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First total synthesis of (±)-AM6898A and (±)-AM6898D

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Abstract—We have established an effective method for the syntheses of (±)-AM6898D and its possible three diastereoisomers via Claisen rearrangement, stereoselective epimerization, and introduction of one isoprene unit by umpolung. Additionally, we have achieved the total synthesis of (±)-AM6898A from the same intermediate, by intramolecular aldol condensation.

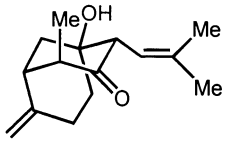
1. Introduction

1: AM6898A and **2**: AM6898D, sesquiterpenes with inhibitory effect against IgE production, were isolated together with related compounds in 1997 from certain strains of *Pseudallescheria* sp. by a group of Asahi Chemical Industry Co. Ltd.[1] However, the absolute stereochemistry of **1**: AM6898A and the relative and absolute stereochemistries of **2**: AM6898D have not been determined. These compounds were reported as possible candidates for antiallergic agents, because they selectively suppress IgE production in immunoglobulin biosynthesis with low cell toxicity.[1] On the other hand, the same carbon skeleton with these compounds is also found in fumagillin, which is a potent inhibitor of angiogenesis.[2] Semisynthetic derivative of fumagillin such as TNP-470 are currently in clinical trial as antitumor agents as well.[3] First total synthesis (±)-fumagillin was reported in 1972 by E. J. Corey.[4] Regarding to the asymmetric synthesis, (−)-fumagillol and (−)-fumagillin were synthesized by independent two groups in 1997 and 1999, respectively.[5,6] It is of interest that **1** and **2** do not have labile epoxides which are found in fumagillin, although all of them have the same framework in it. Due to structural features of **1** and **2**, total synthesis of those compounds will provide us a useful information about the wider biological properties of them together with structure activity relationship among related analogs of fumagillin. In this paper, we describe in detail about the first total synthesis of (±)-AM6898A and (±)-AM6898D together with all possible diastereoisomers[7,8] (Scheme 1).

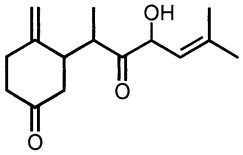
2. Result and discussion

2.1. Synthetic plan

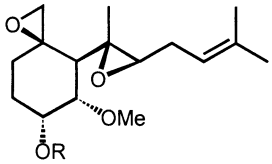
We have to explore a flexible synthetic route which can reach **2**: AM6898D and all possible diastereoisomers as well, because their stereochemistry is unknown. We also planned to prepare **1**: AM6898A from the same intermediate in the synthesis of **2**: AM6898D as shown in Scheme 2. In our retrosynthetic analysis, **1**: AM6898A will be obtained from **3**: dehydroxy-AM6898D by intramolecular aldol condensation. Both **2**: AM6898D and **3** could be synthesized from aldehyde **4** by umpolung C–C bond formation. Accordingly, we have started to synthesize the all possible diastereoisomers of the aldehyde **4** by Claisen rearrangement.



1: AM6898A



2: AM6898D



Fumagillin : R=CO(CH=CH)$_4$CO$_2$H
Fumagillol : R=H
TNP-470 : R=CONHCOCH$_2$Cl

Keywords: AM6898A; AM6898D; intramolecular aldol condensation; Claisen rearrangement.
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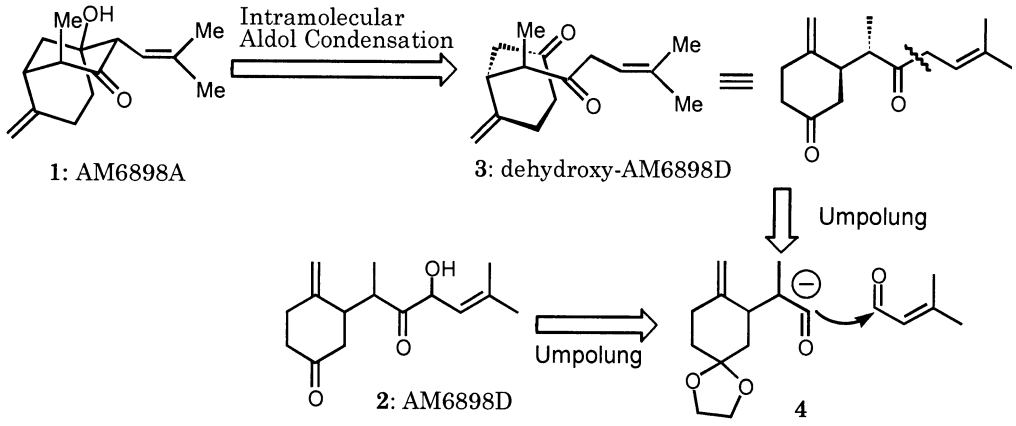
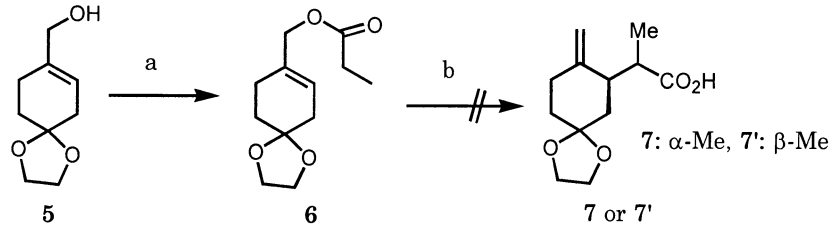


Scheme 2.

