Natural Product Synthesis

Stereocontrolled Total Synthesis of (−)-Aurisides A and B**

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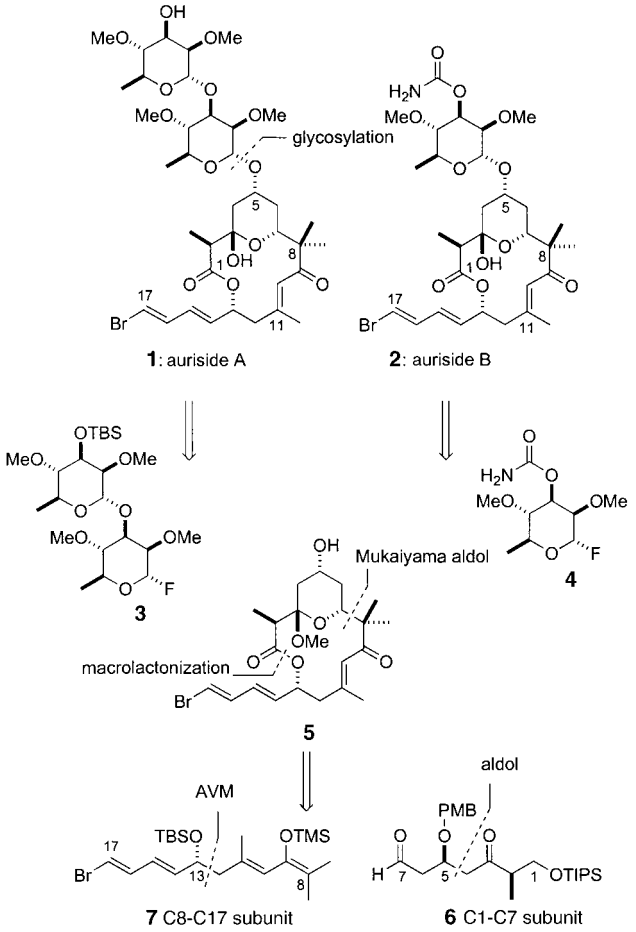
Aurisides A (**1**) and B (**2**) are unique marine polyketides isolated in 1996 by Yamada and co-workers from the Japanese sea hare *Dolabella auricularia*,[1a] an organism that has proved to be a rich source of bioactive secondary metabolites.[2] Initial biological screening of **1** and **2** highlighted significant cytotoxicity, with IC_{50} values against HeLa S_3 cervical cancer cell lines of 0.17 and 1.2 $\mu g\,mL^{-1}$, respectively. The aurisides are 14-membered glycosylated macrolides that contain a six-membered hemiacetal ring, an *E*-trisubstituted enone with an *E*,*E* bromodiene side chain appended at C13, and different sugar moieties attached at C5 (Scheme 1).

The unusual structure of the aurisides, combined with their biological activity and low natural abundance (0.8 mg of **1** was obtained from 278 kg of *D. auricularia*), has generated growing interest in these compounds as synthetic targets.[1b,3] In 1998, the Yamada group reported a synthesis of the aglycon unit, confirming their initial stereochemical assignment. The low yield of their route was the result of several problematic steps in its late stages.[1b] Herein, we report the first total synthesis of aurisides A (**1**) and B (**2**) by appropriate attachment of the required sugar residue, which involves a highly convergent and expedient aldol-based route for the stereocontrolled construction of the common macrolide core.

As outlined in Scheme 1, our synthetic strategy relied on a late-stage, α-selective glycosylation of the equatorial C5 alcohol in lactone **5** with the fluorosugar **3** or **4**, each derived from L-rhamnose. The macrocyclic lactone, in turn, was envisaged to arise from a stereocontrolled Mukaiyama aldol coupling between aldehyde **6** (C1–C7) and silyl enol ether **7** (C8–C17) containing a bromodiene terminus, followed by a suitable macrolactonization step. Introduction of the remote C13 stereocenter in **7** was planned to rely on the application of an asymmetric vinylogous Mukaiyama (AVM) aldol reaction,[4] while the C5 center in **6** would also be installed by a suitable aldol reaction.[5]



Scheme 1. Retrosynthetic analysis for the aurisides.

