2,3-dihydro-1,4-benzodioxin-6-carbaldehyde (**1**). We also required access to the non-commercial pyridyl analogues of this aldehyde **2**–**7**.

Although the synthesis of 2,3-dihydro-1,4-benzodioxin-6-carbaldehyde (**1**) was known and it was commercially available (Fig. 1),[1] aldehydes (**2** and **4**–**7**) were unknown in the literature at this time. For aldehyde **3**, a synthetic route was published by Walker et al.[2] This however, used 2-chloro-3-pyridinol as the starting material. In this publication we describe the synthesis of aldehydes **2**–**7** using kojic acid (**8**) as the sole starting material, allowing maximum diversity from key intermediates.

We first looked at the synthesis of aldehyde **2**. From the work of Erol and Yulug the synthesis of key intermediate **9** was known.[3] We opted to use this methodology to synthesise aldehyde **2** from commercially available kojic acid (**8**) (Scheme 1).[4] Firstly, we protected the more reactive 5-OH group of kojic acid (**8**) using benzyl chloride to give the known key intermediate **9**. Condensation of **9** with concentrated aqueous ammonia resulted in the formation of the desired pyridone **10** in 61% yield. The next two steps involved deprotection and cyclisation with 1,2-dibromoethane to give alcohol **11** in 21% yield over two steps. Finally oxidation using MnO_2 gave the desired aldehyde **2** in 61% yield. Using this route, we were able to produce aldehyde **2** on multigram scale.

For aldehyde **3** (Scheme 2),[6] we required a slightly different protecting group strategy to complete the synthesis. Starting from kojic acid (**8**), we protected the more reactive 5-OH group using *para*-methoxybenzyl chloride (PMBCl) in 64% yield to give **12**. Next, we formed the pyridone ring via condensation with concentrated aqueous ammonia and protected the benzylic-OH group using AcCl to give key intermediate **13** in 33% yield over two steps. O-Activation of pyridone **13** with Tf_2O gave **14** in 70% yield. For the next step, we opted for a Sonogashira approach using propargyl alcohol which gave the desired alkyne **15** in 61% yield.[7] Clean reduction of the alkyne group and PMB group cleavage using Pd/C in an atmosphere of H_2 gave diol **16** and utilising the Mitsunobu reaction for cyclisation allowed access to **17**.[8] The two final steps were acetate deprotection and oxidation to give the desired aldehyde **3** in 60% yield over two steps. Using this route we were able to produce aldehyde **3** on multigram scale.

Aldehyde **4** was synthesised from key intermediate **14** (Scheme 3).[6] Acetate **14** was converted into *tert*-butyl sulfide intermediate **18** using Buchwald and Murata methodology.[9] Deprotection of the PMB group using triethylsilane gave alcohol **19** in 83% yield followed by removal of the *tert*-butyl and acetate groups to

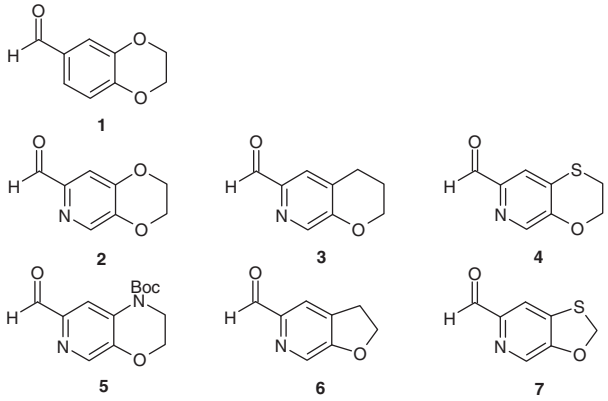

Figure 1. Pyridyl analogues **2**–**7** of aldehyde **1**.

