Synthetic Study toward Antitumour Natural Product Pericosine A

Yoshihide Usami* and Yasuko Ueda
Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094

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The stereoselective total synthesis of methyl (3*R*,4*S*,5*S*,6*R*)-6-chloro-3,4,5-trihydroxy-1-cyclohex-1-enecarboxylate (**1**), which had been reported as the antitumour marine natural product pericosine A, from (−)-quinic acid was achieved. From the total synthesis, it was confirmed that the reported stereostructure of pericosine A was incorrect because the spectroscopic data of the synthetic product were not identical with those of the natural compound.

In 1997, the isolation and structure determination of pericosines A and B, which showed significant cytotoxic activity against P388 lymphocytic leukemia cells and are the metabolites of the fungus *Periconia byssoides* OUPS-N133 that was originally separated from the sea hare *Aplysia kurodai*,[1] had been reported by Numata and co-workers as shown in Figure 1 (**1** and **2**).

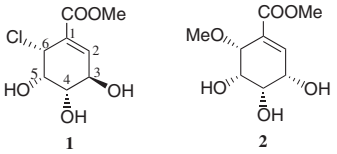
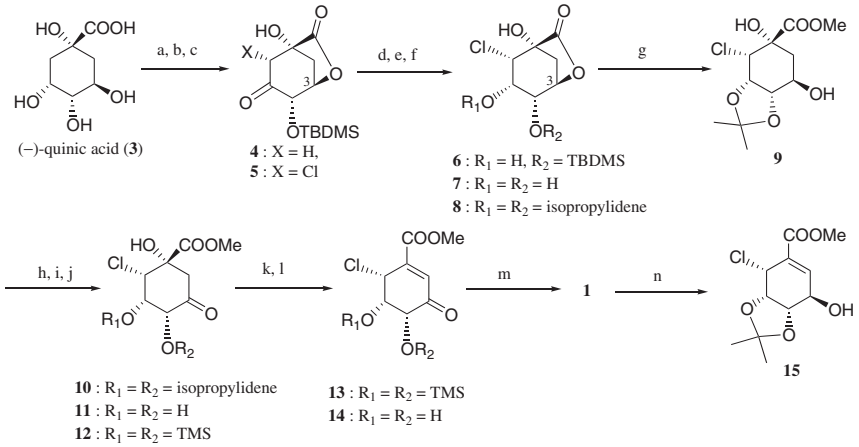


Figure 1.

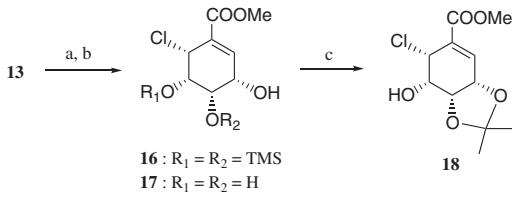
They are thought to be a class of carbasugars. As carbasugars have been reported to have antifungal, antiviral, or antitumour activities,[2] their stereoselective syntheses are an attractive challenge for the synthetic chemist and they have been studied extensively.[3] We have been interested in the synthesis of pericosines and related compounds.[4]

In 1998, the total synthesis of **2** was reported by Donohoe and co-workers,[5] and its absolute configuration was elucidated. However, there has been no report of the absolute stereostructure of **1** so far. Because **1** exhibited significant antitumour activity in vivo, its total synthesis was attempted. Described herein is the stereoselective synthesis of **1** from commercially available (−)-quinic acid (**3**).[6,7]

