The First Total Synthesis of Pyralomicin 1c

Sir:

Pyralomicins 1c and 2c (**1** and **2**) have been isolated from culture broth of *Microtetraspora spiralis* as novel antibiotics including antitumor activities[1]. Sturcturally, **1** and **2** are endowed with 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] (Fig. 1).

Recently, pyralomicin 2c (**2**) was synthesized in our laboratories[4] from the aglycone, pyralomicinone (**5**) and properly protected D-glucose **6** (Fig. 2).

Herein, we describe the total synthesis of pyralomicin 1c (**1**) to confirm the absolute structure.

Since pyralomicinone (**5**) has been synthesized from pyrrole and 2,4-dihydroxytoluene derivatives (for examples: **3** and **4**)[4,5], the first aim in the present synthesis is the effective construction of the carba sugar moiety **23**.

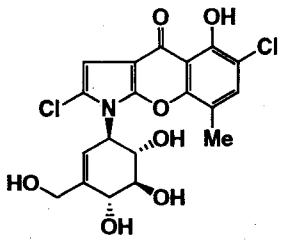
We expected the regio- and stereoselective connection of **23** with pyralomicinone (**5**) to be controlled under Mitsunobu conditions[4] with inversion.

Furthermore, it was anticipated that the carba sugar **23** would be synthesized by the similar strategies as developed by us[6,7] in the synthesis of glyoxalase I inhibitor[8] (**13**) and its precursor, KD16-U1[9] (**12**) (Fig. 3). Both carbocycles **12** and **13** have been synthesized from D-ribonic acid γ-lactone **7** through one-step opening of the furanose **8** followed by aldol condensation (**9**~**11**).

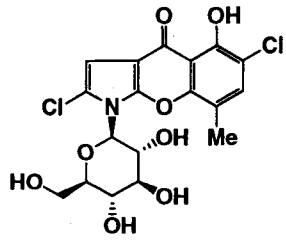
The starting material we came to favor was L-arabinonic acid γ-lactone **14**, which was readily derived from L-arabinose by tritylation and bromine oxidation[10] (Fig. 4).

Silylation of **14** followed by de-*O*-tritylation gave the alcohol **15**, which was submitted to Pfitzner-Moffatt oxidation and acetal formation to afford the acetal **16** (Table 1). Reaction of **16** with lithiated methyl phenyl sulfonate gave the furanose **17** in a quantitative yield. This was silylated to the opened chain **18** in one step by simultaneous formation of an enol silyl ether and an *O*-silyl secondary alcohol as mentioned before[6,7].

Fig. 1.

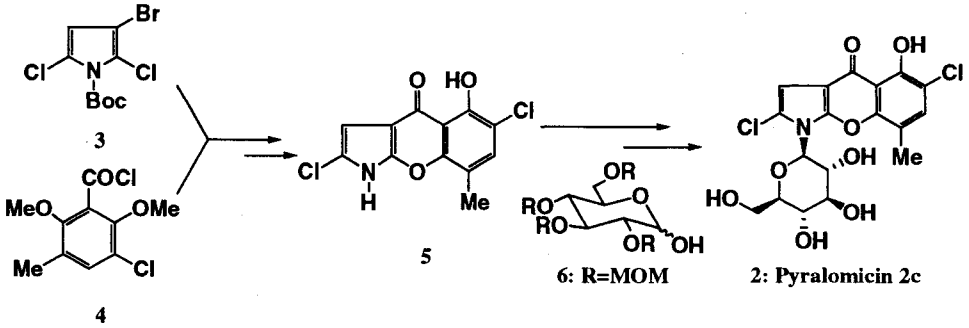


1: Pyralomicin 1c



2: Pyralomicin 2c

Fig. 2.



3

4

5

6: R=MOM

2: Pyralomicin 2c

Fig. 3.