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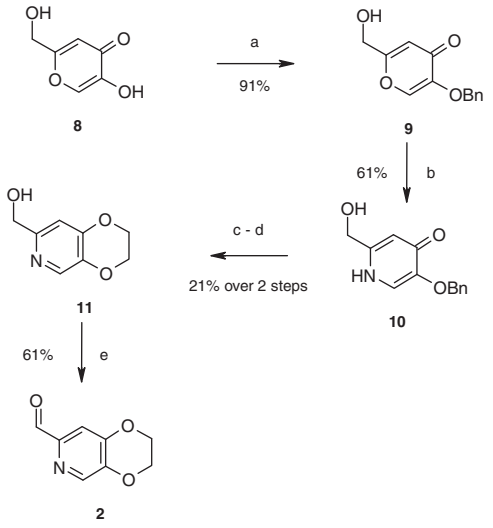
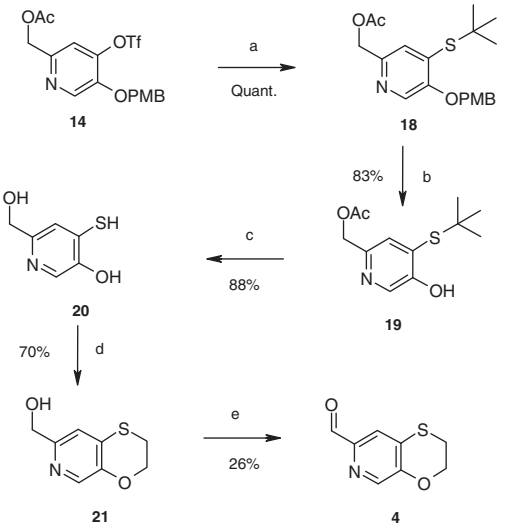


Scheme 1. Synthetic approach to 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carbaldehyde (**2**).[5] (a) BnCl, NaOH, MeOH, reflux, 8 h; (b) concd aq NH_3, EtOH, reflux, o/n; (c) NaOH, Pd/C, H_2, rt, 4 h; (d) $BrCH_2CH_2Br$, K_2CO_3, DMF, 85 °C, o/n; (e) MnO_2, CH_2Cl_2, rt, 3 d, o/n = overnight.

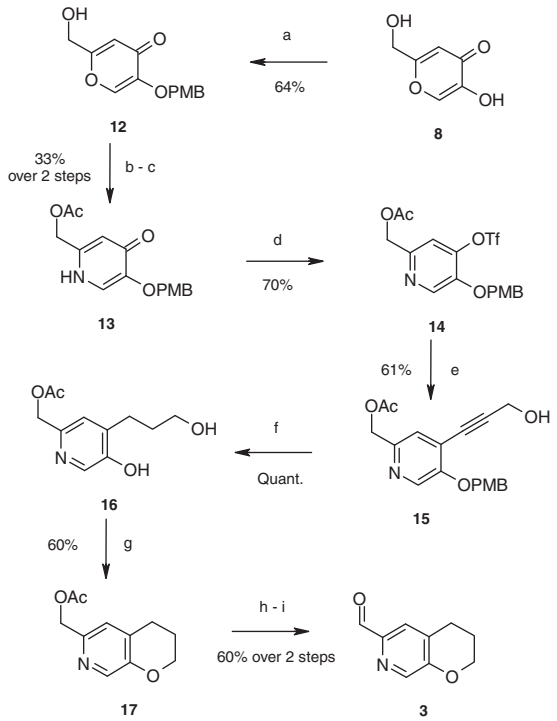


Scheme 3. Synthetic approach to 2,3-dihydro[1,4]oxathiino[2,3-*c*]pyridine-7-carbaldehyde (**4**).[5] (a) $NaSC(CH_3)_3$, $Pd(OAc)_2$, (+)-BINAP, toluene, 60 °C, 3 h, then 70 °C, 18 h; (b) Et_3SiH, CH_2Cl_2, rt, 10 min, then TFA, rt, 3 h; (c) concd HCl, 80 °C, 18 h; (d) DMF, K_2CO_3, rt, 10 min, then $BrCH_2CH_2Br$, 70 °C, 18 h; (e) MnO_2, CH_2Cl_2, rt, o/n.

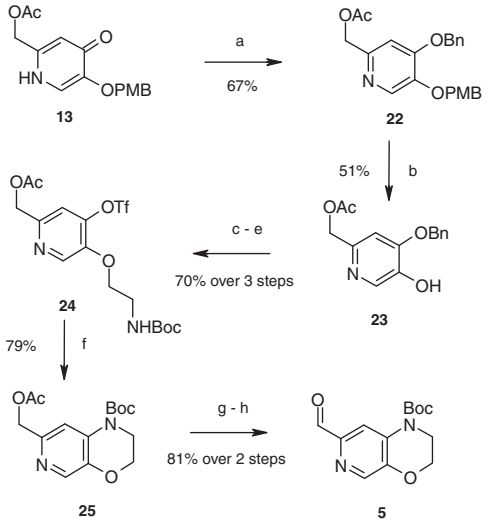
give intermediate **20**. Cyclisation using 1,2-dibromoethane gave alcohol **21** in 70% yield, and finally oxidation gave the desired aldehyde **4** in a moderate 26% yield. Again this route allowed access to aldehyde **4** on multigram scale.