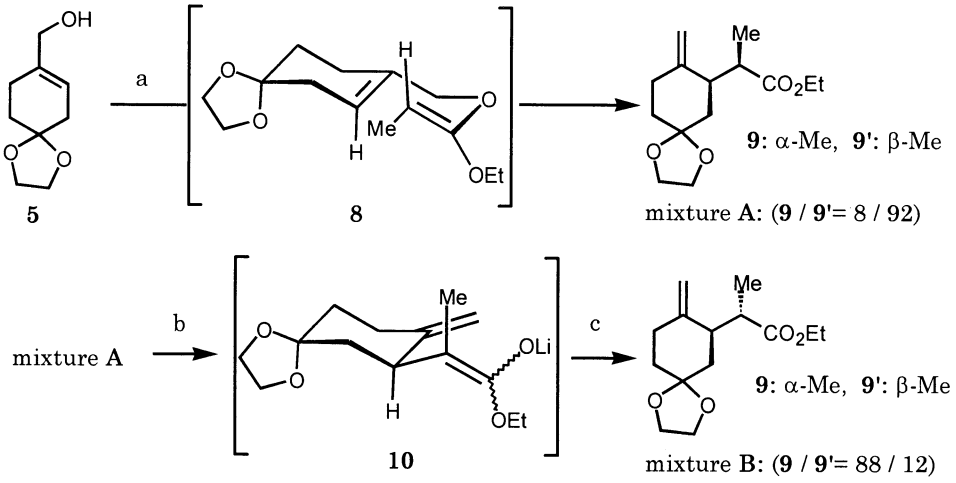
2.2. Claisen rearrangement and stereoselective epimerization

The allylic alcohol **5**, a synthetic intermediate of aldehyde **4**, was prepared by Birch reduction of *p*-methoxybenzyl alcohol, followed by ketalization, according to the procedure of Isobe.[9] Subsequent acylation of this allylic alcohol **5** afforded the propionate ester **6**, which was the precursor of the Claisen rearrangement. However, neither enolate Claisen rearrangement nor Ireland Claisen rearrangement conditions for the propionate ester **6** gave the desired carboxylic acid **7** or **7′**.[10] (Scheme 3)

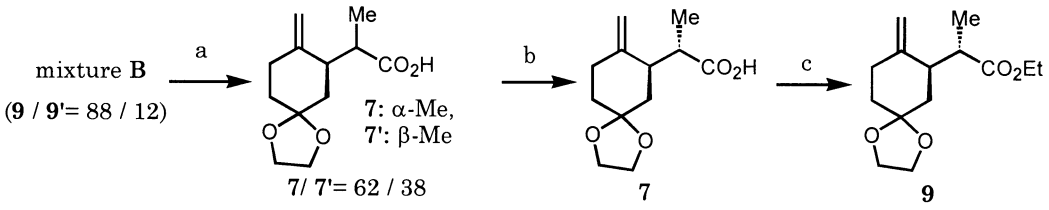
On the other hand, the thermal rearrangement of this allylic alcohol **5** in triethyl orthopropionate with catalytic amount of propionic acid, afforded the diastereomer mixture **A** (**9**/**9′**=8/92) in 76.9% yield.[11] It is postulated that the major ethyl ester isomer **9′** would have *syn*-stereochemistry by considering the chair-form conformation of the allylic ether **8** which is regarded as the reaction intermediate of this rearrangement. In order to epimerize the β-methyl isomer **9′** to the α-methyl isomer **9**, the diastereomer mixture **A** (**9**/**9′**=8/92) was treated with LDA followed by protonation with EtOH. This reaction afforded the diastereomer mixture **B** (**9**/**9′**=88/12) containing the *anti*-ethyl ester **9** as the major



Scheme 3. (a) Propionyl chloride, DMAP, Et_3N/CH_2Cl_2, (86.1%); (b) LDA/THF or TMSCl, LDA/THF.



Scheme 4. (a) Cat. $EtCO_2H/EtC(OEt)_3$, 140°C, 3 h (76.9%); (b) LDA/THF, −78°C; (c) EtOH (93.3% in 2 steps).



Scheme 5. (a) 2N NaOHaq/EtOH, 80°C, 3 h (quant.); (b) recrystallization from Et_2O and *n*-hexane (26.2%); (c) EtOH, DCC, DMAP/CH_2Cl_2, −10°C, 2 h (65.5%).

isomer. The preferred diastereoselectivity of this epimerization would be attained by β-face selective-protonation at the enolate moiety of the reaction intermediate **10**, because the α-side was considerably shielded by *exo*-double bond. (Scheme 4)

The relative stereochemistry of the ethyl ester **9** and **9′** was confirmed by chemical conversion as shown in Scheme 5. The carboxylic acid **7** was prepared as a single isomer, by saponification of the diastereomer mixture **B** and subsequent recrystallization. The X-ray crystallographic analysis proved the *anti*-stereochemistry of the carboxylic acid **7** as shown in Fig. 1. Additionally, esterification of the carboxylic acid **7** afforded the ethyl ester **9** without epimerization.[12] From these results, the *anti*-stereochemistry of the ethyl ester **9** was confirmed. Accordingly, the *syn*-stereochemistry of the other isomer **9′** was supported. (Scheme 5)

2.3. Synthesis of AM6898D and its three possible diastereoisomers by umpolung

We have investigated to introduce one isoprene unit into the side chain of the ethyl ester **9** or **9′** by umpolung methodology as shown in Schemes 6 and 7. It should be noted that, only the major isomers are shown with regards to the stereochemistry in these schemes. At first the aldehyde **11** prepared from the mixture **A** was converted to the 1,3-dithiane **12**. In this reaction condition, both aldehyde and 1,3-dioxolane moieties in **11** were converted to the 1,3-dithianes. However, subsequent umpolung coupling of the 1,3-dithiane **12** with 3-methyl-2-butenal in basic conditions

