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Direct glycosylation: synthesis of α-indoline ribonucleosides

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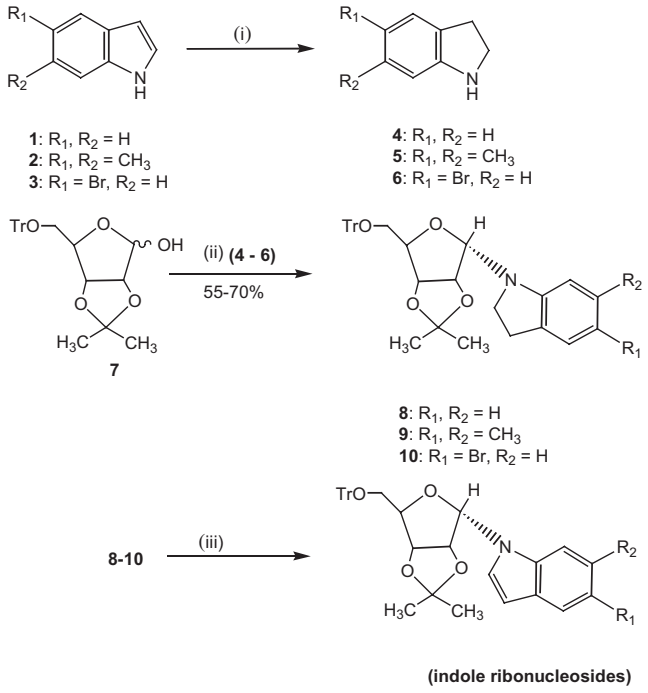
Abstract—A selective synthesis of α-anomers of indoline nucleosides is described. Ribonucleosides of indoline, dimethylindoline and 5-bromoindoline are readily prepared in good yield by reacting indoline bases directly with the protected sugar, 2,3-*O*-(1-methylethylidene) 5-*O*-(triphenylmethyl)-D-ribofuranose in dry ethanol or methylene chloride in presence of molecular sieves at 40–60 °C.

1. Introduction

α-Ribonucleosides[1,2] are rare in nature, but occur, for example, as the lower axial ligand (5,6-dimethyl-α-D-ribofuranosylbenzimidazole)[3] in coenzyme B_{12}. Analogs of coenzyme B_{12} with altered axial nucleoside ligands are of interest as probes of the function of the axial ligand in the enzymatic activation of the coenzyme for carbon–cobalt bond homolysis.[4–7] As such, α-indole nucleosides, which lack a coordinating nitrogen but otherwise maintain the structural integrity of the coenzyme, can probe the importance of axial coordination to enzymatic activation. However, the necessary synthetic routes to α-ribonucleosides are rare. We recently reported the successful synthesis of the α-ribonucleosides of indoline and 5,6-dimethylindoline and corresponding indole ribonucleosides[8,9] via a multistep route requiring protection of the indoline and the use of an expensive coupling reagent, 2-fluoro-1-methylpyridinium tosylate.[10] Here we report an alternative route in which an unprotected indoline may be directly coupled to 2,3-*O*-(1-methylethylidene)5-*O*-(triphenylmethyl)-D-ribofuranose[11] in dry ethanol/methylene chloride, in the presence of Type 4 Å molecular sieves to give the α-ribonucleoside in 55–70% yield without any detectable β-ribonucleosides.

The dimethylindole[12,13] bases were prepared by standard procedures from 5-nitropseudocumene in three steps. For the coupling reaction the dimethylindole base was converted in to dimethylindoline[14,15] (Scheme 1) in excellent yield by sodium cyanoborohydride reduction[14] at 12 °C. 2,3-*O*-(1-Methylethylidene)-5-*O*-(triphenylmethyl)-D-ribofuranose was prepared from D-ribose in two steps in fairly good yield. A dry solution of 2,3-*O*-(1-methylethylidene)5-*O*-(triphenylmethyl)-D-ribofuranose[11] in ethanol was added directly dimethylindoline



Scheme 1. Reagents and conditions: (i) sodium cyanoborohydride, AcOH, 10–15 °C; (ii) molecular seives, ethanol/methylene chloride, 40–60 °C, 4–6 h; (iii) MnO_2, benzene or methylene chloride, molecular sieves.

