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The First Total Synthesis of Pyralomicin 2c

Kuniaki Tatsuta*, Masaaki Takahashi, and Noboru Tanaka

Department of Applied Chemistry, School of Science and Engineering, Waseda University
3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

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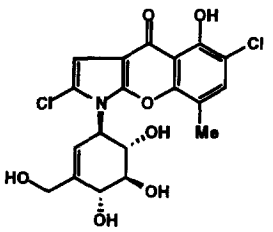
Abstract: Pyralomicin 2c (**2**) has been synthesized by *N*-glucosylation of the aglycone **16**, which was prepared from the appropriately substituted pyrrole and benzoyl chloride (**5** and **9**).

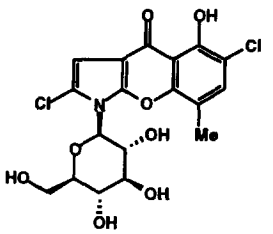
Pyralomicin 1c and 2c (**1** and **2**) have been isolated, together with their families, from the culture broth of *Microtetraspora spiralis* as novel antibiotics,[1] and were determined to possess the 5-hydroxy-8-methyl-[1]-benzopyrano[2,3-b]pyrrol-4-(1*H*)-one structure as a common core binding a carba sugar and a sugar moiety, respectively.[2,3]

The aglycone, pyralomycinone (**16**), has been recently synthesized by Kelly and Moiseyeva.[4]

Herein, we describe the first total synthesis of pyralomicin 2c (**2**) to confirm the absolute structure. To this end, we naturally selected the aglycone **16** as our first target, and independently accomplished an alternative and effective synthesis.



Pyralomicin 1c (1)



Pyralomicin 2c (2)

The starting material, pyrrole, was regioselectively chlorinated with NCS to give the 2,5-dichloro derivative **3**[5](oil), which was *N*-protected with Boc_2O to give **4** (90% in 2 steps, oil). Bromination of **4** with NBS provided the mono-bromide **5** (80%, oil).

The other starting material **6** was lithiated and treated with Dry-Ice to give the benzoic acid **7** (72%, mp 120°C). This was regioselectively chlorinated with SO_2Cl_2 to **8** (92%, mp 75°C), which was converted by $SOCl_2$ into the labile acid chloride **9** (90%, oil). The structure **8** was confirmed by NOE enhancement (4.2 %) between H-4 and Me-5.