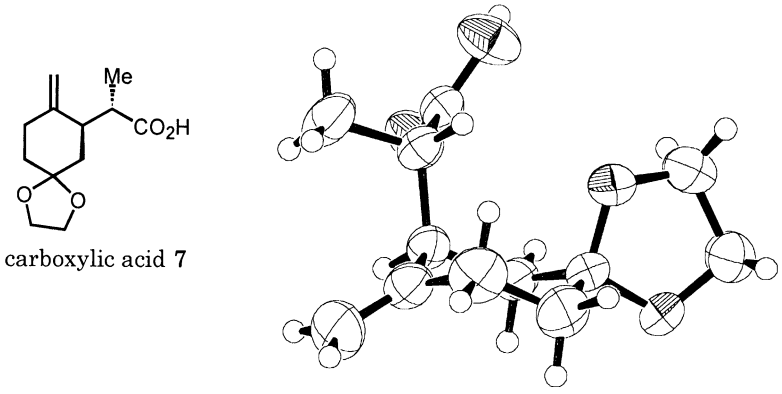
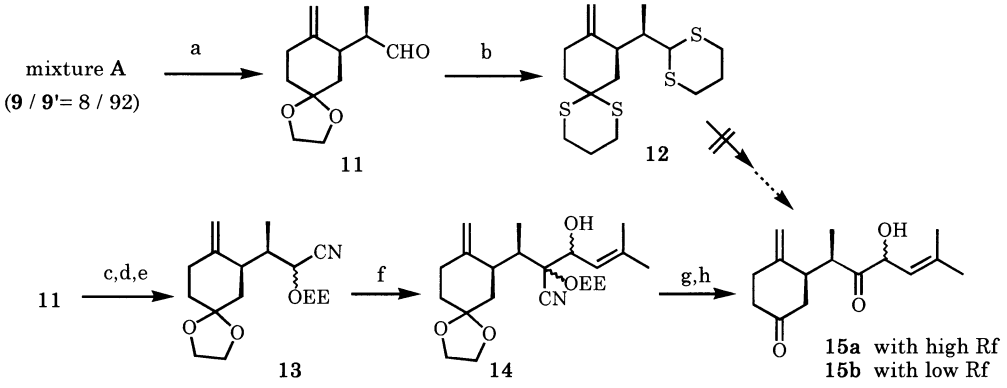
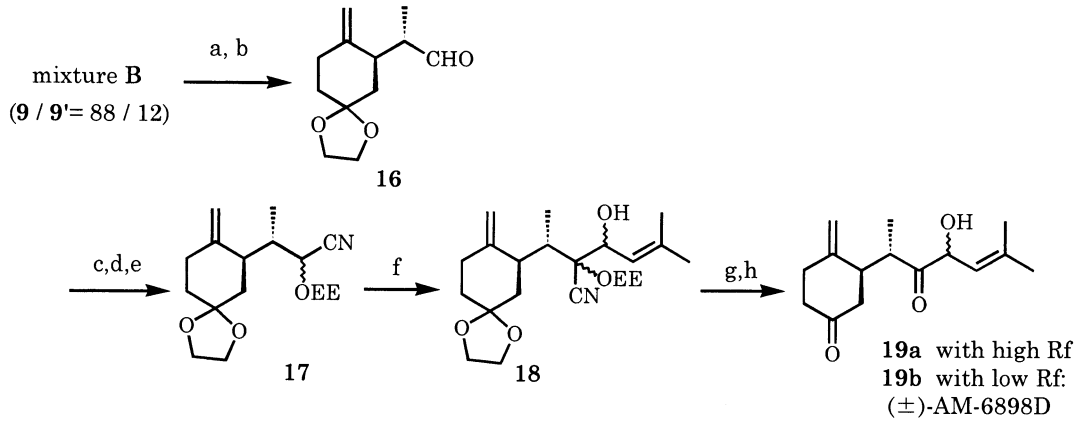


Figure 1. Comment: the crystal of the carboxylic acid **7** was obtained as racemic compound. In this ORTEP drawing only one enantiomer is shown.



Scheme 6. (a) 1.1 equiv. DIBAL/toluene; (b) 2 equiv. 1,3-Propanedithiol, 1 equiv. BF_3OEt/CH_2Cl_2 (65.5% in 2 steps from mixture **A**); (c) cat. KCN·dicyclohexano-18-crown-6/TMSCN, 0°C; (d) $PhCH_2NMe_3F/H_2O$, THF; (e) cat. TsOH, ethyl vinyl ether/benzene (93.1% in 4 steps from mixture **A**); (f) LDA/THF, then 3-methyl-2-butenal, −10°C; (g) 5% H_2SO_4 aq./MeOH, over night; (h) 0.5N NaOH/Et_2O, 15 min (**15a**: 31.2%, **15b**: 18.3%, in 3 steps from **13**).



Scheme 7. (a) 2.2 equiv. DIBAL/toluene; (b) oxalyl chloride, DMSO/CH_2Cl_2, then TEA, −78°C to 0°C; (c) cat. KCN·dicyclohexano-18-crown-6/TMSCN, 0°C; (d) $PhCH_2NMe_3F/H_2O$, THF; (e) cat. TsOH, ethyl vinyl ether/benzene (93.8% in 5 steps from mixture **B**); (f) LDA/THF, then 3-methyl-2-butenal, −10°C; (g) 5% H_2SO_4 aq./MeOH, over night; (h) 0.5N NaOH/Et_2O, 15 min (**19a**: 8.05%, **19b**: 6.81%, in 3 steps from **17**).

was unsuccessful, probably, due to the steric hindrance of the α-position substituents of the 1,3-dithiane in the side chain. Alternatively, the protected cyanohydrin **13** was prepared from the aldehyde **11** according to the procedure of Takahashi in 3 steps.[13,14] This protected cyanohydrin **13** was treated with LDA, followed by addition of 3-methyl-2-butenal to give the adduct **14**. Acidic deprotection of the 1,3-dioxolane and 1-ethoxyethyl ether in this adduct **14**, followed by treatment with 0.5N NaOH afforded the two major products (**15a** and **15b**). Subsequently, these two products were separated by silica gel column chromatography. However, both the ^1H NMR spectra of the **15a** and **15b** were not identical with the reported spectra of the natural **2**: AM6898D suggesting that the stereochemistry of the aldehyde **11** was not desired one. (Scheme 6)

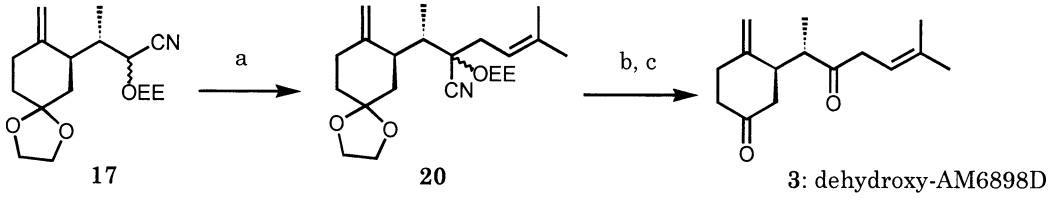
In the same manner, the mixture **B** was converted to the protected cyanohydrin **17** through the aldehyde **16**. Following C–C bond formation and deprotection afforded the two major products (**19a** and **19b**). These two products were purified by silica gel column chromatography to give two single isomers. Eventually, the ^1H and ^{13}C NMR spectra of the **19b** with low R_f were identical with the reported spectra of the natural **2**: AM6898D. However, the yields of the conversions from **17** to **19a** and **19b** were not good. Similarly, it is noted that the yield using 3-methyl-2-butenal as electrophile was not good.[15] By considering these results, one of the factors would be the law reactivity of 3-methyl-2-butenal. (Scheme 7).

