A Stereoselective Synthesis of C26-C36 Fragment of Arenicolide A

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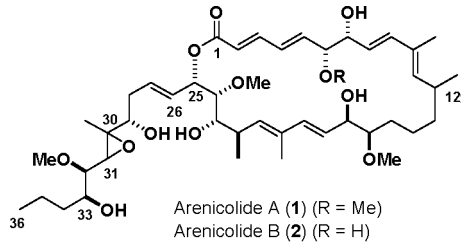
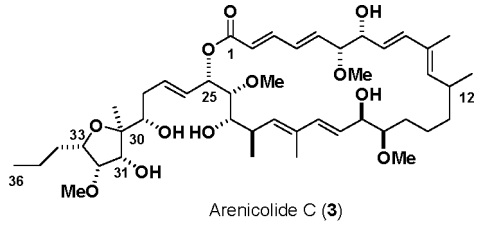
Recently, arenicolides A (**1**) and B (**2**) were isolated from the large-scale fermentation of the *S. arenicola* strain CNR-005 and its relative stereochemical relationship except C-12, C-30, and C-31 chiral centers was proposed by ^{1}H NMR, ^{13}C NMR, Mass, IR, UV, CD, chemical degradation methods.[1] Arenicolides A (**1**) and B (**2**) are 26-membered macrolides with three conjugated dienes and nine chiral centers in the ring. There is one side chain which comprises the C-26 ~ C-36 carbon chain with five consecutive chiral centers. Arenicolide A (**1**) also showed moderate anti-cancer activity toward the human colon adenocarcinoma cell line HCT-116 (IC_{50}: 30 μg/mL) and three cell lines in the National Cancer Institute, and no activity against antimicrobial assay using methicillin-resistant *S. aureus* (MRSA) and vancomycinresistant *E. faecium* (VREF).[1]

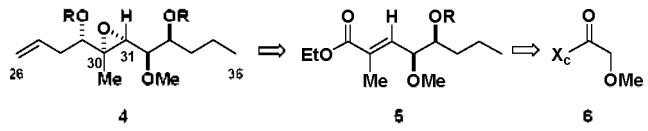


Arenicolide C (**3**) was also isolated along with arenicolides A (**1**) and B (**2**). And we proposed that the cyclic ether moiety in **3** might be derived biologically from arenicolide A (**1**) *via* the acid-catalyzed opening of epoxide and S_N2 type addition of the C-33 hydroxyl group. In this paper, we report the stereoselective synthesis of the plausible C-26 ~ C-36 side chain (**10**) of arenicolide A (**1**) based on this assumption.

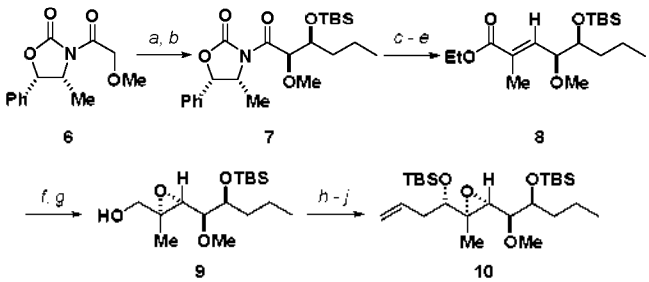


Retrosynthesis is summarized in Scheme 1. The homoallyl chiral center at C-31 of **4** would be introduced by asymmetric allylation of aldehyde.[2] Conformational control from the allylic 1,3-strain and approach of the epoxidizing reagent *anti* to the methoxy group in **5** should provide the desired stereochemistry of C-30 and C-31 epoxide in **4**.[3] Finally, diastereoselective 1,2-*syn* aldol strategy of α-methoyacetate moiety **6** would be used to construct the C-32 and C-33 chiral centers.[4]

The synthesis of target molecule **10** was summarized in Scheme 2. Evans-*syn* aldol reaction of α-methoyacetate **6** with *n*-butanal provided the 1,2-*syn* aldol product in 96% yield,[4] and the free β-hydroxyl group was treated by TBSOTf and 2,6-lutidine to afford the TBS-ether **7** in 84% yield. The chiral auxiliary group of **7** was removed by reduction with $LiBH_4$ in 94% yield,[5] the resulting hydroxyl group was oxidized by Swern oxidation in 91% yield, and the resulting aldehyde was treated with stabilized Wittig reagent to afford the α,β-unsaturated ester **8** in 92% yield. The ester group of **8** was reduced to primary alcohol by DIBAL in methylene chloride in 94% yield and the diastereselective epoxidation by *m*CPBA provided the desired epoxide **9** and its isomer in 72%.[3] Swern



