Short Communication

Synthesis of Ambrein

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(+)-Ambrein (**1a**) is a major constituent of ambergris,¹⁾ which can be obtained as an intestinal concretion of spermwhale, and is used for the production of expensive perfumes. Here, the authors report the first synthesis of **1a**.

(+)-Ambreinolide (**3**) is a key intermediate for the synthesis of (+)-**1a** and amber-odorous compounds,²⁾ and chiral (+)-**3** was obtained by oxidation of (+)-**1a** with potassium permanganate.¹⁾ (±)-**3** had already been prepared by the cyclization of farnesylacetic acid (**2**) with formic acid or stannic chloride in low yields (2.0% or 3.3% respectively) by Stork *et al.*³⁾ Cyclization of (4*E*,8*E*)-**2**⁴⁾ (0.01 mol) with chlorosulfonic acid (0.04 mol) in 2-nitropropane at -70°C for 20 min, and subsequent purification by silica gel chromatography, gave

(±)-**3**, mp 138–140°C (from hexane–EtOAc) in a 71% yield. ¹H-NMR (CDCl₃, 100 MHz) δ: 0.82 (3H, s), 0.85 (3H, s), 0.90 (3H, s), 1.39 (3H, s), 2.50–2.80 (2H, m). The ¹H-NMR spectrum (100 MHz) of (±)-**3** was identical with that of natural (+)-**3**. Treatment of the sodium salt of (±)-**3** with quinine hydrochloride in methanol gave a quinine salt of (+)-**3**, mp 172–173°C (from CH₃CN), [α]_D²⁰ -127.0° (c=0.24, CHCl₃), which was then treated with dilute hydrochloric acid to give (+)-**3**,¹⁾ mp 142°C, [α]_D²⁰ +34.0 (c=2.0, EtOH). Reduction of (+)-**3** with diisobutylaluminum hydride in THF at -70°C gave (-)-hemiacetal (**4**),⁵⁾ mp 195–197°C, [α]_D²⁰ -9.0° (c=0.5, CHCl₃), in a 90% yield. The condensation of (-)-**4** with 1-(ethoxycarbonyl)ethylidenetriphenylphosphorane in boiling benzene gave unsaturated ester **6a**,⁵⁾ mp 79–80°C, [α]_D²⁰ +11.9° (c=2.0, EtOH), as a major product. Preparative TLC of the mother liquor with silica gel (benzene–ethyl acetate=4:1) gave minor product **5a**, mp 48°C (**5a**:**6a**=1:16). ¹H-NMR of **5a** (CDCl₃) δ: 0.78 (6H, s), 0.87 (3H, s), 1.16 (3H, s), 1.29 (3H, t, *J*=7 Hz), 1.25–1.75 (14H), 1.89 (3H, d, *J*=1.2 Hz), 2.48 (2H, m), 4.19 (2H, q, *J*=7 Hz), 5.91 (1H, d, t, *J*=2 and 8 Hz). The reduction of esters **5a** and **6a** with lithium aluminum hydride in ether gave allylic alcohols **5b**, mp 89–90°C, and **6b**,⁵⁾ mp 129°C, [α]_D²⁰ +3.6° (c=2.0, EtOH), respectively. ¹H-NMR of **5b** (CDCl₃) δ: 0.78 (6H, s), 0.87 (3H, s), 1.14 (3H, s), 1.81 (3H, d, *J*=1 Hz), 1.25–

1.75 (14H), 2.17 (2H, q, $J=7$ Hz), 4.09 (2H, s, CH_2O), 5.35 (1H, t, $J=7$ Hz). The (*Z*)-methyl protons in the system of $\text{ACH}_2\text{CCH}_3=\text{CHCH}_2\text{B}$ show lower chemical shifts⁶⁾ than those of the (*E*)-methyl protons in the ^1H -NMR spectra. Therefore, it is obvious that compounds **6a** and **6b** (δ : 1.83 and 1.68 ppm for each methyl proton) had the (*E*)-configuration, with the (*Z*)-configuration for **5a** and **5b** (δ : 1.89 and 1.81 ppm for each methyl proton), although in the previous paper⁵⁾ compounds **6a** and **6b** were erroneously assigned as the (*Z*)-isomer from their chemical shifts near to the value of the ordinary (*Z*)-isomer. (*E*)-Alcohol **6b** was acetylated with acetic anhydride-pyridine at 15°C for 12 hr to yield monoacetate **6c** as an oil in a 98% yield. IR ν_{max} (film) cm^{-1} : 3500, 1750, 1240, 1030, 945. Treatment of **6c** with dihydropyran in the presence of *p*-toluenesulfonic acid catalyst in benzene for 4 hr gave acetoxyl-tetrahydropyranyl (THP) ether **7** as an oil in a 97% yield, $[\alpha]_{\text{D}}^{20} -4.2^\circ$ ($c=2.0$, benzene). MS m/z : 435 (M^+ , $\text{C}_{27}\text{H}_{46}\text{O}_4$), 376 ($\text{M}^+ - \text{COCH}_3$), 333 ($\text{M}^+ - \text{H}_2\text{O}$, DHP). ^1H -NMR (CDCl_3) δ : 0.78 (3H, s), 0.81 (3H, s), 0.86 (3H, s), 1.14 and 1.21 (each s, *ca.* 4:6, $\text{CH}_3\text{-C-O-THP}$ diastereomers), 1.54 (m)–1.66 (s) (6H, THP), 1.25–2.14 (16H), 2.08 (3H, s, COCH_3), 3.50 and 3.92 (each 1H, m, OCH_2 of THP), 4.45 (2H, s, CH_2O), 4.86 (1H, m, OCHO of THP), 5.51 (1H, t, $J=8$ Hz). IR ν_{max} (film) cm^{-1} : 1750, 1400, 1240, 1080, 1030, 900.