2.4. Synthesis of AM6898A by intramolecular aldol condensation

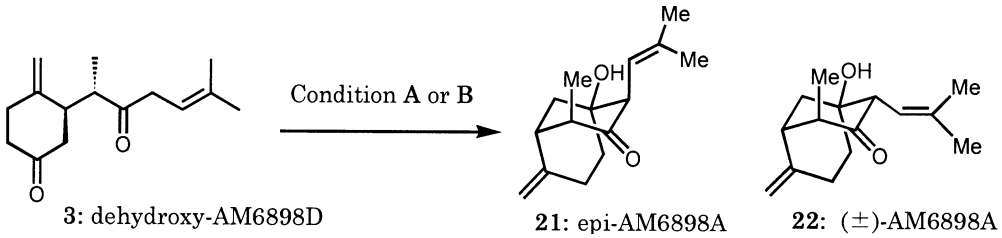
Thus, total synthesis of **19b**: (±)-AM6898D and its three possible diastereoisomers has been completed via Claisen rearrangement, stereoselective epimerization, and introduction of the isoprene unit by umpolung methodology. From this investigation, we supposed that **3**: dehydroxy-AM6898D, which is the key intermediate for **1**: AM6898A, would be easily synthesized. (Scheme 2) Additionally, by considering the X-ray data of the carboxylic acid **7**, the conformation of **3**: dehydroxy-AM6898D is expected to be suitable for the conversion to **1**: AM6898A. The X-ray results in which a bulky side chain was positioned at axial in the carboxylic acid **7** could be explained by A-strain effect of the exocyclic olefin.[16] (Fig. 1) For the same reasons, in **3**: dehydroxy-AM6898D, the side chain would be positioned at axial. Taking advantage of this conformation, **3**: dehydroxy-AM6898D would be converted to **1**: AM6898A by intramolecular aldol condensation.

In Scheme 8, preparation of **3**: dehydroxy-AM6898D is summarized. The protected cyanohydrin **17** was treated with LDA, followed by addition of 1-bromo-3-methyl-2-butene to give the adduct **20**. Deprotection of the adduct **20**, followed by purification using silica gel column chromatography, afforded the desired **3**: dehydroxy-AM6898D as a single isomer.

In Scheme 9, the conversion of **3**: dehydroxy-AM6898D into **22**: (±)-AM6898A by intramolecular aldol condensation



Scheme 8. (a) LDA/THF, then 1-bromo-3-methyl-2-butene, −10°C; (b) 5% H_2SO_4 aq./MeOH, over night; (c) 0.5N NaOH/Et_2O, 15 min (34.8% in 3 steps from **17**).



Scheme 9. Condition **A**: 1.5 equiv. LDA/THF, −15°C (46.2%, **21/22**=88/12); Condition **B**: 1.5 equiv. LDA/THF and HMPA (THF/HMPA=77/23), −78°C to 0°C (76.2%, **21/22**=10/90).

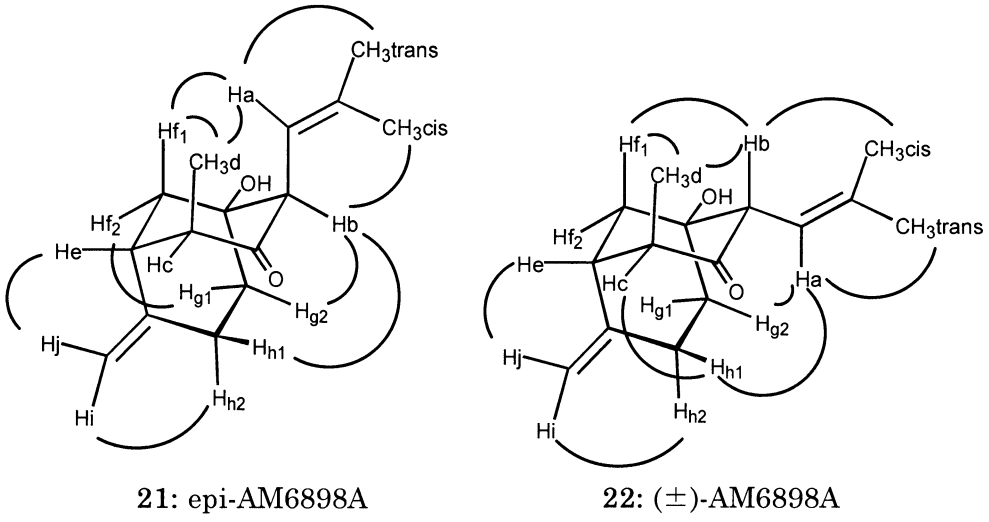


Figure 2. All protons were assigned from the $^{1}H-^{1}H$ COSY spectra, and the key NOEs were observed in the NOESY spectra as shown. The assignments and coupling constants were shown in the experimental section. In **21**: *epi*-AM6898A the coupling constant of the protons H_{g1} and H_{h1} is 14 Hz, while in **22**: (±)-AM6898A the coupling constant of the corresponding protons is 13 Hz. From these results, each pair of the protons positions at antiperiplanar. These results supported the above conformations.

is shown. In the reaction condition **A**, into the THF solution of **3**, LDA was added to give the product containing **21**: *epi*-AM6898A as the major product (**21/22**=88/12). While in the reaction condition **B**, HMPA was used as cosolvent to give the product containing **22**: (±)-AM6898A as the major product (**21/22**=10/90) with an increased yield. Probably, in the condition **B**, **22**: (±)-AM6898A was obtained as thermodynamically controlled product. The ^{1}H and ^{13}C NMR spectra of **22** were identical with the reported spectra of the natural **1**: AM6898A. Additionally, the conformations and configurations of **21**: *epi*-AM6898A and **22**: (±)-AM6898A were confirmed by the NOEs and the coupling constant as shown in Fig. 2.

3. Conclusion

In conclusion, we have completed the first total synthesis of **19b**: (±)-AM6898D and its three possible diastereoisomers via Claisen rearrangement, stereoselective epimerization, and introduction of the isoprene unit by umpolung methodology. Additionally, we have achieved the first total synthesis of **22**: (±)-AM6898A from the common protected cyanohydrin **17** using intramolecular aldol condensation as key reaction.

