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First total synthesis of (±)-AM6898A by stereoselective aldol cyclization

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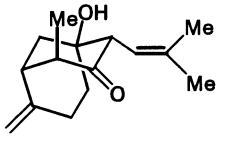
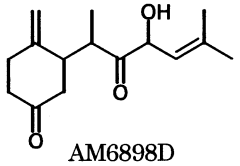
Abstract

First total synthesis of (±)-AM6898A has been achieved by stereoselective aldol cyclization via a thermodynamically controlled condition.

We have already reported the total synthesis of AM6898D together with all possible diastereoisomers.[1] Here we report the first total synthesis of a related compound, AM6898A (**1**). AM6898A (**1**), a sesquiterpene with inhibitory activity against IgE production, was isolated together with AM6898D in 1997 from certain strains of *Pseudallescheria* sp. by the group of Asahi Kasei [2] In these related compounds, only AM6898A (**1**) has the characteristic bicyclo[3.3.1]nonane system, and its biological activity inhibiting IgE production is most potent. For these reasons, we decided to synthesize AM6898A and its analogues to explore the biological aspects of these compounds which strongly inhibit IgE production (Scheme 1).



1: AM6898A



AM6898D

Scheme 1.

We planned to prepare AM6898A (**1**) by aldol cyclization as outlined in Scheme 2. The conformation of the starting material **2** is expected to be suitable for the aldol cyclization on considering the X-ray data of the related compound **3** obtained in the synthesis of AM6898D

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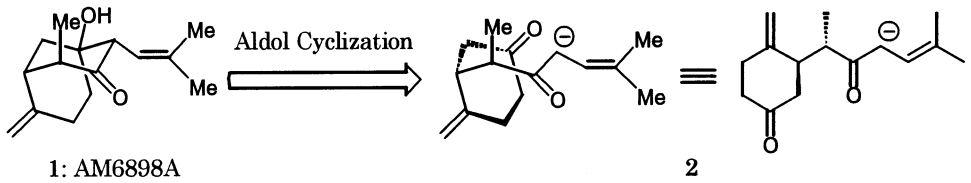
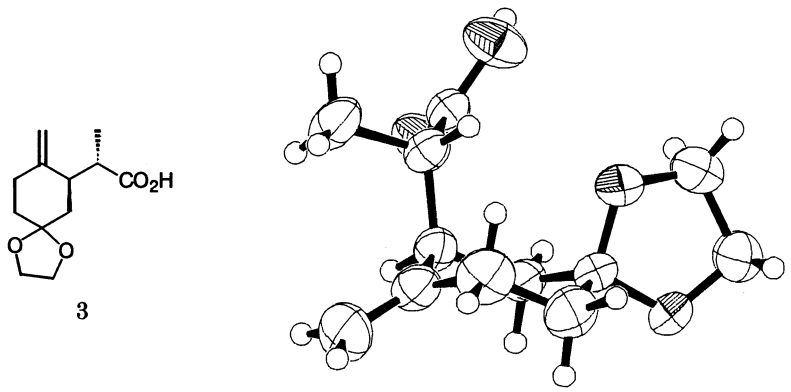
(Fig. 1).[1] The results showing that the bulky side chain positions at axial could be explained by the A-strain effect of the exocyclic olefin.[3] Additionally, the anion to be produced is stabilized by neighboring ketone and allyl substituents. Based on these conformational and kinetic requirements, we expected a stereoselective aldol cyclization was feasible.



1: AM6898A 2

Scheme 2.

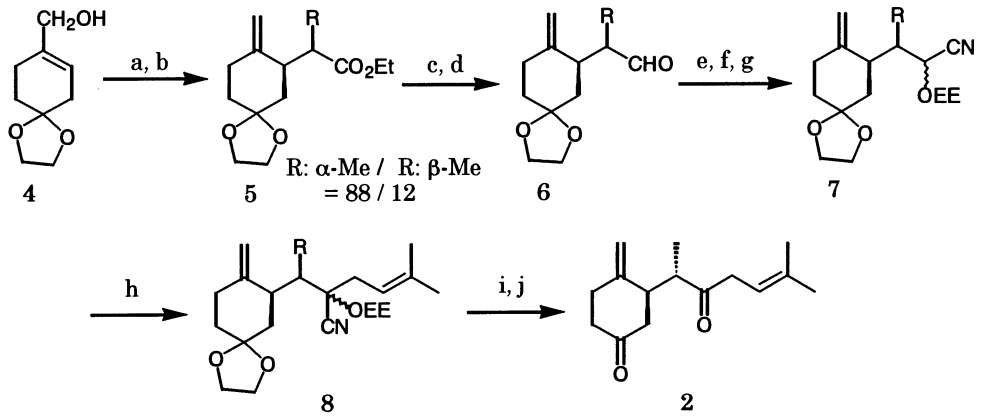


3

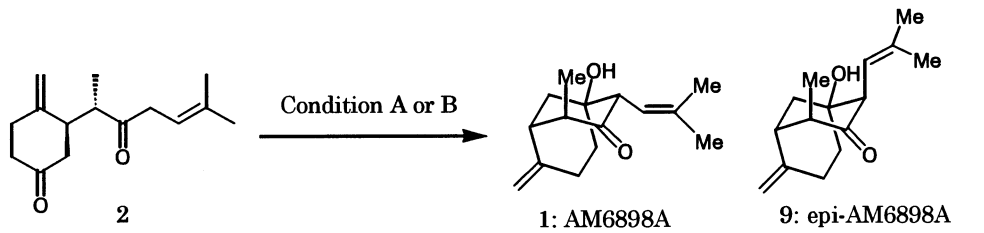
Figure 1. Comment: The crystal of the carboxylic acid **3** was obtained as a racemic compound. In this ORTEP drawing only one enantiomer is shown

In Scheme 3, preparation of the starting material **2** is summarized. Previously, we reported the preparation of the protected cyanohydrin **7** from allyl alcohol **4** in the synthesis of AM6898D.[1,4] This protected cyanohydrin **7** was treated with LDA, followed by addition of 1-bromo-3-methyl-2-butene to give the adduct **8**. Deprotection of the adduct **8**, followed by purification using silica gel column chromatography, afforded the desired **2** as a single isomer.

