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First total synthesis of (±)-AM6898D and its three diastereoisomers by Claisen rearrangement and stereoselective epimerization

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Abstract

An effective method for the synthesis of (±)-AM6898D and its three diastereoisomers has been established via Claisen rearrangement, stereoselective epimerization of the α-ester stereochemistry and introduction of one isoprene unit by umpolung.

AM6898D (**1**), a sesquiterpene with inhibitory effect against IgE production, was isolated together with related compounds in 1997 from certain strains of *Pseudallescheria* sp. by a group of Asahi Kasei KK.[1] The same carbon skeleton is also found in fumagillin, which is a potent inhibitor of angiogenesis and a lead compound for antitumor agents.[2] In AM6898D the unstable epoxides are absent, and this characteristic structure might make AM6898D a new lead compound for drug discovery. For this reason we have decided to synthesize AM6898D and evaluate its biological activities. In practice, we have to explore a flexible synthetic approach to AM6898D and its three diastereoisomers, because the relative and absolute stereochemistry of AM6898D have not been determined. Accordingly, we planned to prepare AM6898D by Claisen rearrangement to construct the *exo*-olefin and the neighboring two chiral centers followed by introduction of the isoprene unit by umpolung (Scheme 1).

Allyl alcohol **5** was prepared according to the procedure of Isobe in two steps from *p*-methoxybenzyl alcohol.[3] Thermal rearrangement of this allyl alcohol **5** afforded the mixture **A** containing the ester **7′** as the major isomer (**7**:**7′**=8:92).[4] And it was anticipated that the major product **7′** would have *syn*-stereochemistry on considering the chair-form conformation of the ketene acetal **6** which is the reaction intermediate of this rearrangement**.** To convert the stereoselectivity of this rearrangement, ester enolate Claisen rearrangement and Ireland Claisen rearrangement for the propionate ester of allyl alcohol **5** were attempted, but neither reaction method afforded the desired product. Then the mixture **A** (**7**:**7′**=8:92) was treated with LDA followed by EtOH to epimerize the α-ester stereochemistry. This reaction afforded the

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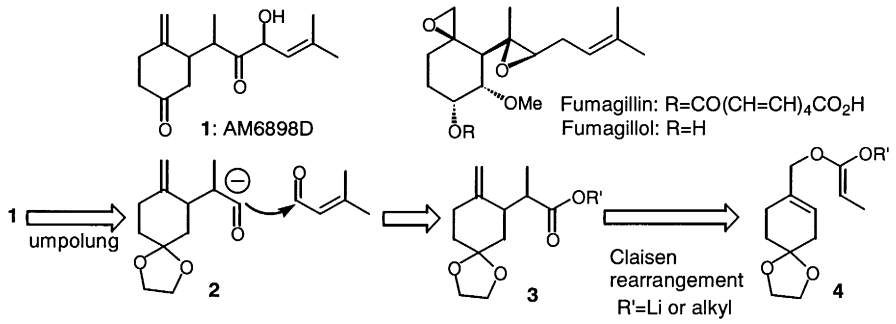
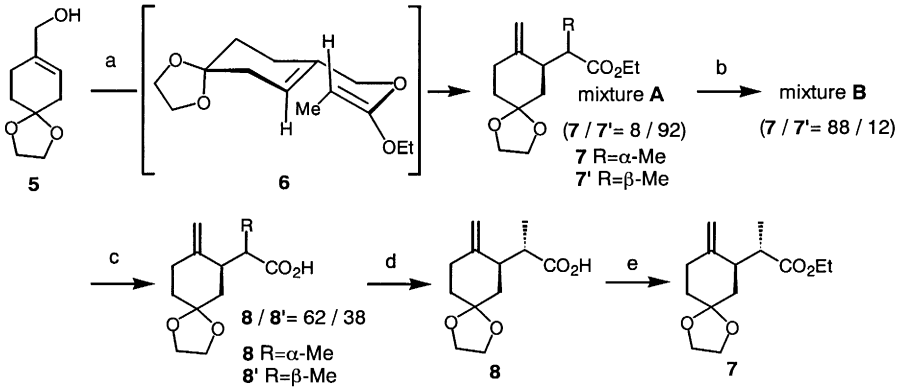


Scheme 1.

mixture **B** containing the ester **7** as the major isomer (**7**:**7**′=88:12). The *anti*-stereochemistry of the ester **7** was confirmed by X-ray crystallographic analysis of the major carboxylic acid **8** (Scheme 2).[5,6]



Scheme 2. 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) 2N NaOHaq/EtOH, 80°C, 3 h (quant.); (d) recrystallization from Et_2O and *n*-hexane (26%); (e) EtOH, DCC, $DMAP/CH_2Cl_2$, −10°C, 2 h (67%)

Conformational search using **9** corresponding to the *Z*-enolate anion derived from the mixture **A** was carried out for over a thousand steps by employing corner flipping and Monte Calro methods. Every local minimized conformation was optimized with PM3 semi-empirical molecular orbital calculation including solvent effect (H_2O). It was shown that the conformation having an equatorial side chain is more stable than the conformation having an axial side chain, and the dihedral angle among atoms at C1–C2–C3–C4 of the most stable conformation is nearly 110° as shown in Fig. 1. It is assumed that the perfect diastereoselectivity would be attained by β-face selective-protonation because α-side at C2 was considerably shielded by *exo*-double bond.