4. Experimental

4.1. General methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Unity-400 (400 MHz) NMR spectrometer system or Varian Unity Inova-500 (500 MHz) NMR spectrometer system. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Unity-400 (100 MHz) NMR spectrometer system or Varian Unity Inova-500 (125 MHz) NMR spectrometer system. NOESY and $^{1}H-^{1}H$ COSY spectra were recorded on Varian Unity Inova-500 (500 MHz) NMR spectrometer system. All melting points were measured on a Shibayama micro melting point apparatus and are uncorrected. IR spectra were recorded on JASCO FT/IR-300E spectrophotometer. High resolution mass spectra (HRMS) were recorded on JEOL JMS-SX 102AQQ instrument, and reported in *m/z*. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel coated glass plates 60F-254 (Merck, Art5715). For flash column chromatography, Merck Silicagel 60 (230–400 mesh) was used. Non-aqueous reactions were carried out under nitrogen atmosphere. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co., Inc.

All other commercially available reagents were used as received.

4.1.1. Propionate ester 6. The allylic alcohol **5** (3.00 g, 17.6 mmol) prepared using Isobe's procedure, triethylamine (3.70 ml, 26.5 mmol), and 4-(dimethylamino)pyridine (30.0 mg, 0.246 mmol) was dissolved in CH_2Cl_2 (20 ml). The solution was cooled to 0°C, and propionyl chloride (1.8 ml, 20.7 mmol) was added. The reaction mixture was stirred for 30 min at rt, and then water was added. The resulting mixture was extracted with CH_2Cl_2(×2), and the combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=1/5) to afford the propionate ester **6** as a colorless oil (3.4 g, 86.1%).

NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, J=6.8 Hz), 1.75–1.81 (2H, m), 2.20–2.38 (6H, m), 3.98 (4H, s), 4.49 (2H, s), 5.62–5.68 (1H, m); IR (KBr) ν_{max} 1740, 1680 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_4(M^+)$ 226.1205, found 226.1201.

4.1.2. Diastereomer mixture A (9/9′=8/92). The allylic alcohol **5** (7.00 g, 41.1 mmol) and propionic acid (70 mg, 0.94 mmol) was dissolved in triethyl orthopropionate (23 ml, 114 mmol). The mixture was heated at 140°C for 3 h, and then cooled to rt. To the reaction mixture, sat. $NaHCO_3$ was added, and the solution was extracted with AcOEt (×3). The combined organic layer was washed with water and brine, and dried over Na_2SO_4, then concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=1/9) to afford the diastereomer mixture **A** (**9/9′**=8/92) as a colorless oil (8.03 g, 76.9%).

9′: NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, d, J=6.8 Hz), 1.22 (3H, t, J=7.2 Hz), 1.56–1.77 (3H, m), 1.78–1.85 (1H, m), 2.20–2.29 (1H, m), 2.33–2.42 (1H, m), 2.57–2.65 (1H, m), 2.83–2.92 (1H, m), 3.89–4.00 (4H, m), 4.09 (2H, q, J=7.2 Hz), 4.67 (1H, s), 4.74 (1H, s); IR (KBr) ν_{max} 1730, 1650 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_4(M^+)$ 254.1518 found 254.1525.

4.1.3. Diastereomer mixture B (9/9′=88/12) (epimerization of diastereomer mixture A). To a solution of diisopropylamine (1.40 ml, 9.99 mmol) in THF (15 ml), *n*-butyl lithium solution in THF (1.53 M, 5.80 ml, 8.87 mmol) was added at −10°C. After stirring for 10 min, the flask was cooled to −78°C. To the solution, the diastereomer mixture **A** (1.50 g, 5.90 mmol) in THF (5 ml) was added as dropwise. After stirring for 1 h, EtOH (2.5 ml) was added, and then the mixture was warmed to rt. The reaction mixture was quenched with sat. NH_4Cl, and extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure, to afford the diastereomer mixture **B** (**9/9′**=88/12) as a colorless oil (1.40 g, 93.3%).

9: NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J=6.8 Hz), 1.27 (3H, t, J=7.2 Hz), 1.64–1.79 (4H, m), 2.16–2.31 (2H, m), 2.49–2.56 (1H, m), 2.91–3.00 (1H, m), 3.86–4.01 (4H, m), 4.15 (2H, q, J=7.2 Hz), 4.74 (1H, s), 4.84 (1H, s); IR (KBr) ν_{max} 1730, 1650 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_4(M^+)$ 254.1518 found 254.1548.

4.1.4. Carboxylic acid 7. To a solution of the diastereomer mixture **B** (150 mg, 0.590 mmol) in EtOH (2 ml), 2N NaOH (2 ml) was added. The solution was heated to reflux with stirring for 1 h, and then cooled to rt. After addition of 1N HCl (4.3 ml), the mixture was extracted with AcOEt (×3). The combined organic layer was washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure, to give a carboxylic acid diastereoer mixture (**7/7′**=62/38). This ratio of **7/7′** was determined by ^1H NMR (400 MHz, $CDCl_3$) spectrum. Recrystallization (Et_2O and *n*-hexane) of the diastereomer mixture afforded the carboxylic acid **7** (35 mg, 26.2%) as a single isomer. Continuous recrystallization (Et_2O and *n*-hexane) gave a single crystal of **7** for X-ray crystallographic analysis.

Mp 102–103°C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, J=5.6 Hz), 1.62–1.72 (1H, m), 1.75–1.89 (3H, m), 2.18–2.32 (2H, m), 2.47–2.55 (1H, m), 2.95–3.04 (1H, m), 3.90–4.05 (4H, m), 4.77 (1H, s), 4.87 (1H, s); IR (KBr) 1700, 1650 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_4(M^+)$ 226.1205 found 226.1197; X-ray crystallographic analysis: the crystal structure data was deposited at the Cambridge Crystallographic Data Cent. Deposition number: CCDC 178359.

4.1.5. Ethyl ester 9 (esterification of the carboxylic acid 7). The carboxylic acid **7** (15 mg, 0.0663 mmol), EtOH (0.0150 ml, 0.256 mmol), and 4-dimethylamino pyridine (1.0 mg, 0.00819 mmol) were dissolved in CH_2Cl_2 (1 ml). After cooling the flask to −10°C, dicyclohexyl carbodiimide (17.0 mg, 0.0824 mmol) was added. And the solution was stirred for 2 h at the same temperature. After addition of Et_2O (2 ml), the reaction mixture was filtered to remove precipitate. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=1/9) to afford the ethyl ester **9** as a colorless oil (11 mg, 65.5%).

NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J=6.8 Hz), 1.27 (3H, t, J=7.2 Hz), 1.64–1.79 (4H, m), 2.16–2.31 (2H, m), 2.49–2.56 (1H, m), 2.91–3.00 (1H, m), 3.86–4.01 (4H, m), 4.15 (2H, q, J=7.2 Hz), 4.74 (1H, s), 4.84 (1H, s); IR (KBr) ν_{max} 1730, 1650 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_4(M^+)$ 254.1518 found 254.1549.

4.1.6. Aldehyde 11. To a stirring solution of diastereomer mixture **A** (455 mg, 1.79 mmol) in toluene (40 ml) at −78°C, diisobutyl aluminum hydride solution in *n*-hexane (0.95 M, 2.00 ml, 1.90 mmol) was added during 5 min. After stirring for 1 h, MeOH (0.2 ml) was added, and then the mixture was warmed to rt. After addition of sat. potassium sodium tartrate, the resulting mixture was extracted with Et_2O (×2). The combined organic layer was washed with water and brine, and dried over Na_2SO_4, and concentrated under reduced pressure, to afford the aldehyde **11** (450 mg) as crude product. This product was used for following reaction without further purification.

NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, J=6.8 Hz), 1.52–1.82 (4H, m), 2.21–2.42 (2H,

m), 2.65–2.80 (2H, m), 3.90–4.00 (4H, m), 4.64 (1H, s), 4.86 (1H, s), 9.59 (1H, d, J=2.0 Hz).

4.1.7. 1,3-Dithiane 12. The aldehyde **11** (1.50 g, 5.90 mmol), and 1,3-butane dithiol (1.28 g, 11.8 mmol) were dissolved in CH_2Cl_2 (200 ml). After cooling to 0°C, BF_3OEt_2 (0.75 ml, 5.95 mmol) was added dropwise to the solution. After stirring for 30 min, sat. $NaHCO_3$ was added to the reaction mixture. The solution was extracted with CH_2Cl_2 (×2). The combined organic layer was washed with water and brine, and dried over Na_2SO_4, then concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (AcOEt/*n*-hexane=5/95) to afford the 1,3-dithiane **12** as a white amorphous (1.34 g, 65.5% in 3 steps from mixture **A**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, J=7.2 Hz), 1.58–1.67 (1H, m), 1.76–1.90 (2H, m), 1.96–2.14 (3H, m), 2.20–2.54 (5H, m), 2.76–2.97 (9H, m), 4.22 (1H, d, J=5.6 Hz), 4.66 (1H, s), 4.84 (1H, s); IR (KBr) ν_{max} 1645 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{26}S_4(M^+)$ 346.0917 found 346.0909.

4.1.8. Protected cyanohydrin 13. To a solution of the aldehyde **11** (230 mg, 1.09 mmol) in trimethylsilyl cyanide (0.30 ml, 2.25 mmol), catalytic amount of the dicyclohexano-18-crown-6 and KCN complex was added at 0°C. After stirring for 30 min, THF (4.0 ml), H_2O (1.0 ml), benzyltrimethylammonium fluoride (50 mg, 0.295 mmol) was added. The mixture was stirred for 1 h at rt, and then extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure, to afford the cyanohydrin (310 mg) as a crude product. Without purification, the cyanohydrin was dissolved in benzene (15 ml) at 0°C. To the solution, TsOH (20 mg, 0.116 mmol), and ethyl vinyl ether (0.300 ml, 3.13 mmol) was added. After stirring for 30 min, sat. $NaHCO_3$ was added, and then the mixture was extracted with Et_2O (×3). The combined organic layer was washed with water and brine. After drying over Na_2SO_4, the solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=20/80) to afford the protected cyanohydrin **13** (264 mg, 93.1% in 4 steps from mixture **A**) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11–1.27 (6H, m), 1.31–1.39 (3H, m); 1.60–1.92 (4H, m), 2.15–2.52 (4H, m), 3.43–3.76 (2H, m), 3.89–4.00 (4H, m), 4.26–4.94 (4H, m); IR (KBr) ν_{max} 2240, 1650 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{27}NO_4(M^+)$ 309.1940 found 309.1956.

4.1.9. Adduct 14. To a solution of diisopropylamine (0.06 ml, 0.428 mmol) in THF (1.0 ml), *n*-butyl lithium solution in THF (1.53 M, 0.25 ml, 0.384 mmol) was added at −10°C. To the solution, the protected cyanohydrin **13** (100 mg, 0.323 mmol) in THF (0.5 ml, ×2) was added dropwise. After stirring for 10 min, 3-methyl-2-butenal (30 mg, 0.375 mmol) in THF (0.3 ml, ×2) was added, and then the mixture was stirred for 30 min at 0°C. The reaction mixture was quenched with sat. NH_4Cl, and extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure, to afford the crude adduct **14** as a colorless oil (100 mg). This product was used for following reaction without further purification.

4.1.10. 15a and 15b: diastereoisomers of AM6898D. To a solution of the crude adduct **14** (100 mg) in MeOH (2 ml), 2% H_2SO_4 aq. (1 ml) was added, then the mixture was stirred for over night. To this reaction mixture, water was added, then the solution was extracted with Et_2O (×3). The combined organic layer was washed with 0.5N NaOH aq. until the spots of deprotected cyanohydrin disappeared on TLC, and the reaction mixture was washed successively with water and brine. The solution was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=10/90–25/75) to afford the **15a** with high R_f (25.2 mg, 31.2% from **13**) and **15b** with low R_f (14.8 mg, 18.3% from **13**) as colorless oil.

15a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J=6.8 Hz), 1.80 (3H, s), 1.83 (3H, d, J=1.2 Hz), 2.40–2.62 (6H, m), 2.76–2.86 (1H, m), 2.88–2.96 (1H, m), 3.69 (1H, d, J=4.0 Hz), 4.66 (1H, dd, J=10.0, 4.0 Hz), 4.82 (1H, s), 4.85–4.99 (2H, m); IR (KBr) 1710, 1650 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_3$ (M^+) 250.1569 found 250.1584.

15b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, d, J=7.2 Hz), 1.69 (3H, s), 1.76 (3H, s), 2.20–2.38 (6H, m), 2.71–2.75 (1H, m), 2.91–2.99 (1H, m), 3.99 (1H, d, J=9.2 Hz), 4.88–4.95 (3H, m), 5.34 (1H, dd, J=9.2, 1.2 Hz); IR (KBr) 1710, 1670, 1660 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_3(M^+)$ 250.1569 found 250.1584.