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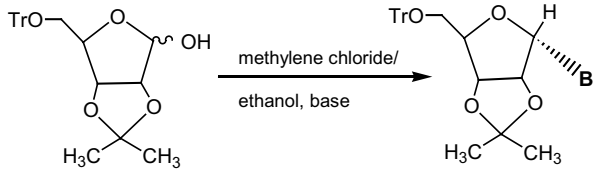
Table 1. Reaction conditions and yields of glycosylation of different bases with 2,3-*O*-(1-methylethylidene)5-*O*-(triphenylmethyl)-D-ribofuranose



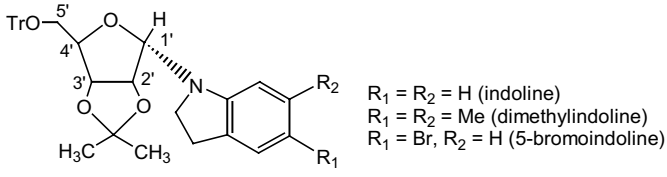
S. no.	Base (B)	Solvent	Reaction temp (°C)	Reaction time (h)	Yield[a]
1	Indoline	Ethanol	60–70	5–6	60
2	Dimethylindoline	Ethanol	60–70	4–5	65
3	5-Bromoindoline	Ethanol	60–70	6–7	55
4	Indoline	Methylene chloride	40	4	65
5	Dimethylindoline	Methylene chloride	40	4	70
6	5-Bromoindoline	Methylene chloride	40	5	60

[a] Isolated yields.

and 4 Å molecular sieves at room temperature and the mixture was heated for 5–6 h under an argon atmosphere while the reaction progress was monitored by TLC and NMR. The reaction proceeded smoothly, and after completion the mixture was cooled to room temperature and filtered, and thoroughly washed with ethanol. By using methylene chloride as a solvent, the observed yield was higher and there was no decomposition of the sugar, as the ethanol method resulting a sluggish reaction and decomposition of 2,3-*O*-(1-methylethylidene)5-*O*-(triphenylmethyl)-D-ribofuranose at higher temperature. The reaction mixture showed only one isomer in NMR after workup. The reaction of dimethylindoline and 2,3-*O*-(1-methylethylidene)5-*O*-(triphenylmethyl)-D-ribofuranose proceeds faster (Table 1) than the reaction with the other indoline bases. 5-Bromoindoline[16] is less reactive and the longer heating time results in lower yields of the corresponding ribonucleoside.

The identity and α-configuration of these ribonucleosides were confirmed based on the previous characterization[8] of the corresponding α-indoline ribonucleosides, which were prepared by the 2-fluoro-1-methylpyridinium tosylate[10] method and fully characterized by X-ray and 2D NMR spectroscopy. The structure of these indoline ribonucleosides, prepared by direct glycosylation, was also confirmed by ^{1}H NMR, ^{13}C NMR, and as well as 2D NMR (COSY, HMQC, and NOESY). The signals for the methyl protons of the isopropylidene in **8** were present at δ 1.38 and 1.60 ppm and the anomeric proton signal was visible at δ 5.44 ppm (Table 2), the same as reported for the indoline ribonucleosides[8] prepared by the 2-fluoro-1-methylpyridinium tosylate method. The indoline methylene protons in dimethylindoline ribonucleoside **9** showed a strong NOE with one of the isopropylidene methyls, which further supports the α-anomeric configuration. For further use as a precursor for B3-deazacobalamins (Fig. 1),

Table 2. ^{1}H NMR/^{13}C NMR comparison of indoline ribonucleosides prepared by direct glycosylation[b]/2-fluoro-1-methylpyridinium tosylate[a] method (chemical shifts, ribose protons, δ ppm)



