Synthesis of the Aglycon of Aurisides A and B, Cytotoxic Macrolide Glycosides of Marine Origin

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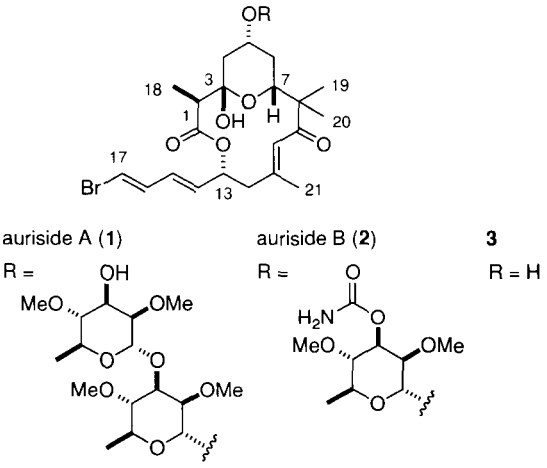
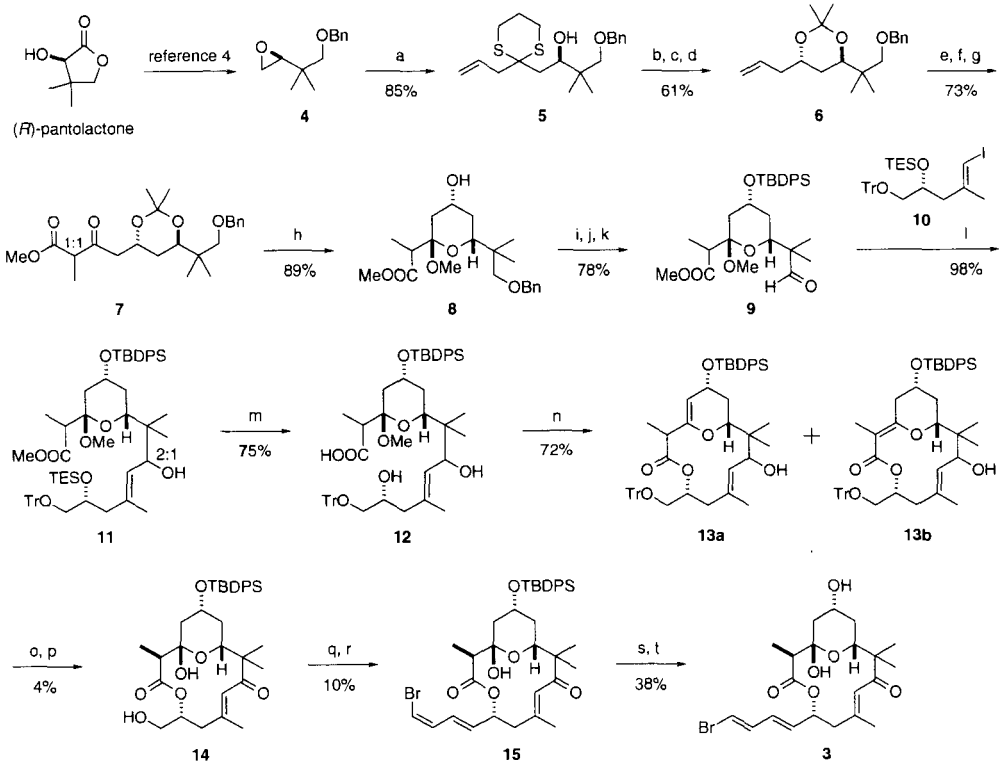
(Received October 1, 1997; CL-970755)

The synthesis of the aglycon of aurisides A and B was achieved from (*R*)-pantolactone in 29 steps using the Nozaki reaction and the Yamaguchi macrolactonization as key steps.