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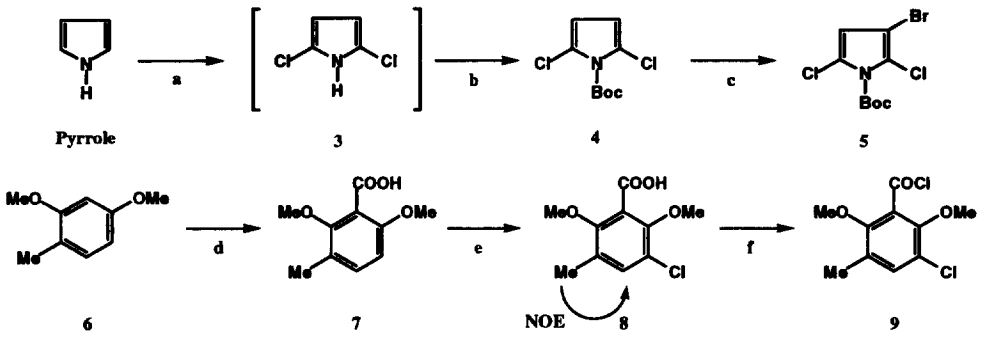
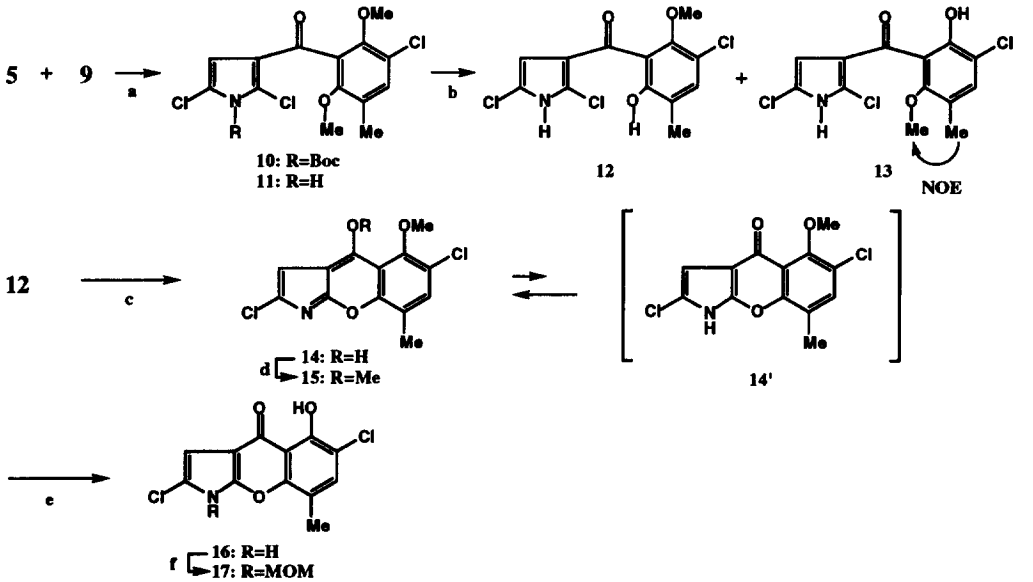
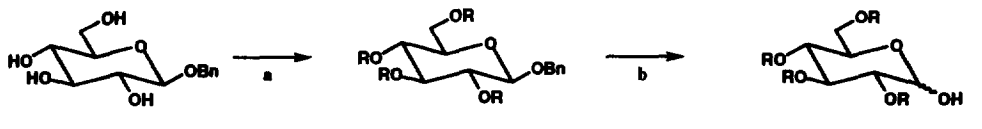


Conditions; (a) NCS/THF, -78°C→ rt, 5h (b) Boc_2O, DMAP/THF, -78°C→ rt, 8h, 90% (c) NBS/THF, -78°C→ rt, 8h, 80% (d) 1) *t*-BuLi/PhMe, -78°C→ rt, 5h 2) Dry-Ice, 72% (e) $SO_2Cl_2/CHCl_3$, rt, 3h, 92% (f) $SOCl_2$/DMF, PhH, reflux, 5h, 90%

Both segments **5** and **9** were combined as follows. The segment **9** reacted with the lithiated **5** to produce the carbonyl compound **10** (76%, oil) and its *N*-deprotected derivative **11** (9%, oil), both of which could be converted to the phenol **12**. Selective de-*O*-methylation of **10** was assayed under a variety of conditions, and a fairly good result was realized by treatment with BBr3 to provide the desired phenol **12** (54%, mp 177°C) and the undesired **13** (19%, oil) with concomitant *N*-deprotection. NOE enhancement between the *O*-Me and *C*-Me groups was observed in **13** (1.2 %), but not in **12**, supporting their structures. Similar de-*O*-methylation of **11** gave **12** and **13** in 56% and 20% yields, respectively. Interestingly, Kelly and Moiseyeva have reported that the *N*-tosyl derivative was de-*O*-methylated without selectivity under similar conditions.[4)]

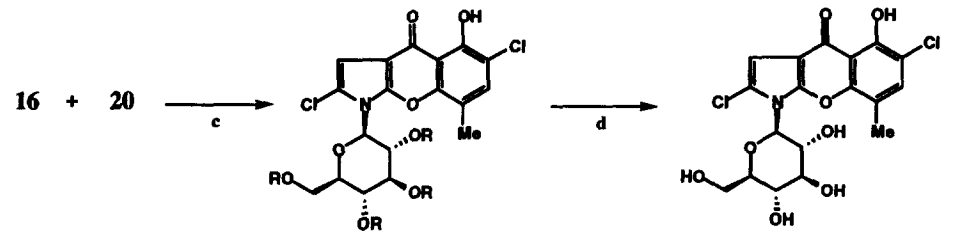


Conditions; (a) 1) **5**, *n*-BuLi/THF, -78°C, 1h , then **9**, -78°C→ rt, 1h (b) BBr_3/CH_2Cl_2, rt, 3h (c) NaH/DMF, 110°C, 36h, 62% (d) $TMSCHN_2$/MeOH, rt, 1h, 95% (e) BBr_3/DMF,CH_2Cl_2, rt, 12h, 70% (f) MOMCl,DIPEA/DMF, rt, 8h, 90%