As shown in Scheme 2, the synthesis of the C1–C7 subunit **6** began with a highly stereoselective boron-mediated aldol reaction of the readily available methyl ketone **8**[6] with 3-

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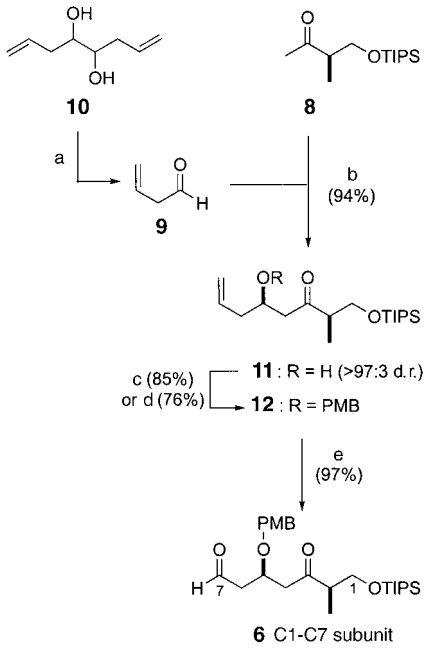
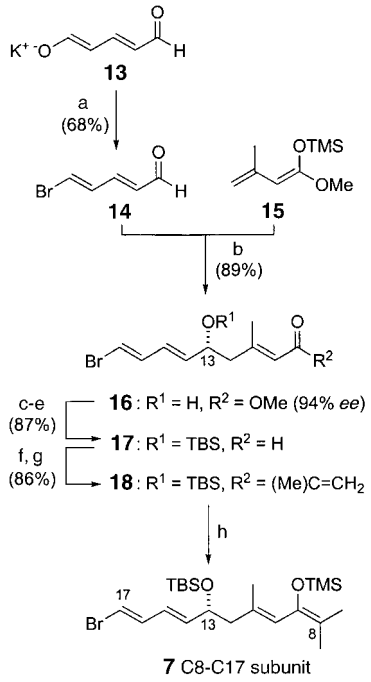


Scheme 2. Synthesis of the C1–C7 subunit **6**. a) $NaIO_4$, CH_2Cl_2, pH 4 buffer, 0 °C, 3 h; b) 1. (+)-Ipc_2BCl, Et_3N, Et_2O, 0 °C, 1 h; 2. **9**, CH_2Cl_2, −78 → −27 °C, 2.5 h; 3. H_2O_2 (30% aq), pH 7 buffer, MeOH, 0 °C → RT, 1 h; c) PMBTCA, TfOH (0.3 mol%), Et_2O, room temperature, 3 h; d) PMBTCA, $Sc(OTf)_3$ (1 mol%), PhMe, 0 °C, 15 min; e) O_3, $NaHCO_3$, CH_2Cl_2, −78 °C, 10 min; then PPh_3, −78 °C → RT, 3 h. Ipc = isopinocampheyl, PMBTCA = *para*-methoxybenzyltrichloroacetimidate, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl.