The synthesis of **1** is summarized in Scheme 1. According to the literature,[8] **3** was converted into lactone (**4**). The trimethylsilyl enol ether derived from **4** was chlorinated with *N*-chlorosuccinimide in DMF in 45% yield. The reaction proceeded with excellent selectivity to give the desired stereoisomer (**5**). The bromination or fluorination of **4** had been reported in literature,[8] whereas this is the first report of the chlorination. The stereochemistry at C-6 was deduced from the low-field shift (3.3 ppm) of the H-2-α proton[8] in the ^{1}H NMR spectrum of **5**. The reagent was surmised to approach the silyl enol ether from the opposite side of the sterically hindered lactone bridge in the molecule. The improvement of the chemical yield of this step remains to be accomplished. Chloroketone **5** was reduced with $NaBH_4$ to give diol (**6**)[9] in 68% yield, which was treated with tetrabutylammonium fluoride to afford triol (**7**) in 67% yield. The lactone ring of acetonide (**8**) derived from **7** was opened with NaOMe to afford diol (**9**) in 90% yield and the generated secondary hydroxyl group was oxidized with Dess–Martin periodinane[10] to give hydroxyketone (**10**)[11] in 78% yield, which was never dehydrated by any reagents. Then, the deprotection of the hydroxyl groups followed by the protection as trimethylsilyl ether gave β-hydroxyketone (**12**), which was dehydrated with Martin's sulfrane dehydrating reagent[12] (bis[α,α-bis(trifluoromethyl)benzyloxy]dipheny sulfur) to afford α,β-unsaturated ketone (**13**)[13] in 65% yield. Enone **13** was treated with trifluoroacetic acid and MeOH to give dihydroxy-α,β-unsaturated



Scheme 1. Reagents and conditions: a) Ref. 8; b) Et_3N, TMSOTf, toluene, reflux; c) NCS, DMF, rt (45% in two steps); d) $NaBH_4$ (68%); e) *n*-Bu_4NF (67%); f) 2,2-dimethoxypropane, CH_2Cl_2, catalytic TsOH (30%); g) NaOMe, MeOH (90%); h) Dess–Martin periodinane, CH_2Cl_2 (78%); i) trifluoroacetic acid (TFA), MeOH (70%); j) TMSCl, Et_3N (71%); k) Martin's sulfrane dehydrating reagent, CH_2Cl_2 (65%); l) TFA, MeOH (quant.); m) $Me_4NBH(OAc)_3$, MeCN/AcOH (64%); n) 2,2-dimethoxypropane, acetone, catalytic TsOH (72%).



Scheme 2. Reagents and conditions: a) $NaBH_4$, MeOH, $-10\,^{\circ}C$; b) TFA, MeOH (quant. in 2 steps); c) 2,2-dimethoxypropane, catalytic TsOH, acetone (55%).

ketone (**14**) quantitatively, and **14** was reduced with tetramethylammonium triacetoxyborohydride[14] in a stereoselective manner to give the desired **1**[15] in 64% yield. The stereochemistry of C-3 in **1** was proved by the following experiments.

As shown in Scheme 2, common intermediate **13** was reduced with $NaBH_4$ to give **16**. The subsequent deprotection of **16** gave **17**,[16] which is different from both **1** and natural pericosine A. 3,4-*O*-acetonide formation of **18** from diastereoisomer **17** implied that 3-OH and 4-OH in **17** had the *cis*-configuration. Observation of the NOESY cross peaks between one of methyl groups of acetonide and H-3, H-4 in **18** led the same assignment. Therefore, the hydroxyl group at C-3 in synthesized **1** must have the β-configuration. However, the spectroscopic data of **1** and those of acetonide (**15**) were not identical with those of natural pericosine A and those of its acetonide reported in the literature.[1] Furthermore, an isopropylidene bridge in **15** was present not between O-3 and O-4 as described in the literature,[1] but between O-4 and O-5. The structure of **15** was suggested by observing the cross peaks between the proton signal of one of two methyl groups of the isopropylidene moiety and H-4 or H-5 in its NOESY spectra. From this synthetic study, it became apparent that **1** is the incorrect stereostructure of pericosine A.

In conclusion, we have accomplished the stereoselective total synthesis of methyl (3*R*,4*S*,5*S*,6*R*)-6-chloro-3,4,5-trihydroxy-1-cyclohex-1-enecarboxylate (**1**) from (−)-quinic acid. The disagreement of the spectroscopic data of **1** with those of natural pericosine A suggested that the reported stereostructure of pericosine A was incorrect. We will continue our synthetic study toward the other stereoisomers in order to elucidate the correct structure of pericosine A.