S. no.	Compound (ribonucleosides)	Me_1	Me_2	5′	5′′	4′	3′	2′	1′
1	Indoline[a] (^{1}H NMR)	1.39	1.61	3.28	3.35	4.19	4.72	4.85	5.455
2	Indoline[b]	1.38	1.59	3.28	3.35	4.17	4.69	4.84	5.44
3	Indoline[a] (^{13}C NMR)	25.56	27.48	63.89	—	82.00	80.67	81.49	92.83
4	Indoline[b]	25.57	27.49	63.92		82.03	80.72	81.52	92.89
5	Dimethylindoline[a] (^{1}H NMR)	1.38	1.60	3.26	3.32	4.19	4.64	4.80	5.41
6	Dimethylindoline[b]	1.39	1.62	3.29	3.33	4.21	4.67	4.83	5.43
7	Dimethylindoline[a] (^{13}C NMR)	25.56	27.51	64.02	—	81.93	80.91	81.58	93.20
8	Dimethylindoline[b]	25.58	27.51	64.05		81.94	80.92	81.58	93.22
9	5-Bromoindoline[a]	1.38	1.60	3.24	3.41	4.14	4.64	4.77	5.32
10	5-Bromoindoline[b]	1.38	1.60	3.28	3.36	4.18	4.69	4.81	5.36

[a] Reported ^{1}H NMR values in (δ ppm), Ref. 8.
[b] Prepared by direct glycosylation.

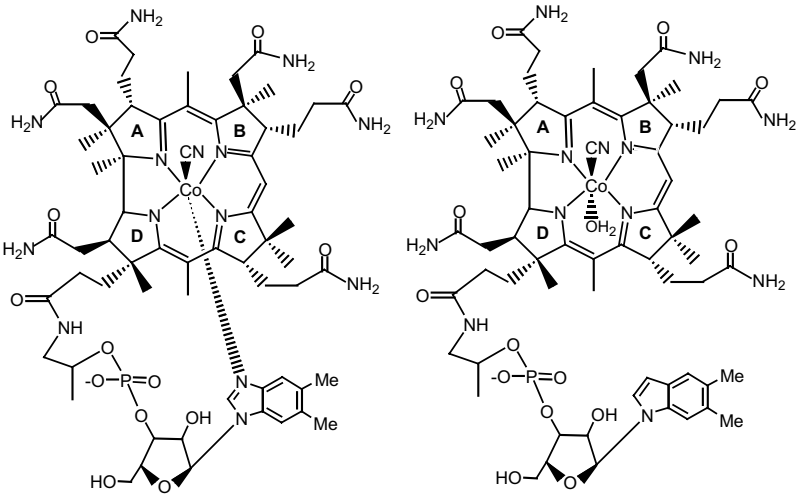


Figure 1.

these indoline ribonucleosides were converted to the corresponding indole ribonucleosides and all spectroscopic data were compared with previously prepared indole ribonucleosides[9] as described earlier (Scheme 1).

2. General procedure for the synthesis of indoline nucleosides 8–10

2.1. Method a: synthesis of 1-(5-*O*-triphenylmethyl-2, 3-*O*-isopropylidene-α-D-ribofuranosyl) indoline[17] (8)

To a solution of indoline **4** (0.336 g, 2.8 mmol) in freshly distilled dry ethanol (15 mL) was added 2,3-*O*-(1-methylethylidene)5-*O*-(triphenylmethyl)-D-ribofuranose, **7** (1.0 g, 2.3 mmol) and type 4Å molecular sieves (5 g). The reaction mixture was stirred at 50–60 °C for 5–6 h under an argon atmosphere and the progress of the reaction was monitored by TLC and ^{1}H NMR. After complete conversion of the sugar, the reaction mixture was filtered and thoroughly washed with methylene chloride (3×10 mL). The solvent was then removed under reduced pressure and the residue was extracted with methylene chloride (2×50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The viscous oil was then passed through a silica gel column and eluted with methylene chloride:hexane (1:1) to give the desired product in 60% yield. The reaction was also repeated in methylene chloride as a solvent which afforded the desired ribonucleoside in higher yield (70%).