The reaction conditions to convert the diketone **2** into AM6898A (**1**) by aldol cyclization were investigated as shown in Scheme 4. In condition **A**, LDA was added into the solution of the **2** in THF to give a product containing *epi*-AM6898A (**9**) as the major product (**1**/**9** = 12/88).[5] In condition **B**, into the solution in THF and HMPA (HMPA/THF = 17/83), LDA was added to give a product containing AM6898A (**1**) as the major product (**1**/**9** = 90/10) with an increased yield.[5] Though attempts to separate these two diastereoisomers by silica gel column chromatography were unsuccessful, the ^{1}H and ^{13}C NMR spectra of the major product in condition **B** were identical with the reported spectra of the natural AM6898A. Additionally, the conformations and configurations of these two diastereoisomers (**1** and **9**) were confirmed by the detailed NMR (500 MHz) study.[6]



Scheme 3. Reagents and conditions: (a) 5 mol% $EtCO_2H/EtC(OEt)_3$, 140°C, 3 h (77%); (b) LDA/THF, −78°C, then EtOH (93%); (c) 2.2 equiv. DIBAL/toluene; (d) oxalyl chloride, $DMSO/CH_2Cl_2$, then TEA, −78 to 0°C; (e) cat. KCN dicyclohexano-18-crown-6/TMSCN, 0°C; (f) $PhCH_2NMe_3F/H_2O$, THF; (g) cat. TsOH, ethyl vinyl ether/benzene (88% in five steps from **5**); (h) LDA/THF, then 1-bromo-3-methyl-2-butene, −10°C; (i) 5% H_2SO_4 aq./MeOH, overnight; (j) 0.5N $NaOH/Et_2O$, 15 min (35% in three steps from **7**)



Scheme 4. Reagents and conditions: Condition **A**: 1.5 equiv. LDA/THF, −78 to 0°C, (60%, **1**/**9** = 12/88); Condition **B**: 1.5 equiv. LDA/THF and HMPA, −78 to 0°C, (98%, **1**/**9** = 90/10)

To confirm the stereochemical course of this cyclization, the product of condition **A** (**1**/**9** = 12/88) was treated with LDA in THF and HMPA (HMPA/THF = 17/83). This reaction afforded a product containing **1** as the major product with the same ratio as obtained in condition **B** (**1**/**9** = 90/10). From these results, in condition **B**, AM6898A (**1**) would be obtained as a thermodynamically controlled product. In conclusion, the first total synthesis of AM6898A (**1**) was achieved by stereoselective aldol cyclization via a thermodynamically controlled condition.

Acknowledgements

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References

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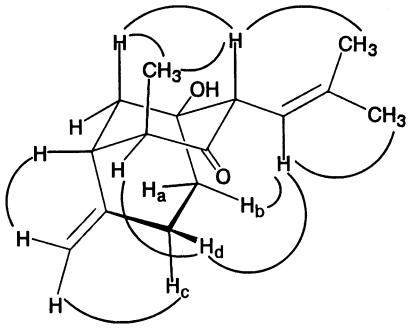
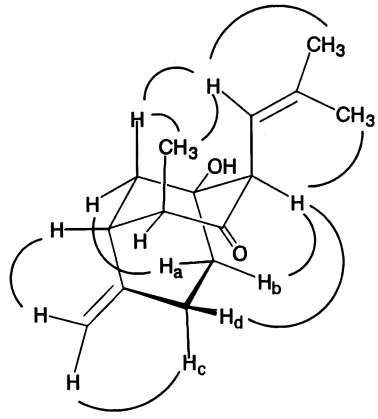
2. Yanaginuma, A.; Ishikawa, S. Japanese Patent, 1997, JP 09309859; Chem. Abstr. **1998**, *128*, 74385n.
3. Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc*. **1965**, *87*, 5493–5494.
4. Preparation of the allyl alcohol **4**: Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *Tetrahedron* **1979**, *35*, 941–948.
5. The **1**/**9** ratio determined by the integration of the ^{1}H NMR (400 MHz) spectra was almost identical with the analytical results obtained by HPLC. Additionally, from this analysis, no other isomer was detected in the product. Selected ^{1}H NMR data of **1** [(δ 1.32 ppm, d, $J=7.2$ Hz, Me-3H), (δ 5.31 ppm, d, $J=9.6$ Hz, olefin-1H)] and **9** [(δ 1.25 ppm, d, $J=7.6$ Hz, Me-3H), (δ 5.19 ppm, d, $J=10$ Hz, olefin-1H)]. HPLC, (column: YMC-Pack, ODS-AM; eluent: acetonitrile/$H_2O=35/65$; flow rate: 1.5 ml/min; detection: UV 250 nm) **1**: $t_R=11.1$ min, **9**: $t_R=13.7$ min.
6. All protons were assigned from the ^{1}H–^{1}H COSY spectra, and the key NOEs were observed in the NOESY spectra as shown below. In AM6898A (**1**) the coupling constant of the protons H_a and H_d is 13 Hz, while in *epi*-AM6898A (**9**) the coupling constant of the corresponding protons is 14 Hz. From these results, each pair of the protons positions at antiperiplanar.



1: AM6898A



9: epi-AM6898A