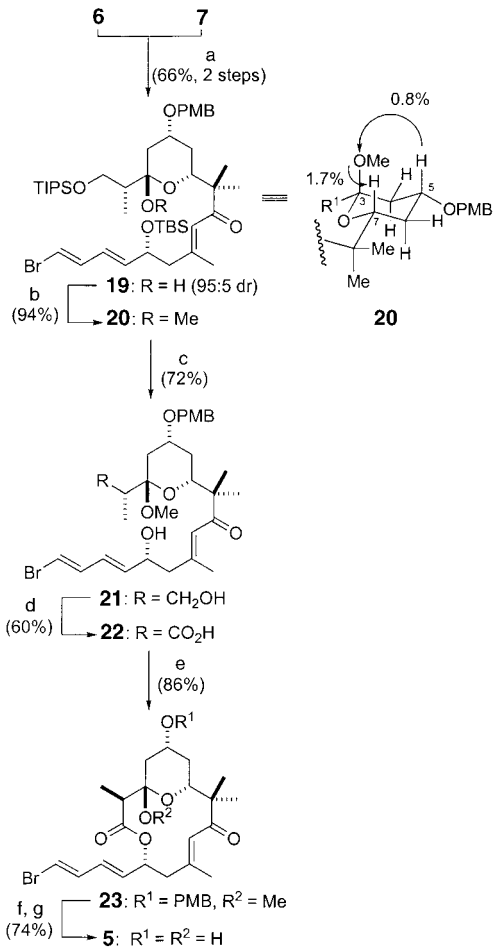
Scheme 3. Synthesis of the C8–C17 subunit **7**. a) Br_2, PPh_3, CH_2Cl_2, 0 °C → RT, 4 h; b) $Ti(OiPr)_4$ (50 mol%), (*R*)-binol (50 mol%), CaH_2, THF, −78 °C, 72 h; c) TBSCl, imidazole, CH_2Cl_2, room temperature, 4 h; d) DIBAL, CH_2Cl_2, −78 °C, 2 h; e) MnO_2, Et_2O, room temperature, 3 h; f) $CH_2{=}CH(Me)MgBr$, THF, −78 → 0 °C, 1.5 h; g) MnO_2, Et_2O, room temperature, 5 h; h) L-Selectride, CaH_2, THF, −78 °C, 15 min; $TMSCl{\cdot}Et_3N$, −78 → −20 °C, 45 min. Binol = 1,1′-bi(2-naphthol), TBS = *tert*-butyldimethylsilyl, DIBAL = diisobutylaluminum hydride, L-Selectride = lithium tri-*sec*-butylborohydride, TMS = trimethylsilyl.

butenal (**9**), derived from the oxidative cleavage of 1,2-glycol **10**.[7] Enolization of **8** with (+)-Ipc_2BCl/Et_3N,[6,8] followed by the addition of a freshly prepared anhydrous solution of **9** at −78 °C, provided the corresponding 1,4-*syn* aldol adduct **11** (94%, >97:3 d.r.). Treatment of **11** with PMBTCA in the presence of catalytic TfOH in Et_2O at room temperature afforded the PMB ether **12** in 85% yield.[9] Alternatively, use of $Sc(OTf)_3$ in toluene at 0 °C provided **12** in 76% yield on a multigram scale,[10] with decreased by-product formation. Subsequent ozonolysis of **12** with reductive PPh_3 workup gave the 1,5-ketoaldehyde **6** in 97% yield.

Synthesis of the C8–C17 subunit **7** (Scheme 3) commenced with the bromination of potassium glutaconaldehyde (**13**),[11] according to the method of Duhamel and co-workers.[12] Treatment of **13** with Br_2 and PPh_3 provided the corresponding *E*,*E* bromodienal **14** (68%). The stage was now set for the critical AVM reaction between **14** and silyl dienolate **15**[13] to introduce the C13 stereocenter, along with the 10*E*-trisubstituted alkene functionality.[5,14] Gratifyingly, treatment of aldehyde **14** with [(*R*)-binol-$Ti(OiPr)_2$] (50 mol%) in THF at −78 °C, generated in situ from (*R*)-binol and $Ti(OiPr)_4$, followed by addition of silyl dienolate **15** provided the vinylogous aldol adduct **16** exclusively in 89% yield and 94% *ee*.

TBS ether formation on the alcohol **16** was followed by conversion into aldehyde **17** by treatment with DIBAL. Subsequent reoxidation with MnO_2 proceeded in 87% yield. Addition of isopropenyl magnesium bromide to **17** and oxidation of the resulting alcohol with MnO_2 provided enone **18** (86%), anticipated as a direct precursor to the silyl enol ether **7**. Initial attempts at this transformation employing Chan hydrosilylation,[15] $LiAlH_4$/CuI/TMSCl,[16] or the Stryker reagent[17] proved unsuccessful. However, when **18** was subjected to L-Selectride in THF at −78 °C, regioselective 1,4-reduction of the less sterically encumbered enone was observed. The resultant enolate was quenched with TMSCl to provide the C8–C17 subunit **7**, which was used directly in the subsequent coupling step.