We have recently reported the isolation and absolute stereostructures of two new macrolide glycosides, aurisides A (**1**) and B (**2**), from the Japanese sea hare *Dolabella auricularia*, which exhibited cytotoxicities against HeLa S_3 cells with IC_{50} values of 0.17 and 1.2 μg/mL, respectively.[1] Aurisides A (**1**) and B (**2**) have unique structures: the aglycon possesses a new type of carbon backbone, 5,7,13-trihydroxy-3,9-dioxohepta-decanoic acid, and contains a bromine-substituted conjugated diene moiety, a 14-membered lactone, and a cyclic hemiacetal part. Only a few natural products structurally related to **1** and **2** have been isolated,[2] and studies have been made on synthesis of these compounds.[3] We describe herein the synthesis of the aglycon (**3**) of aurisides A and B.





Scheme. Reagents and Conditions: (a) 2-allyldithiane, ^{n}BuLi, THF-hexane, −78 → −20 °C. (b) $(CF_3CO_2)_2IPh$, MeOH, 0 °C; H_2O, AcOH, THF, rt. (c) $Me_4NBH(OAc)_3$, AcOH, MeCN, −40 → −20 °C. (d) $(MeO)_2CMe_2$, CSA, acetone, rt. (e) OsO_4, NMO, acetone-^{t}BuOH, rt; $NaIO_4$, H_2O, rt. (f) methyl propionate, LDA, THF-hexane, −78 °C. (g) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 → 0 °C. (h) $CH(OMe)_3$, PPTS, MeOH, 50 °C. (i) TBDPSCl, imidazole, DMF, 0 °C. (j) H_2, 20% Pd(OH)$_2$-C, dioxane, rt. (k) DMSO, SO_3•Py, Et_3N, rt. (l) $NiCl_2$(1%)–$CrCl_2$, DMSO, rt. (m) LiOH, THF-MeOH-H_2O, 50 °C. (n) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt; DMAP, toluene, reflux. (o) Dess–Martin periodinane, CH_2Cl_2, rt. (p) HCO_2H, THF-MeOH-H_2O, rt; HPLC separation. (q) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 → 0 °C. (r) $(EtO)_2P(O)CH_2CH{=}CHBr$, $NaN(SiMe_3)_2$, THF, −78 °C. (s) I_2, benzene, rt. (t) ^{n}Bu$_4$NF, AcOH, THF, rt.

The synthesis of the aglycon (**3**) started from commercially available (*R*)-pantolactone (Scheme). (*R*)-Pantolactone was converted into epoxide **4** by a four-step sequence of reactions.[4] Alkylation of the carbanion of 2-allyldithiane with **4** afforded alcohol **5** (85%). Deprotection[5] of the thioacetal moiety in **5** followed by diastereoselective reduction of the β-hydroxy ketone part with the Saksena–Evans reagent [$Me_4NBH(OAc)_3$][6] gave an *anti*-diol, which was transformed into acetonide **6** (61% from **5**). The stereochemistry of **6** was determined to be *anti* by the ^{13}C NMR analysis.[7] Oxidative cleavage of the double bond in **6** followed by aldol reaction between the resultant aldehyde and methyl propionate yielded a diastereomeric mixture of β-hydroxy esters, Swern oxidation of which afforded β-keto ester **7** (73% from **6**) as a 1:1 mixture of diastereomers concerning the secondary methyl group. Deacetonization of **7** in methanol led to methyl acetal **8** (89% from **7**). Silylation of the hydroxyl group in **8**, removal of the benzyl protecting group, and oxidation of the resultant alcohol yielded aldehyde **9** (78% from **8**).