Utilising key intermediate **13** we were able to synthesise aldehyde **5** (Scheme 4).[10] For this synthetic route we selected a Mitsunobu reaction followed by Pd-catalysed intramolecular carbamate arylation to give acetate **25**. Firstly, O-protection of pyridone **13** with benzyl chloride gave benzyl-protected **22** in 67% yield and then removal of the PMB group allowed access to alcohol **23** in 51% yield. The next steps were Mitsunobu reaction with $HOCH_2CH_2NHBoc$, deprotection of the benzyl group and activation of the pyridone to give triflate **24** in 70% over three steps. Using the conditions described by Buchwald,[11] we were able to access acetate **25**. Finally, deprotection and oxidation gave the desired aldehyde **5** in 81% yield.

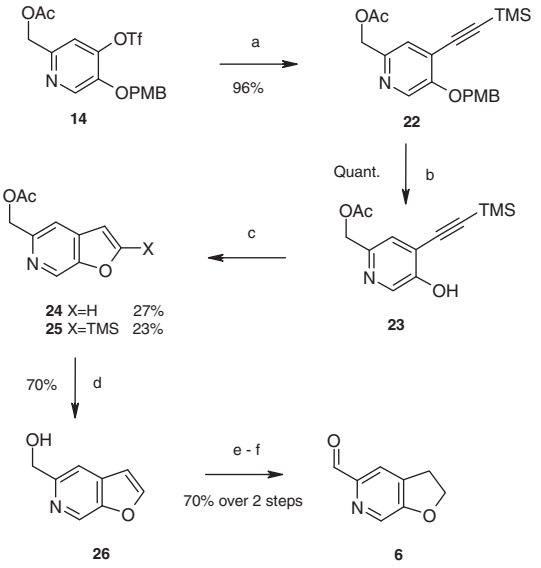
For aldehyde **6** (Scheme 5),[10] we opted to start from intermediate **14**. Using a similar strategy as for aldehyde **3** we introduced trimethylsilylacetylene via Sonogashira coupling followed by PMB deprotection to give alcohol **23** in 96% over two steps. Using the chemistry of Lutjens,[12] we performed a copper-mediated ring closure to give acetates **24** and **25** in 27% and 23% yields, respectively.



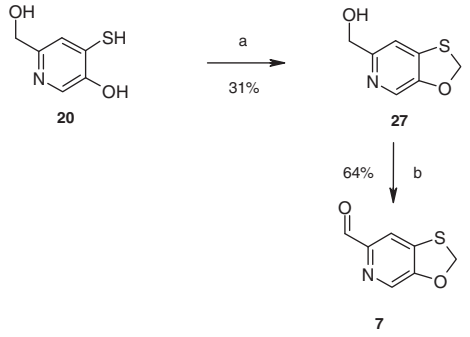
Scheme 2. Synthetic approach to 3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridine-6-carbaldehyde (**3**).[5] (a) Bu^{t}OK, DMF, 0 °C, then 1 h, 5–10 °C, then PMBCl, 50 °C, 30 h, finally 90 °C, 5 h; (b) concd aq NH_3, EtOH, reflux, 18 h; (c) AcCl, pyridine, 5 °C→rt→60 °C, 18 h; (d) Tf_2O, Et_3N, CH_2Cl_2, 0 °C→rt, o/n; (e) $HC{\equiv}CCH_2OH$, CuI_2, $PdCl_2(PPh_3)_2$, NEt_3, CH_3CN, 50 °C, 18 h; (f) Pd/C, H_2, EtOH, rt, 6 h; (g) Ph_3P, DIAD, THF, rt, 1 h then **16**, THF, rt, 2 h; (h) NaOH, H_2O, rt, 2 h; (i) MnO_2, CH_2Cl_2, rt, 3 d.



Scheme 4. Synthetic approach to 1,1-dimethylethyl 7-formyl-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-1-carboxylate (**5**).[5] (a) Ph_3P, DIAD, THF, 0 °C, 10 min, then pyridine, 0 °C, 10 min, finally BnCl, 0 °C, o/n; (b) Et_3SiH, TFA, CH_2Cl_2, rt, 2 h; (c) Ph_3P, DIAD, THF, 0 °C, 30 min, then **23**, Et_3N, 0 °C, 30 min, then rt, 30 min, finally $HOCH_2CH_2NHBoc$, rt, o/n; (d) Pd/C, H_2, EtOH, rt, 16 h; (e) $PhNTf_2$, Et_3N, CH_2Cl_2, rt, 16 h; (f) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, toluene, 100 °C, 16 h; (g) NaOH, 1,4-dioxane, H_2O, rt, 30 min; (h) MnO_2, CH_2Cl_2, rt, o/n.