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9 Diol (**6**) was converted to tetraol (**19**) by treatment with trifluoroacetic acid in methanol under reflux. The stereochemistry of **19** was confirmed by analysis of ^{1}H NMR spectroscopic data. **19**: (CD_3OD) δ 1.81 (1H, dd, $J = 13.5$, 11.7 Hz, H-2β), 2.19 (1H, dd, $J = 13.5$, 5.0 Hz, H-2α), 3.45 (1H, dd, $J = 9.6$, 3.0 Hz, H-4), 3.78 (3H, s, COOMe), 3.98 (1H, ddd, $J = 11.7$, 9.6, 5.0 Hz, H-3), 4.10 (1H, dd, $J = 3.0$, 2.8 Hz, H-5), 4.49 (1H, d, $J = 2.8$ Hz, H-6). Observation of the NOESY cross peaks H-6/H-4, H-6/H-2β, and H-4/H-2β in **19** supported the conformation shown below. These results elucidated the stereochemistry of C-6 in **5** or C-5 in **6**.

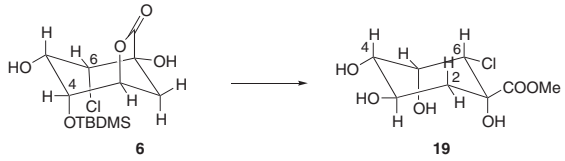

Figure 2.

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11 Observing the NOESY cross peaks H-6/H-4, H-6/H-2β, and H-4/H-2β in **10** as in **19** suggested the configuration at C-4 as shown in Scheme 1.
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13 Observation of the NOESY cross peak between H-4 and H-6 in **13** suggested that H-4 and H-6 had the *cis*-configuration. And as described in text part, observation of the cross peaks between the proton signal of one of acetonide-methyl groups and H-4 or H-5 in the NOESY spectra of **15**, which was derived from **13** via **1**, implied that H-4 and H-5 had *cis*-configuration in **13**. Therefore the possibility of epimerization at C-4 or C-6 during transformation from **12** to **13** was denied.
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15 Spectroscopic data of **1**: oil; $[\alpha]_D^{30}$ −71.1 (*c* 0.09, EtOH); IR (liquid film) ν_{max} 3383 (OH), 1721 (C=O), 1652 (C=C) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.72 (1H, dd, $J = 5.9$, 2.3 Hz, H-4), 3.77 (3H, s, COOMe), 4.16 (1H, dd, $J = 4.1$, 2.3 Hz, H-5), 4.46 (1H, m, H-3), 5.07 (1H, dt, $J = 4.1$, 1.4 Hz, H-6), 6.73 (1H, d, $J = 3.0$, 1.4 Hz, H-2). ^{13}C NMR (acetone-d_6) δ 52.22 (q), 57.99 (d), 69.56 (d), 70.64 (d), 75.28 (d), 130.87 (d), 141.63 (s), 166.44 (s). HRCIMS Calcd for $C_8H_{12}O_5$ ^{35}Cl $(M+H)^+$, 223.0372; Found, 223.0360.
16 Spectroscopic data of **17**: oil; $[\alpha]_D^{30}$ +58.3 (*c* 0.01, EtOH); IR (liquid film) ν_{max} 3373 (OH), 1726 (C=O), 1653 (C=C) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.76 (3H, s, COOMe), 3.94 (1H, dd, $J = 5.0$, 2.1 Hz, H-5), 4.09 (1H, m, H-4), 4.33 (1H, m, H-3), 4.99 (1H, br d, $J = 5.0$ Hz, H-6), 6.79 (1H, br dd, $J = 2.5$, 1.3 Hz, H-2). ^{13}C NMR (acetone-d_6) δ 52.32 (q), 56.46 (d), 68.83 (d), 68.98 (d), 71.59 (d), 132.03 (d), 142.71 (s), 168.00 (s). HRCIMS Calcd for $C_8H_{12}O_5$ ^{35}Cl $(M+H)^+$, 223.0372; Found, 223.0379.

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