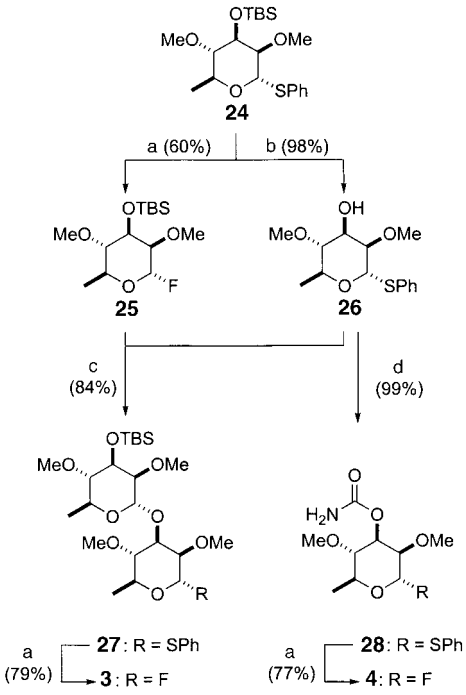
With key subunits **6** and **7** in hand, attention was focused on their Mukaiyama-type aldol union to introduce the C7 stereocenter, relying on 1,3-*anti* induction from the C5 ether through an open transition state, following the Evans polar model,[18] thus completing the carbon backbone of aglycon **5** (Scheme 4). In practice, exposure of **6** and **7** to $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −95 °C provided the adduct in 66% yield (from **18**) with 95:5 d.r. which was present in solution in the closed hemiacetal form **19**. Treatment of **19** with PPTS, $(MeO)_3CH$, and MeOH cleanly provided methyl acetal **20.** To confirm the stereochemistry of **20**, irradiation of 5-H provided a diagnostic NOE interaction with the C3-OMe, consistent with their 1,3-diaxial relationship, whereas irradiation of the C3-OMe in turn, provided a further NOE interaction with 7-H. Cleavage of the silyl ethers with TASF in wet DMF gave diol **21** (72%).[19] Selective oxidation of the C1 terminus to *seco* acid **22** was next attempted and required careful optimization. Under the conditions developed by Piancatelli and co-work-



Scheme 4. Synthesis of the auriside aglycon **5**. a) $BF_3{\cdot}OEt_2$, CaH_2, CH_2Cl_2, −95 °C, 10 min; b) PPTS (20 mol%), $CH(OMe)_3$, MeOH, room temperature, 4 h; c) TASF, H_2O, DMF, 0→15 °C, 5 h; d) 1. TEMPO, $PhI(OAc)_2$, MeCN, pH 7 buffer, 6 h; 2. $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, 2-methyl-2-butene, room temperature, 30 min; e) 1. 2,4,6-trichlorobenzoyl chloride, Et_3N, PhMe, room temperature, 1 h; 2. DMAP, room temperature, 4 h; f) DDQ, CH_2Cl_2, pH 7 buffer, room temperature, 30 min; g) *p*TsOH·H_2O, THF, H_2O, room temperature, 16 h. PPTS = pyridinium *p*-toluenesulfonate, TASF = (diethylamino)sulfur trifluoride, DMF = *N*,*N*-dimethylformamide, TEMPO = 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl, DMAP = 4-*N*,*N*-dimethylaminopyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, *p*TsOH = *para*-tolunenesulfonic acid.

ers,[20] treatment of **21** with TEMPO and $PhI(OAc)_2$ in MeCN/pH7 buffer (5:1) provided the intermediate aldehyde, which was further oxidized with $NaClO_2$ to give **22** in 60% yield. This intermediate readily underwent Yamaguchi macrolactonization to provide the desired 14-membered macrocycle **23** cleanly (86%).[21] Cleavage of the PMB ether with DDQ and hydrolysis of the methyl acetal then afforded auriside aglycon **5** in 74% yield. At this stage, the ^1H and ^{13}C NMR spectroscopic data and specific rotation agreed with those reported by the Yamada group.[1b]

With aglycon **5** in hand, attention was now directed toward the preparation of the activated fluorosugar units **3** and **4** (Scheme 5). Following work reported by the Nicolaou group, a nine-step sequence starting from L-rhamnose was