4.1.11. Aldehyde 16. To a stirring solution of diastereomer mixture **B** (1400 mg, 5.51 mmol) in toluene (60 ml) at −78°C, diisobutyl aluminum hydride solution in *n*-hexane (1.00 M, 12 ml, 12.0 mmol) was added for 5 min. After stirring for 1 h, MeOH (0.25 ml) was added, and then the mixture was warmed to rt. After addition of sat. potassium sodium tartrate, the resulting mixture was extracted with Et_2O (×2). The combined organic layer was washed with water and brine, and dried over Na_2SO_4, and concentrated under reduced pressure, to afford the corresponding alcohol (1500 mg) as crude product. This crude alcohol was subjected to following Swern oxidation.

To a solution of oxalyl chloride (0.8 ml) in CH_2Cl_2 (100 ml), DMSO (1.30 ml) solution in CH_2Cl_2 (5 ml) was added as dropwise at −78°C. To this solution the alcohol (1500 mg) solution in CH_2Cl_2 (5 ml) was added, and stirring was continued for 20 min at the same temperature. After warming the mixture to −20°C, triethylamine (6.4 ml) was added. The reaction mixture was washed with water and brine, and dried over Na_2SO_4, then concentrated under reduced pressure to afford the aldehyde **16** (1250 mg) as crude product. This product was used for following reaction without further purification.

NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, J=6.8 Hz), 1.65–1.83 (4H, m), 2.21–2.44 (2H, m), 2.55–2.63 (1H, m), 2.88–2.98 (1H, m), 3.88–4.00 (4H, m), 4.70 (1H, s), 4.86 (1H, s), 9.70 (1H, d, J=2.4 Hz).

4.1.12. Protected cyanohydrin 17. To a solution of the aldehyde **16** (1250 mg, 5.94 mmol) in trimethylsilyl cyanide (1.5 ml, 11.2 mmol), catalytic amount of the dicyclohexano-18-crown-6 and KCN complex was added at 0°C. After stirring for 30 min, THF (20 ml), H_2O (5.0 ml), benzyltrimethylammonium fluoride (325 mg, 1.92 mmol) was added. The mixture was stirred for 1 h at rt, and then extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure, to afford the cyanohydrin (1600 mg) as a crude product. Without purification, the cyanohydrin was dissolved in benzene (70 ml) at 0°C. To the solution, TsOH (90 mg, 0.522 mmol), and ethyl vinyl ether (1.00 ml, 10.5 mmol) was added. After stirring for 30 min, sat. $NaHCO_3$ was added, then the mixture was extracted with Et_2O (×3). The combined organic layer was washed with water and brine, and dried over Na_2SO_4, then concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=20/80) to afford the protected cyanohydrin **17** (1600 mg, 93.8% in 5 steps from mixture **B**) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.08 (3H, m), 1.12–1.28 (3H, m), 1.31–1.42 (3H, m), 1.50–1.65 (2H, m), 1.74–1.90 (2H, m), 2.12–2.48 (4H, m), 3.43–3.76 (2H, m), 3.88–4.00 (4H, m), 4.54–4.97 (4H, m); IR (KBr) ν_{max} 2240, 1650 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{27}NO_4(M^+)$ 309.1940 found 309.1940.

4.1.13. Adduct 18. To a solution of diisopropylamine (0.06 ml, 0.428 mmol) in THF (1.0 ml), *n*-butyl lithium solution in THF (1.60 M, 0.25 ml, 0.400 mmol) was added at −10°C. To the solution, the protected cyanohydrin **17** (100 mg, 0.323 mmol) in THF (0.5 ml ×2) was added dropwise. After stirring for 10 min, 3-methyl-2-butenal (30 mg, 0.375 mmol) in THF (0.3 ml ×2) was added, then the mixture was stirred for 30 min at 0°C. The reaction mixture was quenched with sat. NH_4Cl, and extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, then concentrated under reduced pressure, to afford the crude adduct **18** as a colorless oil (128 mg). This product was used for following reaction without further purification.

4.1.14. 19a: Diastereoisomer of AM6898D and 19b: (±)-AM6898D. To a solution of the crude adduct **18** (128 mg) in MeOH (2 ml), 2% H_2SO_4 aq. (1 ml) was added, then the mixture was stirred for over night. To this reaction mixture, water was added, and then the solution was extracted with Et_2O (×3). The combined organic layer was washed with 0.5N NaOH aq. until the spots of deprotected cyanohydrin disappeared on TLC, and the reaction mixture was washed successively with water and brine. The solution was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=10/90–25/75) to afford **19a** with high R_f (6.50 mg, 8.05% from **17**) and **19b** with low R_f (5.50 mg, 6.81% from **17**) as colorless oil.

19a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, J=6.8 Hz), 1.81 (3H, s), 1.86 (3H, s), 2.05–2.13 (1H, m), 2.24–2.57 (5H, m), 2.66–2.77 (1H, m), 3.04–3.12 (1H, m), 3.55–3.58 (1H, m), 4.93–5.03 (3H, m), 5.04 (1H, s); IR (KBr) 1708, 1650 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_3(M^+)$ 250.1569 found 250.1598.

19b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, J=6.8 Hz), 1.80 (3H, d, J=1.2 Hz), 1.86 (3H, d, J=1.2 Hz), 2.08–2.16 (1H, m), 2.30–2.66 (6H, m), 2.89–2.96 (1H, m), 3.67 (1H, d, J=4.0 Hz), 4.89–5.07 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 18.7, 26.0, 30.9, 41.7, 42.3, 45.7, 48.2, 76.5, 114.3, 120.2, 141.0, 143.9; IR (KBr) 1708, 1650 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_3$ (M^+) 250.1569 found 250.1570.

4.1.15. Adduct 20. To a solution of diisopropylamine (0.06 ml, 0.428 mmol) in THF (1.0 ml), *n*-butyl lithium solution in THF (1.60 M, 0.25 ml, 0.400 mmol) was added at −10°C. To the solution, the protected cyanohydrin **17** (95 mg, 0.307 mmol) in THF (0.5 ml ×2) was added dropwise. After stirring for 10 min, 1-bromo-3-methyl-2-butene (45 mg, 0.302 mmol) in THF (0.3 ml ×2) was added, and the mixture was stirred for 1 h at 0°C. The reaction mixture was quenched with sat. NH_4Cl, and extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure, to afford the crude product. To separate remaining starting material, this crude product was purified by flash column chromatography (AcOEt/*n*-hexane=10/90). This colorless oil of adduct **20** (65 mg) was used for following reaction without further purification.