18 19: R=MOM 20: R=MOM

Conditions; (a) MOMCl,DIPEA/CH_2Cl_2, rt, 48h, 96% (b) H_2,10%Pd/C, rt, 12h, 99%



21: R=MOM Pyralomicin 2c (2)

Conditions; (c) DEAD,PPh_3/DMF,THF, -40°C, 3h, 66% (d) 10%HCl-MeOH, 40°C, 5h, 90%

Cyclization of **12** was effectively achieved with NaH to give the tricyclic compound **14** [62%, mp 173°C (decomp.)]. The ^{1}H-NMR showed a broad signal around δ 13.25 due to the enol proton, indicating that it existed in the enol form **14** rather than the keto form **14'**. Furthermore, treatment of **14** with $TMSCHN_2$ gave the methyl enol ether **15** (95%, mp 206°C). These results suggested **14** not to be an appropriate segment for the following *N*-glycosylation.

De-*O*-methylation of **14** with BBr_3 afforded the aglycone **16** (70%, mp ›300°C), the physico-chemical characteristics of which were identical with the previously reported data.[4] Methoxymethylation of **16** afforded exclusively the corresponding *N*-substituted derivative **17** (90%, oil), which showed a phenol singlet at δ 13.54 in the ^{1}H-NMR. We anticipated that, in **16**, an intramolecular hydrogen bond between the carbonyl and phenol groups would be formed, thus leading to the desired *N*-glycosylation.

With the appropriate aglycone portion **16** in hand, we turned to the glycosylation. The glucose donor **20** was prepared from benzyl β-D-glucopyranoside (**18**).[6] Methoxymethylation of **18** to give **19** [oil, $[\alpha]_D$ -2.9° (MeOH)] followed by hydrogenolysis afforded almost quantitatively the glucose derivative **20** [a mixture of α- and β-anomers (approximately 1 : 1), oil, $[\alpha]_D$ +47° (MeOH)], where migration of the *O*-methoxymethyl group to the anomeric position was not observed at all.

Coupling of **20** with **16** was accomplished by using Mitsunobu's conditions[7] to give predominantly the desired *N*-β-glucoside **21** [foam: 66%, $[\alpha]_D$ +3.8° (MeOH)], which was submitted to methanolysis to produce pyralomicin 2c (**2**) [90%, mp 266°C(decomp.), $[\alpha]_D$ +4.6° (DMF)]. The synthetic product **2** was identical with the natural product[8] in all respects; thus, the first total synthesis has been completed.

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4. Kelly, T. R.; Moiseyeva, R. L. *J. Org. Chem.*, **63**, 3147-3150 (1998).
5. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. Optical rotations were measured in MeOH, except for **2** in DMF, using a 0.5 dm tube at 22°C. Significant ^{1}H-NMR spectral data (270, 300 and 400 MHz, δ; TMS= 0) are the following.