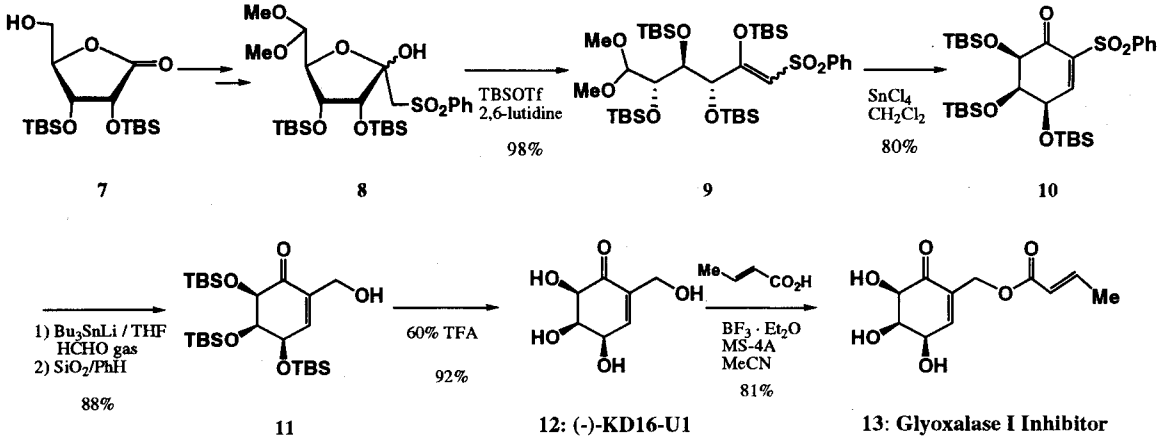
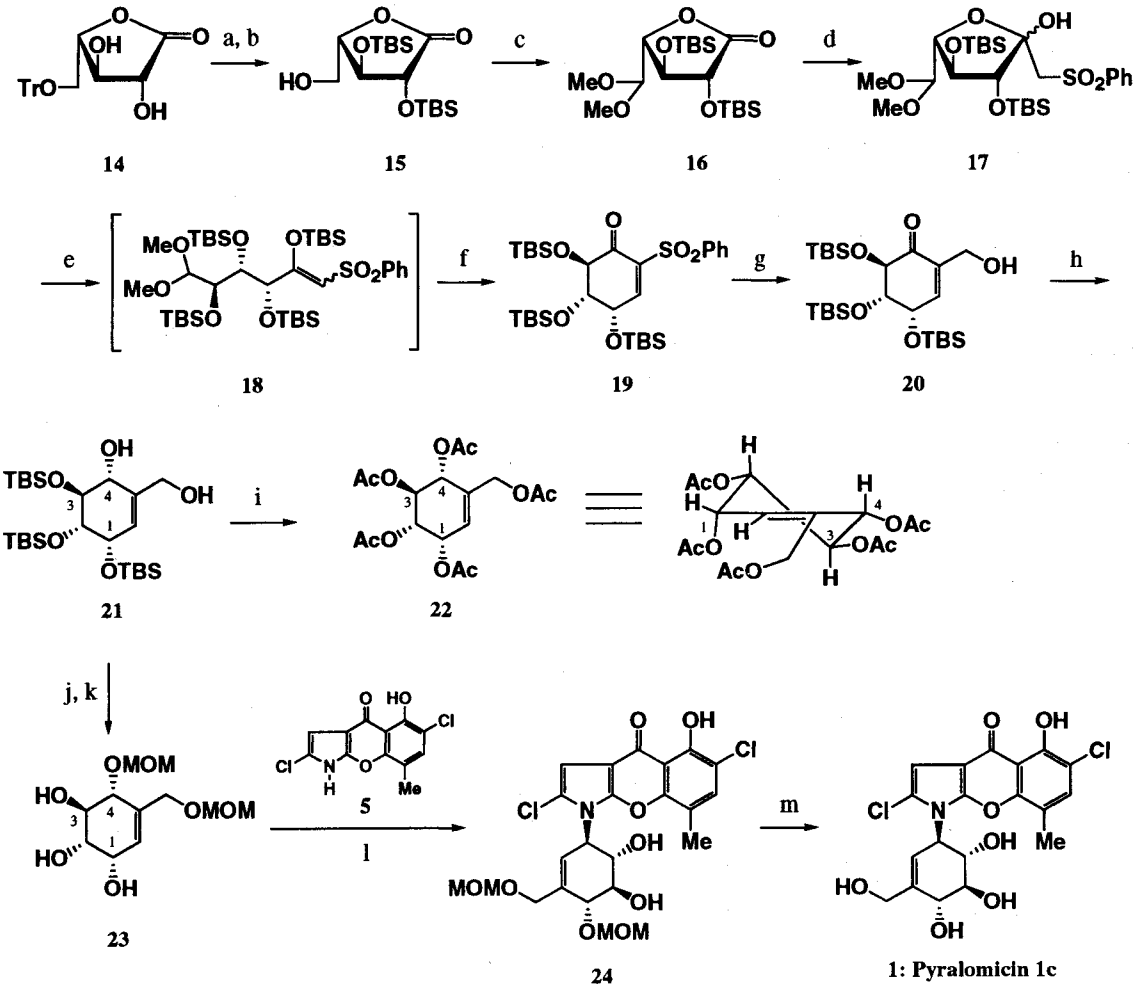


Fig. 4.