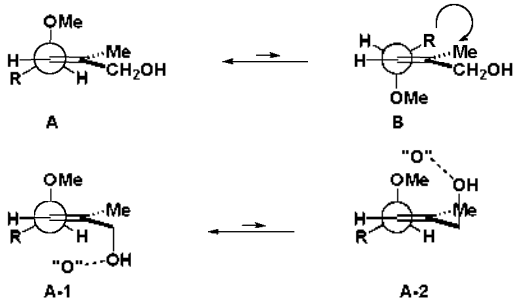
Scheme 1. Retrosynthesis



Scheme 2. Synthesis of C26-C36 Fragment (**4**). (a) *n*-Bu_2BOTf (1.5 eq), Et_3N (1.6 eq), butyraldehyde (2.0 eq), CH_2Cl_2, −78 °C, 4 hr, 96%. (b) TBSOTf (1.2 eq), 2,6-lutidine (2.0 eq), CH_2Cl_2, −78 °C, 3 hr, 84%. (c) $LiBH_4$ (1.12 eq), water (1.12 eq), ether, rt, 45 min, 94%. (d) $(COCl)_2$ (2.5 eq), DMSO (4.5 eq), Et_3N (7.5 eq), CH_2Cl_2, −78 °C, 1.5 hr, 91%. (e) Ph_3P=C(Me)CO_2Et (2.5 eq), benzene, reflux, overnight, 92%. (f) DIBAL (5.0 eq), CH_2Cl_2, −78 °C, 2 hr, 94%. (g) *m*CPBA (1.5 eq), K_2HPO_4 (3.0 eq), CH_2Cl_2, rt, 18 hr, 72%. (h) $(COCl)_2$ (2.0 eq), DMSO (4.0 eq), Et_3N (5.0 eq), CH_2Cl_2, −78 °C, 40 min, 88%. (i) (-)-Ipc_2BOMe (1.2 eq), allylmagnesium bromide (2.0 eq), ether, −100 °C, 3 hr, 67%. (j) TBSOTf (1.5 eq), 2,6-lutidine (2.0 eq), CH_2Cl_2, −78 °C, 30 min, 88%.

oxidation of primary alcohol **9** (88%) and chiral-ligand assisted asymmetric allylation of the resulting aldehyde (67%)[2] produced the homoallylic alcohol with the correct stereochemistry at C-29 in 67% yield along with its isomer in 19% yield. Finally, protection of the secondary alcohol with TBSOTf and 2,6-lutidine completed the synthesis of plausible C-26 ~ C-36 side chain moiety (**10**) of arenicolide A (**1**).

The origin of diastereoselectivity in the epoxidation reaction can be rationalized by conformational preferences of conformation **A** over conformation **B** due to the $A^{1,3}$-strain.[6] In addition, hydroxyl-group directed epoxidation[7] and *anti*-periplanar approach of the electrophilic oxygen to the best σ-electron acceptor (methoxy group)[8] clearly lead to the desired stereochemistry in **9** through the assembly **A-1** over the **A-2**.



In order to further confirm the relative stereochemical relationship of epoxide **9**, the primary hydroxyl group of **9** was converted to the benzyl ether by treatment with sodium hydride and benzyl bromide in THF in 91% yield, and the TBS-ether was deprotected by TBAF in THF to give the secondary alcohol **11** in 63% yield. After conversion of the secondary alcohol **11** to carbamate **12** by reaction with dimethylcarbamyl chloride in 87% yield. Intramolecular BF_3-assisted epoxide-opening and cyclization were carried out in methylene chloride to afford the cyclic carbonate **13** in 52% yield.[9] NOE experiment of **13** confirmed the relative stereochemistry of **13** and therefore that of **9**, an intermediate in the synthesis of target molecule **10**.[10]

In summary, the plausible C-26 ~ C-36 side chain **10** of arenicolide A (**1**) was prepared concisely and efficiently in 10 steps. The key steps are Evans 1,2-*syn* aldol reaction, diastereoselective epoxidation, and asymmetric allylation of aldehyde.

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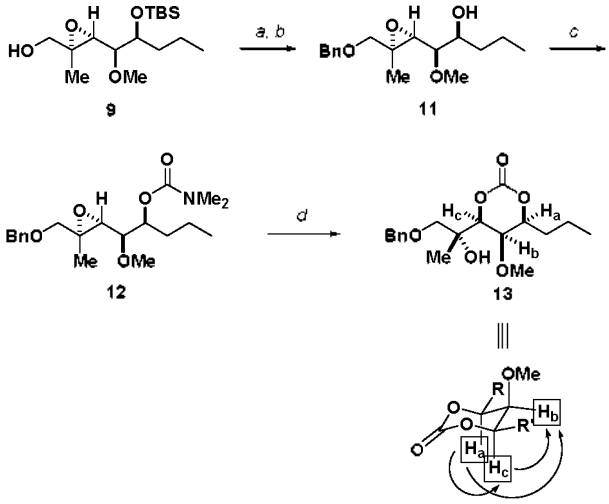

Scheme 3. Confirmation of relative stereochemistry of epoxide **9**. (a) BnBr (1.10 eq), NaH (1.10 eq), *n*-Bu_4NI (0.40 eq), THF, rt, 3 hr, 91%. (b) TBAF (2.5 eq), THF, rt, 3.5 hr, 63%. (c) Dimethylcarbamyl chloride (1.5 eq), NaH (1.2 eq), DMAP (0.3 eq), DMF, rt, 8 hr, 87%. (d) BF_3-OEt_2 (1.6 eq), CH_2Cl_2, rt, overnight, 52%.

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10. $[\alpha]_D$= +11.2 (c = 0.0017 MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86 ~ 5.81 (m, 1H), 5.10 ~ 5.03 (m, 2H), 3.78 ~ 3.74 (dd, 1H), 3.38 (s, 3H), 3.29 ~ 3.27 (dd, 1H), 2.93 ~ 2.90 (m, 1H), 2.84 ~ 2.82 (d, 1H), 2.45 ~ 2.40 (m, 1H), 2.33 ~ 2.29 (m, 1H), 1.66 ~ 1.64 (m, 2H), 1.50 ~ 1.47 (m, 2H), 1.35 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.087 (s, 3H), 0.079 (s, 3H), 0.059 (S, 3H), 0.035 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.276, 117.008, 80.291, 76.892, 74.172, 60.052, 58.558, 39.179, 35.752, 26.227, 26.022, 13.352, -4.239, -4.287; IR (neat) 2949, 2930, 2857, 1470, 1378, 1243, 1104, 914, 831, 779, 660 cm^{-1}; HRMS (ESI) calculated for $C_{25}H_{52}O_4Si_2$ $[M+Na]^+$ m/z 495.3301, found 495.3305.