2.2. Method b: synthesis of 1-(5-*O*-triphenylmethyl-2, 3-*O*-isopropylidene-α-D-ribofuranosyl) 5,6-dimethylindoline (9)

To a solution of 5,6-dimethyl-2,3-dihydro-1*H*-indole,[15] **5** (0.200 g, 1.3 mmol) in dry methylene chloride (4 mL) was added 2,3-*O*-(1-methylethylidene)5-*O*-(triphenylmethyl)-D-ribofuranose **7** (0.30 g, 0.7 mmol) and the mixture was heated at 40 °C for 4 h under an argon atmosphere, the progress of the reaction mixture was monitored by TLC (ether: benzene 20:80). After complete conversion of the sugar, the reaction mixture was cooled and silica gel (5 g) was added, and the solvent was removed under reduced pressure. The silica gel powder was loaded on to a silica gel column packed in benzene. After elution with benzene it afforded the pure dimethylindoline ribonucleoside in 70% yield.

Acknowledgements

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15. 5,6-Dimethyl-2,3-dihydro-1*H*-indole (**5**): A solution of dimethylindole (**2**) (1.1 g, 7.5 mmol) in acetic acid (20 mL) was stirred for 10 min at 12 °C and sodium cyanoborohydride (1.6 g, 25 mmol) was added portion wise under a nitrogen atmosphere at the same temperature. The reaction mixture was further stirred for 2 h at 12 °C and was monitored by TLC. After completion of the reaction, the mixture was neutralized with 50% sodium hydroxide (30 mL). Finally ether (100 mL) was added and the mixture was stirred for 30 min. The ether layer was separated, the extraction was repeated two more times, and the combined ether layers were washed with brine. The organic layer was dried over anhydrous potassium carbonate, and finally the ether layer was removed under reduced pressure to afford a viscous oil. The oil was finally purified on silica gel column. Yield: 95%; white solid; ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.98 (t, J = 8.4 Hz, 2H, CH_2), 3.53 (t, J = 8.8 Hz, 2H, CH_2), 6.54 (s, 1H, Ar), 6.93 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$): δ 19.19 (CH_3), 19.93 (CH_3), 29.67 (CH_2), 47.53 (CH_2), 111.52 (CH), 125.82 (CH), 126.86 (Cquat), 127.05 (Cquat), 135.10 (Cquat), 149.16 (Cquat); MS (EI) *m*/*z*: 147 (M^+), 132, 117.
16. 5-Bromo-2,3-dihydro-1*H*-indole (**6**): 5-Bromo-2,3-dihydro-1*H*-indole was similarly prepared from 5-bromoindole as described for 5,6-dimethylindoline (**5**), above. Yield: 90%; low melting solid. ^{1}H NMR ($CDCl_3$): δ 2.99 (t, J = 8 Hz, 2H, CH_2), 3.53 (t, J = 8.5 Hz, 2H, NCH_2), 3.7 (br s, 1H, NH), 6.46 (d, J = 8.5 Hz, 1H, Ar), 7.06 (d, J = 6.5 Hz, 1H, Ar), 7.17 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$): δ 29.62 (CH_2), 47.47 (CH_2), 110.01 (Cquat), 110.50 (Cquat), 127.44 (CH), 129.68 (CH), 131.71 (CH), 150.55 (Cquat); MS (EI) *m*/*z*: 198 (M^+), 118 (M−Br).