4.1.16. 3: Dehydroxy AM6898D. To a solution of the adduct **20** (65 mg) in MeOH (2.5 ml), 2% H_2SO_4 aq. (1.25 ml) was added, then the mixture was stirred for over night at rt. To this reaction mixture, water was added, and the solution was extracted with Et_2O (×3). The combined organic layer was washed with 0.5N NaOH aq. until the spots of deprotected cyanohydrin disappeared on TLC, and the reaction mixture was washed successively with water and brine. The solution was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/*n*-hexane=5/95–10/90) to afford **3** (25.0 mg, 34.8% from **17**) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J=6.8 Hz), 1.63 (3H, s), 1.77 (3H, s), 2.14–2.21 (1H, m), 2.34–2.65 (6H, m), 2.91–2.99 (1H, m), 3.13–3.28 (2H, m), 4.97 (1H, s), 5.01 (1H, s), 5.26–5.32 (1H, m); IR (KBr) 1712, 1650 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_2$ (M^+) 234.1620 found 234.1643.

4.1.17. 21: *epi*-AM6898A. *Preparation of 0.2 M LDA solution in THF*: To a solution of diisopropylamine (0.06 ml, 0.428 mmol) in THF (1.75 ml), *n*-butyl lithium solution in THF (1.60 M, 0.25 ml, 0.400 mmol) was added at −10°C.

To a solution of **3** (5.2 mg, 0.0222 mmol) in THF (1 ml), the 0.2 M LDA solution in THF (0.1 ml, 0.0200 mmol) was added at −15°C. After stirring for 30 min, the reaction mixture was quenched with sat. NH_4Cl, and extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, then concentrated under

reduced pressure, to afford the crude product. This crude product was purified by flash column chromatography (AcOEt/*n*-hexane=15/85) to afford the product (**21**/**22**=88/12) (2.40 mg, 46.2%) as colorless oil.

***21**: epi-AM6898A*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, d, J=7.6 Hz), 1.62–1.68 (1H, m), 1.79 (3H, s), 1.80 (3H, s), 1.81–1.89 (2H, m), 2.03–2.16 (1H, m), 2.22–2.40 (3H, m), 2.52–2.56 (1H, m), 3.46 (1H, d, J=10 Hz), 4.64 (1H, s), 4.71 (1H, s), 5.19 (1H, d, J=10 Hz); ^{1}H NMR (500 MHz, benzene-d_6) δ 1.04 (3H, d, J=7.8 Hz, CH_{3d}), 1.53 (1H, m, d, J=14 Hz, H_{f2}), 1.58 (3H, s, CH_{3trans}), 1.61 (1H, dd, J=14, 3 Hz, H_{g2}), 1.72 (1H, ddd, J=14, 14, 6.0 Hz, H_{g1}), 1.77 (3H, s, CH_{3cis}), 2.00 (1H, dd, J=16, 6 Hz, H_{h2}), 2.11–2.19 (2H, m, H_{f1} and H_{h1}), 2.24–2.26 (1H, m, H_e), 2.40 (1H, td, J=7.8, 1.2 Hz, H_c); 3.53 (1H, d, J=10 Hz, H_b), 4.56 (1H, s, H_i), 4.62 (1H, s, H_j), 5.18 (1H, d, J=10 Hz, H_a); IR (KBr) 1700, 1650 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_2$(M^+) 234.1620 found 234.1604.

4.1.18. 22: (±)-AM6898A. Preparation of 0.2 M LDA solution in THF: To a solution of diisopropylamine (0.06 ml, 0.428 mmol) in THF (1.75 ml), *n*-butyl lithium solution in THF (1.60 M, 0.25 ml, 0.400 mmol) was added at −10°C.

To a solution of **3** (7.80 mg, 0.0333 mmol) in THF (1.00 ml) and HMPA (0.30 ml), the 0.2 M LDA solution in THF (0.25 ml, 0.0500 mmol) was added at −78°C. The mixture was warmed to 0°C, and stirred for 30 min. The reaction mixture was quenched with sat. NH_4Cl, and extracted with Et_2O (×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, then concentrated under reduced pressure, to afford the crude product. This crude product was purified by flash column chromatography (AcOEt/*n*-hexane=15/85) to afford the product (**21**/**22**=10/90) (5.90 mg, 76.2%) as colorless oil.

***22**: (±)-AM6898A*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, d, J=7.6 Hz), 1.42–1.51 (1H, m), 1.69 (3H, s), 1.88 (3H, s), 1.82–2.02 (3H, m), 2.15–2.23 (1H, m), 2.34–2.40 (1H, m), 2.41–2.49 (1H, m), 2.61–2.65 (1H, m), 3.45 (1H, d, J=9.6 Hz), 4.65 (1H, s), 4.74 (1H, s), 5.31 (1H, d, J=9.6 Hz); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (3H, d, J=7.5 Hz, CH_{3d}), 1.46 (1H, ddd, J=13.0, 13.0, 6.0 Hz, H_{g1}), 1.70 (3H, s, CH_{3cis}), 1.86–1.91 (2H, m, H_{f2} and H_{g2}), 1.89 (3H, s, CH_{3trans}), 1.97 (1H, ddd, J=13.0, 13.0, 3.0 Hz, H_{h1}), 2.19 (1H, dd, J=13.0, 6.0, H_{h2}), 2.37 (1H, dd, J=12.7, 3.0 Hz, H_{f1}), 2.45 (1H, q, J=7.5 Hz, H_c), 2.60–2.65 (1H, m, H_e), 3.45 (1H, d, J=9.6 Hz, H_b), 4.65 (1H, s, H_i), 4.74 (1H, s, H_j), 5.31 (1H, d, J=9.6 Hz, H_a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 18.8, 26.4, 28.8, 36.6, 37.0, 46.5, 49.5, 56.8, 74.7, 109.0, 116.6, 139.8, 149.3, 214.1; IR (KBr) 1700, 1650 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_2$ (M^+) 234.1620 found 234.1604.

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