Scheme 5. Synthetic approach to 2,3-dihydrofuro[2,3-*c*]pyridine-5-carbaldehyde (**6**).[5] (a) HC≡CTMS, $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN, 45 °C, 18 h; (b) Et_3SiH, TFA, CH_2Cl_2, rt, 18 h; (c) pyridine, CuI, reflux, 18 h; (d) **24**, NaOH, 1,4-dioxane, H_2O, rt, 18 h; (e) Pd/C, H_2, EtOH, rt, 18 h; (f) MnO_2, CH_2Cl_2, reflux, 18 h.



Scheme 6. Synthetic approach to [1,3]oxathiolo[5,4-*c*]pyridine-6-carbaldehyde (**7**).[5] (a) K_2CO_3, DMF, 10 min, rt, then $BrCH_2Br$, 55 °C, 24 h; (b) MnO_2, CH_2Cl_2, rt, o/n.

Both compounds were separated and the desired acetate **24** was carried onto the next step. This involved acetate deprotection to give alcohol **26** in 70% yield. Finally, hydrogenation of the double bond followed by oxidation of the alcohol gave the desired aldehyde **6** in 70% yield over two steps.

For the final aldehyde **7**,[6] we used the same general route as for aldehyde **4**, but used dibromomethane instead of 1,2-dibromoethane for the cyclisation (Scheme 6).

In conclusion, we have demonstrated that all six aldehydes can be accessed from key intermediates that were derived from kojic acid (**8**). This has allowed a diverse range of aldehydes to be synthesised and the ability to deliver multi-gram quantities of material.

Acknowledgements

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5. *Selected analytical data*. Compound **2**: White solid; mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (s, 4H), 7.38 (s, 1H), 8.21 (s, 1H), 9.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.3, 64.8, 110.9, 139.8, 144.2, 147.6, 149.9, 192.0. ESI-HRMS: *m*/*z* calcd for $C_8H_8NO_3$: 166.0504; found 166.0503 $[M+H]^+$.
Compound **3**: White solid; mp 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97–2.05 (m, 2H), 2.79 (t, 2H, *J* = 7 Hz), 4.25 (t, 2H, *J* = 7 Hz), 7.63 (s, 1H), 8.18 (s, 1H), 9.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 24.0, 67.0, 123.2, 130.5, 139.8, 145.2, 155.5, 192.2. ESI-HRMS: *m*/*z* calcd for $C_9H_{10}NO_2$: 164.0712; found 164.0708 $[M+H]^+$.
Compound **4**: White solid; mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.17 (t, 2H, *J* = 7 Hz), 4.48 (t, 2H, *J* = 7 Hz), 7.62 (s, 1H), 8.13 (s, 1H), 9.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 65.1, 120.9, 129.3, 139.8, 145.6, 151.5, 191.8. ESI-HRMS: *m*/*z* calcd for $C_8H_8NO_2S$: 182.0276; found 182.0273 $[M+H]^+$.
Compound **5**: Off-white solid; mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 9H), 3.94 (t, 2H, *J* = 7 Hz), 4.37 (t, 2H, *J* = 7 Hz), 8.31 (s, 1H), 8.60 (s, 1H), 9.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 41.8, 65.0, 83.4, 115.4, 133.3, 140.1, 145.1, 146.3, 151.3, 192.1. ESI-HRMS: *m*/*z* calcd for $C_{13}H_{17}N_2O_4$: 265.1188; found 265.1184 $[M+H]^+$.
Compound **6**: Light brown solid; mp 83–86 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.32 (t, 2H, *J* = 7 Hz), 4.73 (t, 2H, *J* = 7 Hz), 7.89 (s, 1H), 8.32 (s, 1H), 9.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.6, 72.4, 119.0, 131.8, 137.2, 146.8, 160.8, 191.8. ESI-HRMS: *m*/*z* calcd for $C_8H_8NO_2$: 150.0555; found 150.0553 $[M+H]^+$.
Compound **7**: White solid; mp 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (s, 2H), 7.77 (s, 1H), 8.13 (s, 1H), 9.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.2, 115.7, 131.3, 139.1, 148.4, 157.1, 191.5. ESI-HRMS: *m*/*z* calcd for $C_7H_6NO_2S$: 168.0119; found 168.0117 $[M+H]^+$.
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