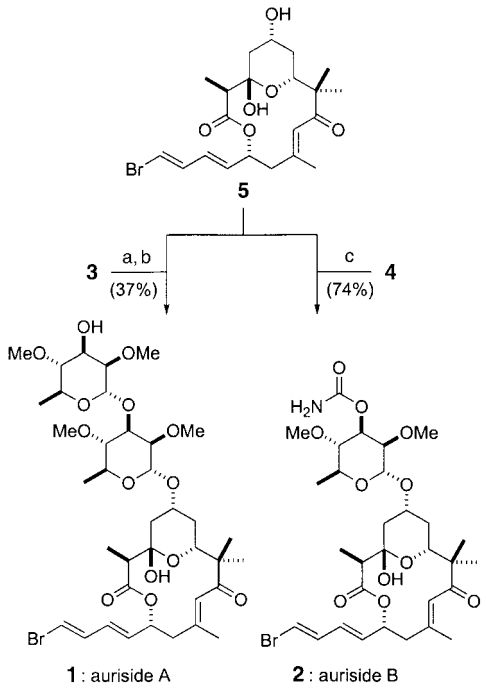


Scheme 5. Synthesis of fluorosugar units **3** and **4**. a) DAST, NBS, −15 °C, 15 min; b) TBAF, THF, 0 °C→RT, 4 h; c) $SnCl_2$, $AgClO_4$, molecular sieves (4 Å), Et_2O, 0 °C→RT, 4 h; d) $Cl_3CC(O)NCO$, CH_2Cl_2, room temperature, 1 h; K_2CO_3, MeOH, room temperature, 2 h. DAST = (diethylamino)sulfur trifluoride, NBS = *N*-bromosuccinimide, TBAF = tetrabutylammonium fluoride.

used to access common precursor **24**.[22,23] Formation of the disaccharide **3** began with the activation of **24** with DAST/NBS to provide exclusively α-fluorosugar **25** in 60% yield.[24] Mukaiyama glycosylation between **25** and **26**,[25] obtained by deprotection of **24** with TBAF, provided **27** as the α-anomer exclusively (84%). Activation of **27** with DAST/NBS then afforded **3** in 79% yield. The fluorosugar **4** required for auriside B (**2**) was readily synthesized in 77% yield by treatment of **26** with trichloroacetyl isocyanate to afford carbamate **28** (99%),[26] followed by activation with DAST/NBS.

Completion of the total synthesis, as shown in Scheme 6, required the coupling of aglycon **5** with either activated sugar **3** or **4** to directly provide auriside A (following silyl deprotection) and auriside B, respectively. Under the Mukaiyama protocol, the reaction of **3** and **5** followed by desilylation with HF·pyr afforded (−)-auriside A (**1**) in 37% yield ($[\alpha]_D^{20} = -16.3$ ($c = 0.033$ in MeOH) Ref. [1a] −43.0 ($c = 0.050$ in MeOH)). Similarly, the reaction of **4** and **5** proceeded smoothly to afford (−)-auriside B in 74% yield ($[\alpha]_D^{20} = -21.6$ ($c = 0.10$ in MeOH), Ref. [1a] −30.0 ($c = 0.090$ in MeOH)). In each case, analytical data (^1H, ^{13}C NMR and IR spectroscopy, MS, and specific rotation) for the synthetic material were in excellent agreement with those reported for natural aurisides A and B, allowing confirmation of the relative and absolute configurations of these compounds.[27]

In conclusion, we have completed an expedient total synthesis of (−)-aurisides A and B that proceeds in 18 steps (1.7% overall yield) and 17 steps (3.5% overall yield),



Scheme 6. Completion of the total synthesis of aurisides A (**1**) and B (**2**). a) $SnCl_2$, $AgClO_4$, molecular sieves (4 Å), Et_2O, 0 °C→RT, 16 h; b) HF·py, THF, 0 °C→RT, 16 h; c) $SnCl_2$, $AgClO_4$, molecular sieves (4 Å), Et_2O, 0 °C→RT, 8 h.

respectively. By building the *E*,*E* bromodiene of the side chain into the silyl enol ether **7**, the key Mukaiyama aldol coupling with aldehyde **6** delivers the advanced intermediate **19** in a highly convergent manner. This can then be converted into the aurisides by α-selective glycosylation of the derived macrolide core **5** with the fluorosugars **3** and **4**. This work also highlights an efficient enantioselective vinylogous Mukaiyama aldol reaction, which in tandem with our diastereoselective boron-mediated aldol methodology provides a rapid synthetic entry into this structurally unique class of bioactive marine macrolides.

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[27] Copies of ^1H and ^{13}C NMR spectra for aglycon **5** and aurisides A (**1**) and B (**2**) are provided in the Supporting Information.