Conditions; (a) TBSOTf, 2,6-lutidine/CH_2Cl_2, rt, 3 hours; 94% (b) H_2, Pd-C/$CHCl_3$, rt, 12 hours; 85% (c) 1) DCC, Py•TFA, DMSO/Et_2O, rt, 3 hours 2) CSA, $HC(OMe)_3$/MeOH, 50°C, 36 hours; 81% (d) $MeSO_2Ph$, *n*-BuLi/THF, -78°C, 1.5 hours; 97% (e) TBSOTf, 2,6-lutidine/CH_2Cl_2, 40°C, 24 hours; 94% (f) $SnCl_4$/CH_2Cl_2, -78°C, 15 minutes; 71% (g) *n*-Bu_3SnLi, HCHO/ THF, -78°C to 40°C, 24 hours; 74% (h) $NaBH_4$, $CeCl_3$•$7H_2O$/MeOH-CH_2Cl_2, -78°C, 3.5 hours; 69% (i) 1) TBAF/THF, rt, 4 hours 2) Ac_2O, Py, rt, 12 hours; 94% (j) MOMCl, *n*-Bu_4NI, DIPEA/CH_2Cl_2, 50°C, 24 hours; 92% (k) TBAF/THF, rt, 4 hours; 95% (l) *n*-Bu_3P=CHCN/THF, 40°C, 12 hours; 51% (m) 5%HCl/MeOH, 50°C, 4 hours; 97%

Table 1. Physico-chemical properties of compounds.

No.	Mp (°C)	$[\alpha]_D$ ($CHCl_3$)	^{1}H-NMR (270, 300 or 600MHz; $CDCl_3$; δ ppm; *J* Hz)
1	283-286 (decomp.)	-148° (*c* 0.24, DMF)	(DMF-d_7): δ 2.34(3H, s), 3.70(1H, ddd, *J*=5.0, 8.0&10.2), 4.18-4.40(4H, m), 4.86-4.92(1H, m), 5.14(1H, br s), 5.28(1H, d, *J*=5.0), 5.32(1H, br d, *J*=6.2), 5.58(1H, br s), 5.72(1H, br s), 6.72(1H, s), 7.70(1H, s), 13.82(1H, br s)
14	Foam	+17° (*c* 1.18)	δ 3.37(1H, dd, *J*=4.0&10.4), 3.54(1H, dd, *J*=3.8&10.4), 4.25(1H, ddd, *J*=3.8, 4.0&8.2), 4.36(1H, dd, *J*=8.2&8.2), 4.45(1H, d, *J*=8.2), 7.20-7.46(15H, m)
15	Foam	-5.6° (*c* 1.15)	δ 0.13(3H, s), 0.14(3H, s), 0.15(3H, s), 0.21(3H, s), 0.90(9H, s), 0.94(9H, s), 1.94(1H, br s), 3.73(1H, ddd, *J*=3.8, 8.0&14.0), 3.95(1H, ddd, *J*=2.2, 6.0&14.0), 4.11(1H, ddd, *J*=2.2, 3.8&7.0), 4.33(1H, dd, *J*=7.0&7.0), 4.38(1H, d, *J*=7.0)
16	Syrup	+16° (*c* 1.28)	δ 0.10(3H, s), 0.11(3H, s), 0.16(3H, s), 0.19(3H, s), 0.88(9H, s), 0.92(9H, s), 3.44(3H, s), 3.45(3H, s), 4.17(1H, dd, *J*=4.6&5.0), 4.19(1H, d, *J*=4.6), 4.26(1H, dd, *J*=4.6&4.6), 4.47(1H, d, *J*=5.0)
19	131-132	+87° (*c* 0.74)	δ -0.08(3H, s), -0.06(3H, s), -0.02(3H, s), 0.05(3H, s), 0.15(3H, s), 0.17(3H, s), 0.57(9H, s), 0.81(9H, s), 0.95(9H, s), 3.81(1H, d, *J*=5.0), 4.01(1H, ddd, *J*=2.0, 2.0&5.0), 5.10(1H, dd, *J*=1.0&2.0), 7.49(3H, m), 7.74(1H, dd, *J*=1.0&2.0), 7.94-8.00(2H, m)
20	Syrup	+73° (*c* 1.20)	δ 0.04(3H, s), 0.05(3H, s), 0.06(3H, s), 0.12(3H, s), 0.13(6H, s), 0.81(9H, s), 0.87(9H, s), 0.93(9H, s), 2.22(1H, t, *J*=7.0), 3.83-4.06(2H, m), 4.19(1H, dd, *J*=6.0&14.0), 4.31(1H, dd, *J*=5.0&14.0), 4.85-4.95(1H, m), 6.51(1H, br s)
21	Syrup	+35° (*c* 2.18)	δ 0.08(3H, s), 0.09(3Hx3, s), 0.12(3H, s), 0.13(3H, s), 0.85(9H, s), 0.87(9H, s), 0.92(9H, s), 2.17(1H, br s), 3.17(1H, d, *J*=12.0), 3.75(1H, d, *J*=12.0), 3.88-3.93(1H, m), 4.04(1H, dd, *J*=2.0&4.2), 4.15-4.30(2H, m), 4.59(1H, dd, *J*=2.0&2.0), 5.52(1H, dd, *J*=2.0&2.0)
22	Syrup	+51° (*c* 0.54)	δ 2.02(3H, s), 2.04(3H, s), 2.06(3H, s), 2.07(3H, s), 2.11(3H, s) 4.41(1H, d, *J*=13.0), 4.71(1H, d, *J*=13.0), 5.16(1H, dd, *J*=4.0&10.4), 5.53(1H, dd, *J*=7.6&10.4), 5.62(1H, dd, *J*=4.0&5.8), 5.70(1H, d, *J*=7.6), 5.97(1H, d, *J*=5.8)
23	111-113	+5.3° (*c* 2.18)	(CD_3OD): δ 3.30(3H, s), 3.39(3H, s), 3.40(1H, dd, *J*=4.2&10.0), 3.80(1H, dd, *J*=7.6&10.0), 3.92(1H, dd, *J*=1.0&7.6), 4.03(1H, d, *J*=12.4), 4.11-4.15(2H, m), 4.56(1H, d, *J*=6.0), 4.59(1H, d, *J*=6.0), 4.71(1H, d, *J*=6.0), 4.88(1H, d, *J*=6.0), 5.88(1H, dd, *J*=2.0&5.0)
24	214-216	-104° (*c* 0.31)	δ 2.28(3H, s), 3.30(3H, s), 3.53(3H, s), 3.74(1H, d, *J*=2.4), 3.86(1H, dd, *J*=7.8&8.2), 4.12-4.24(3H, m), 4.38(1H, ddd, *J*=2.4, 8.2&8.2), 4.60(1H, d, *J*=5.8), 4.62(1H, d, *J*=5.8), 4.74(1H, br s), 4.84(1H, d, *J*=7.0), 4.91(1H, d, *J*=7.0), 5.20(1H, br d, *J*=2.4), 5.77(1H, br s), 6.49(1H, s), 7.37(1H, s), 13.29(1H, s)