Coupling between aldehyde **9** and silyl ether **10**[8] was effected by means of the Nozaki reaction[9] to give alcohol **11** in 98% yield as a 2:1 mixture of diastereomers concerning the allylic hydroxyl group (Scheme). Both the ester group and the triethylsilyl ether group in **11** were hydrolyzed under basic conditions to provide seco acid **12** (75% from **11**). The macrolactonization of **12** was accomplished by the Yamaguchi method[10] to yield a mixture of the 14-membered conjugated and deconjugeted lactones (**13a**, **13b**) with concomitant elimination of methanol (72%). Dess–Martin oxidation[11] of the mixture (**13a**, **13b**) furnished a mixture of conjugated enones, which was treated with aqueous acid to give hemiacetal **14**[12] (4%[13] from **13a** and **13b**). Swern oxidation of **14** produced the corresponding aldehyde, which was allowed to react with diethyl 3-bromo-2-propenylphosphonate[14] to afford dienyl bromide **15** (10%[15] from **14**) as a single stereoisomer. Finally, isomerization of **15** with iodine followed by removal of the sliyl group gave the aglycon (**3**)[16] of aurisides A and B (38%[17] from **15**). Synthetic aglycon (**3**) thus obtained proved to have the same stereostructure as that of the aglycon part in aurisides A (**1**) and B (**2**) by the spectral comparison including the 2D NMR technique (^1H-^1H COSY, HSQC, HMBC, and NOESY).

This work was supported in part by Grant-in-Aid for COE Research (No. 07CE2004) from the Ministry of Education, Science, Sports, and Culture, Japan. A fellowship from Japan Society for the Promotion of Science for Japanese Junior Scientists to H.S. is gratefully acknowledged.

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8 Commercially available (*R*)-glycidyl trityl ether was converted into silyl ether **10** (23%) as follows: (a) $LiC{\equiv}CH{\bullet}NH_2CH_2CH_2NH_2$, THF-DMSO, rt. (b) TBSCl, imidazole, DMF, rt. (c) Cp_2ZrCl_2, Me_3Al, CH_2ClCH_2Cl-toluene, 50 °C; I_2, THF, 0 °C.[18] (d) TrCl, Et_3N, DMAP, CH_2Cl_2, rt. (e) TESCl, imidazole, DMF, 0 °C.

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12 C2-*epi*-**14** was also obtained (6% yield from **13a** and **13b**). C2-*epi*-**14** could be isomerized to **14** under acidic conditions (AcOH-dioxane-H_2O, 110 °C).

13 Under these acidic conditions the major products were a mixture of several compounds that were presumably produced by elimination of silanol from the mixture of conjugated enones followed by addition of water.

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15 The aldehyde was recovered in 56% yield.

16 Colorless oil; R_f = 0.35 (5:1 benzene/acetone), 0.2 (2:1 hexane/EtOAc); $[\alpha]^{31}_D$ +6.7° (*c* 0.045, MeOH); IR (CCl_4) 3620, 3460, 1715, 1680, 1620 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.40 (dd, *J* = 13.7, 10.8 Hz, 1 H), 6.32 (s, 1 H), 5.91 (d, *J* = 13.7 Hz, 1 H), 5.65 (dd, *J* = 15.1, 10.8 Hz, 1 H), 5.57 (m, 1 H), 5.19 (dd, *J* = 15.1, 6.3 Hz, 1 H), 4.82 (d, *J* = 3.0 Hz, 1 H), 3.94 (m, 1 H), 3.87 (dd, *J* = 11.8, 2.0 Hz, 1 H), 2.47 (q, *J* = 7.3 Hz, 1 H), 2.29 (d, *J* = 1.0 Hz, 3 H), 1.99 (m, 1 H), 1.97 (dd, *J* = 13.2, 11.7 Hz, 1 H), 1.82 (dd, *J* = 13.2, 2.5 Hz, 1 H), 1.53 (m, 1 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.07 (m, 1 H), 0.98 (d, *J* = 7.3 Hz, 3 H), 0.81 (dt, *J* = 3.0, 11.2 Hz, 1 H), one proton (5-OH) was not observed; FABMS *m/z* 481, 479 $(M + Na)^+$; HRFABMS Found: *m/z* 479.1016, Calcd for $C_{21}H_{29}{}^{79}BrNaO_6$: (M + Na), 479.1045.

17 In the isomerization reaction of **15** with iodine, **15** was recovered in 53% yield.

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