17. Selected data for **8**: yield: 90%; R_f 0.6; white foam; ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3H, CH_3, isopropylidene), 1.59 (s, 3H, CH_3, isopropylidene), 2.91–2.97 (m, 2H, CH_2, indoline), 3.28 (dd, J = 4.5, 5.0 Hz, 1H, 5′), 3.35 (dd, J = 4.5, 5 Hz, 1H, 5′′), 3.52–3.55 (m, 1H, CH of NCH_2, indoline), 3.59 (q, 1H, CH, indoline), 4.17–4.21 (m, 1H, CH, 4′), 4.67–4.69 (m, 1H, CH, 3′), 4.83–4.85 (m, 1H, CH, 2′), 5.44 (d, J = 3.78 Hz, 1H, CH, 1′), 6.76 (d, J = 7.5 Hz, 1H, CH, Ar), 6.80 (d, J = 8 Hz, 1H, Ar), 7.06–7.12 (m, 2H, Ar), 7.25–7.46 (m, 15H, Ar, trityl); ^{13}C NMR ($CDCl_3$): δ 25.57 (CH_3), 27.49 (CH_3), 28.28 (CH_2), 47.35 (CH_2), 63.92 (CH_2, 5′), 80.72 (C 3′), 81.52 (C 2′), 82.03 (C 4′), 86.72 (Cquat), 92.89 (C 1′), 108.95 (CH, Ar), 114.03 (Cquat), 119.20 (CH), 124.61 (CH), 127.00 (CH), 127.77 (CH), 127.91, 128.73, 130.44 (Cquat), 143.78 (Cquat); HRMS: *m*/*z*: 534.2644 (calcd for $C_{35}H_{36}NO_4$: 534.2643) (M+H); MS: (FAB) *m*/*z* 534, 491, 430, 355, 281, 243, 165. Compound **9**: yield: 70%. White foam. R_f; 0.6 (methylene chloride), ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 3H, CH_3, isopropylidene), 1.62 (s, 3H, CH_3, isopropylidene), 2.18 (s, 3H, CH_3, Ar), 2.21 (s, 3H, CH_3, Ar), 2.86–2.992 (m, 2H, CH_2, indoline), 3.29 (dd, J = 4.5, 5 Hz, 2H, 5′), 3.33 (dd, J = 4.5, 5 Hz, 2H, 5′′), 3.46–3.44 (m, 1H, indoline), 3.55 (q, 1H, indoline), 4.21 (q, J = 4.5 Hz, 1H, 4′), 4.66–4.68 (m, 1H, 3′), 4.82–4.84 (m, 1H, H 2′), 5.43 (d, J = 3.5 Hz, 1H, 1′), 6.63 (s, 1H, Ar), 6.89 (s, 1H, Ar), 7.23–7.29 (m, 9H, trityl), 7.46 (d, 6H, trityl); ^{13}C NMR ($CDCl_3$): δ 19.17 (CH_3, Ar), 20.20 (CH_3, Ar), 25.58 (CH_3, isopropylidene), 27.51 (CH_3, isopropylidene), 28.11 (CH_2, indoline), 47.29 (CH_2, indoline), 64.050 (CH_2, 5′), 80.92 (C 3′), 81.58 (C 2′), 81.94 (C4′), 86.68 (Cquat), 93.22 (C1′), 110.61 (CH), 113.91 (Cquat), 125.87 (CH), 126.98, 127.76, 127.911 (CH), 128.63 (CH), 128.72 (CH), 135.04 (Cquat), 143.81 (Cquat), 148.16 (Cquat), HRMS: *m*/*z*: 561.2882 (calcd for $C_{37}H_{39}NO_4$: 561.2868); MS: (FAB) *m*/*z* 561, 318, 244, 243, 165. Compound **10**: white foam. R_f: 0.7 (methylene chloride), ^{1}H NMR ($CDCl_3$): δ 1.385 (s, 3H, CH_3, isopropylidene), 1.602 (s, 3H, CH_3, isopropylidene), 2.90–2.96 (m, 2H, CH_2, indoline), 3.28 (dd,J = 4.5 Hz, 1H, 5′), 3.36 (dd, 1H, 5′′), 3.53–3.56 (q, 1H, NCH_2, indoline), 3.58 (q, 1H, NCH_2, indoline), 4.17–4.20 (m, 1H, CH, 4′), 4.68–4.70 (m, 1H, CH, 3′), 4.80–4.83 (m, 1H, CH, 2′), 5.36 (d, J = 3.8 Hz, 1H, CH, 1′), 6.67 (d, J = 8.5 Hz, 1H, Ar), 7.14 (d, J = 8.5 Hz, 1H, Ar), 7.19 (s, 1H, Ar), 7.24–7.28 (m, 9H, trityl), 7.41 (d, J = 7 Hz, 6H, trityl).