The $SnCl_4$-promoted aldol condensation of the **18** resulted in the formation of the cyclohexenone **19**, which was treated with tributylstannyl lithium[11] followed by reation with formaldehyde to yield the α-hydroxymethyl-cyclohexenone **20** with elimination of Bu_3Sn and $PhSO_2$ groups.

Stereoselective reduction of the carbonyl group of **20** was assayed in a variety of conditions, and the best result was realized by using $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ to give the desired α-alcohol **21** in 69% yield with 10% of the β-

alcohol. The configuration of the newly produced C-4 hydroxy group was not determined by the ^{1}H-NMR studies of **21**, while the configuration was unambiguously disclosed by those of the corresponding penta-*O*-acetate **22**, which reasonably presented in a half-chair conformation[12] as shown in Fig. 4: $J_{1,2}$=4.0 Hz, $J_{2,3}$=10.4 Hz, $J_{3,4}$=7.6 Hz, and $J_{1,6}$=5.8 Hz.

The alcohol **21** was protected with methoxymethyl group followed by de-*O*-silylation to give quantitatively the triol **23**. Although **23** possessed three free hydroxy groups, the allyl hydroxy group at C-1 was expected to be more reactive than others.

With pyralomicinone (**5**) and the alcohol **23** in hand, we turned to their connection.

Both components **5** and **23** were coupled under modified Mitsunobu's conditions[13] using a novel reagent, *n*-Bu_3P=CHCN to give predominanlty the desired product **24** with inversion. As expected, the by-products which would result from the reaction of other hydroxy groups with **5** were not significantly observed.

Acidic deprotection of **24** produced pyralomicin 1c (**1**), which was identical with the natural product[1~3] in all respects, completing the first total synthesis.

Now that the synthesis of pyralomicins 1c (**1**) and 2c (**2**) including a carba sugar and a sugar moiety, respectively, have been accomplished, the synthesis of other families[1~3] is the subject of current studies.

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