   2(DMF-*d7*): 2.45(3H, s), 3.61(3H, m), 3.73(1H, m), 3.89(1H, m), 4.36(1H, br.t), 4.79(1H, br.t), 5.35(1H, br.s), 5.50(1H, br.s), 5.51(1H, d, *J*=9.6Hz), 5.89(1H, br.s), 6.78(1H, s), 7.74(1H, s), 13.67(1H, br.s). **3**($CDCl_3$): 5.97(2H, d, *J*=3.0Hz), 8.28(1H, br.s). **4**(CDCl3): 1.63(9H, s), 6.08(2H, s). **5**($CDCl_3$): 1.61(9H, s), 6.18(1H, s). **7**($CDCl_3$): 2.25(3H, d, *J*=1.0Hz), 3.86(3H, s), 3.88(3H, s), 6.67(1H, d, *J*=9.0Hz), 7.21(1H, dd, *J*=9.0, 1.0Hz). **8**($CDCl_3$): 2.27(3H, d, *J*=1.0Hz), 3.84(3H, s), 3.94(3H, s), 7.28(1H, d, *J*=1.0Hz). **10**($CDCl_3$): 1.62(9H, s), 2.24(3H, s), 3.68(3H, s), 3.78(3H, s), 6.41(1H, s), 7.25(1H, s). **11**($CDCl_3$): 2.25(3H, s), 3.70(3H, s), 3.79,(3H, s), 6.32(1H, d, *J*=3.0Hz), 7.24(1H, s), 8.24(1H, br.s). **12**($CDCl_3$): 2.23(3H, d, *J*=1.0Hz), 3.58(3H, s), 6.39(1H, d, *J*=3.0Hz), 7.29(1H, d, *J*=1.0Hz), 8.59(1H, br.s), 9.78(1H, s). **13**($CDCl_3$): 2.21(3H, d, *J*=1.0Hz), 3.59(3H, s), 6.37(1H, d, *J*=3.0Hz), 7.27(1H, d, *J*=1.0Hz), 8.05(1H, s), 8.85(1H, br.s). **14**(DMF-*d7*): 2.44(3H, d, *J*=1.0Hz), 3.90(3H, s), 6.48(1H, s), 7.74(1H, d, *J*=1.0Hz), 13.25(1H, br.s). **15**($CDCl_3$): 2.48(3H, d, *J*=1.0Hz), 3.68(3H, s), 3.97(3H, s), 6.59(1H, s), 7.50(1H, d, *J*=1.0Hz). **16**(DMF-*d7*): 2.38(3H, s), 6.55(1H, s), 7.64(1H, s), 14.20(1H, s). **17**($CDCl_3$): 2.42(3H, s), 3.44(3H, s), 5.48(2H, s), 6.64(1H, s), 7.48(1H, s), 13.54(1H, s). **19**($CDCl_3$): 3.38(3H, s), 3.39(3H, s), 3.42(3H, s), 3.44(3H, s), 3.45-3.64(3H, m), 3.65(1H, dd, *J*=8.4, 8.0Hz), 3.73(1H, dd, *J*=11.6, 5.0Hz), 3.92(1H, dd, *J*=11.6, 2.0Hz), 4.42(1H, d, *J*=8.0Hz), 4.59-4.94(10H, m), 7.27-7.35(5H, m). **20**($CDCl_3$): 4.62(0.5H, d, *J*=8.0Hz, H-1_{ax}), 5.34(0.5H, d, *J*=4.0Hz, H-1_{eq}). 3.38, 3.39, 3.41, 3.43, 3.44 & 3.45(12H in total, each s, OMe) **21**($CDCl_3$): 2.44(3H, s), 2.78(3H, s), 3.26(3H, s), 3.45(3H, s), 3.47(3H, s), 3.70(2H, m), 3.76(1H, m), 3.83(1H, dd, *J*=9.6, 8.2Hz), 3.90(1H, br.t, *J*=9.6Hz), 4.38(1H, d, *J*=7.6Hz), 4.40(1H, t, *J*=8.0Hz), 4.60(2H, s), 4.70(1H, d, *J*=7.6Hz), 4.80(1H, d, *J*=6.0Hz), 4.87(1H, d, *J*=6.4Hz), 4.92(1H, d, *J*=6.4Hz), 4.93(1H, d, *J*=6.0Hz), 5.43(1H, d, *J*=8.2Hz), 6.61(1H, s), 7.48(1H, s), 13.49(1H, br.s).
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8. An authentic sample of pyralomicin 2c (**2**) was kindly provided by Dr. Hiroshi Naganawa, Institute of Microbial Chemistry.