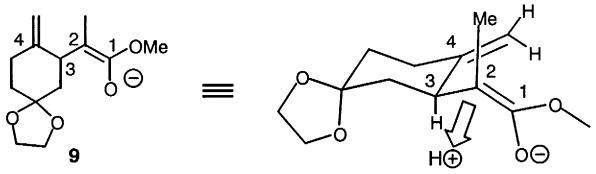
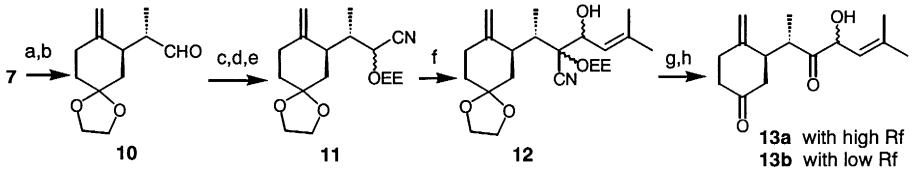


Fig. 1.

In Scheme 3, introduction of one isoprene unit into the mixture **B** (**7**:**7**′=88:12) by umpolung is summarized, and as regards the intermediates only the major isomers are shown. The aldehyde **10** prepared from the major isomer **7** was converted to the protected cyanohydrin **11** according to

the procedure of Takahashi in three steps, taking advantage of the mild conditions.[7] This protected cyanohydrin **11** was treated with LDA, followed by addition of 3-methyl-2-butenal to give the adduct **12**. Acidic deprotection of the 1,3-dioxolane and 1-ethoxyethyl ether in this adduct **12**, followed by treatment with 0.5 N NaOH afforded the two major products (**13a** and **13b**). These two products were separated by silica gel column chromatography. The ^{1}H and ^{13}C NMR spectra of the **13b** with low Rf were identical with the reported spectra of the natural AM6898D. In the same manner the other two diastereoisomers of AM6898D were prepared from the mixture **A** (**7**:**7′**=8:92) (Scheme 3).



Scheme 3. Reagents and conditions: (a) 2.2 equiv. DIBAL/toluene; (b) Swern oxidation; (c) cat. KCN·dicyclohexano-18-crown-6/TMSCN, 0°C; (d) $PhCH_2NMe_3F/H_2O$, THF; (e) cat. TsOH, ethyl vinyl ether/benzene (88% in five steps from mixture **B**); (f) LDA/THF, then 3-methyl-2-butenal, −10°C; (g) 5% H_2SO_4/MeOH, overnight; (h) 0.5N NaOH/ Et_2O, 15 min (**13a**; 9%, **13b**; 14%, in three steps)

Thus, total synthesis of (±)-AM6898D (**13b**) and its three diastereoisomers has been completed via Claisen rearrangement, stereoselective epimerization of the α-ester stereochemistry, and introduction of the isoprene unit by umpolung. From these synthetic results, the partial relative stereochemistry of AM6898D, excepting the unstable α-keto allyl alcohol moiety, has been proved to be the *anti*-stereochemistry corresponding to the ethyl ester **7**.

Acknowledgements

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3. Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *Tetrahedron* **1979**, *35*, 941–948.
4. Selected ^{1}H NMR ($CDCl_3$, 400 MHz) data of **7**: [(δ 1.07 ppm, d, J=6.8 Hz, Me-3H), (δ 4.74, 4.84 ppm, brs×2, AB-system, *exo*-olefin-2H)] and **7′**: [(δ 1.16 ppm, d, J=6.8 Hz, Me-3H), (δ 4.65, 4.74 ppm, brs×2, AB-system, *exo*-olefin-2H)].
5. Selected ^{1}H NMR ($CDCl_3$, 400 MHz) data of **8**: [(δ 1.11 ppm, d, J=6.8 Hz, Me-3H), (δ 4.77, 4.86 ppm, brs×2, AB-system, *exo*-olefin-2H)] and **8′**: [(δ 1.22 ppm, d, J=6.8 Hz, Me-3H), (δ 4.71, 4.79 ppm, brs×2, AB-system, *exo*-olefin-2H)].
6. Crystallographic data of **8**: $C_{12}H_{18}O_4$, F.W. 226.27, triclinic, space group $P\bar{1}$(#2), a=8.537(2) Å, b=13.646(3) Å, c=5.5827(8) Å, α=100.43(1)°, β=106.04(2)°, γ=85.92(2)°, V=614.6(2) Å^3, Z=2, d_{calc}=1.223 gcm^{-3}, F(000)=244, μ(CuKα)=7.53 cm^{-1}, λ(CuKα)= 1.54178 Å, 3114 reflections measured, 3114 observed (I>0.00σ(I)), 146 variables, R=0.063, R_w=0.120, R1=0.061 (2912 reflections), GOF 3.26.
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