According to Stella's method,⁷⁾ 1-bromomethyl-3,3-dimethyl-1-cyclohexene (**8**, 0.1 mmol) was reacted with *N,N*-dimethylaminoacetonitrile (0.1 mmol) in the presence of K_2CO_3 (0.15 mmol) in DMF for 48 hr at 20°C. The product, separated by extraction with hexane, was treated with 0.5% aqueous silver nitrate (0.1 mmol) in THF-ether (2:1) for 30 min to give ($\pm$)- γ -cyclogeraniol (**9**), bp 103–105°C (50 mm Hg), in a 92% yield. Reduction of ($\pm$)-**9** with lithium aluminum hydride in ether gave ($\pm$)- γ -cyclogeraniol (**10**), bp 71–75°C (6 mm Hg), in a 97% yield. IR ν_{max} (film) cm^{-1} : 3430, 1650, 1160, 1130, 1040, 900. ^1H -NMR (CDCl_3) δ : 0.87

(3H, s), 0.97 (3H, s), 1.30–1.70 (4H), 2.10 (2H), 3.60–3.71 (2H, CH_2O), 4.77 and 4.96 (each 1H, $=\text{CH}_2$). Halogenation of ($\pm$)-**10** with carbon tetrachloride in the presence of trioctylphosphine⁶⁾ at 20°C for 1 hr, which was followed by distillation, afforded ($\pm$)- γ -cyclogeranyl chloride (**11**), bp 104–105°C (45 mm Hg), in an 84% yield. IR ν_{max} (film) cm^{-1} : 3090, 1660, 1370, 900. ^1H -NMR (CDCl_3) δ : 0.86 (3H, s), 1.00 (3H, s), 1.30–1.70 (4H, m), 2.07–2.23 (3H, m), 3.46–3.87 (2H, m), 4.72 (1H, s) and 4.94 (1H, t, $J=1$ Hz) ($=\text{CH}_2$). MS m/z (rel. int.): 173 (M^+ , $\text{C}_{10}\text{H}_{17}\text{Cl}$, 45), 157 (11), 136 (64), 129 (100), 128 (62).

As it was already known that (*E*)-crotyl acetate reacted regio and stereoselectively with butylmagnesium bromide in the presence of copper catalyst to yield (*E*)-2-octene, (*Z*)-2-octene from (*Z*)-crotyl acetate,⁹⁾ the combination of diterpene unit **7a** with monoterpene unit **11** was accomplished by the use of this Grignard coupling. Chloride ($\pm$)-**11** (3 mmol) was reacted with magnesium (3 mmol) in THF to give the corresponding Grignard reagent, which was coupled with (*E*)-allylic acetate **7** (1 mmol) in the presence of dilithium tetrachlorocuprate¹⁰⁾ (0.01 mmol) in THF at 20°C for 12 hr. The product was chromatographed on silica gel (benzene) to yield the ambrein THP ether (**1b**) as an oily (17*RS*)-diastereomeric mixture in a 45% yield. $[\alpha]_{\text{D}}^{20} -4.0^\circ$ ($c=2.1$, benzene). MS m/z (rel. int.): 513 (M^+ , $\text{C}_{35}\text{H}_{60}\text{O}_2$, 0.9), 429 ($\text{M}^+ - \text{THP}$, 5), 411 (100), 397 (77). ^1H -NMR (CDCl_3) δ : 0.78 (3H), 0.81 (3H, s), 0.85 (6H, s), 0.91 (3H, s), 1.14 and 1.20 (each s, $\text{CH}_3\text{-C-O-THP}$ diastereomers), 1.46–1.55 (6H, m, THP), 1.59 (3H, s, $\text{CH}_3\text{C=}$), 1.25–2.20 (27H), 3.50 and 3.94 (each 1H, m, OCH_2 of THP), 4.53–4.55 and 4.70–4.75 (each 1H, $=\text{CH}_2$), 4.91 (1H, m, OCHO of THP), 5.15 (1H, t, $J=7$ Hz). Removal of the THPoxy group of **1b** with 35% acetic acid in THF at 60°C for 4 hr, which was followed by silica gel chromatography with benzene elution, gave an oily diastereomeric mixture of (17*S*)-ambrein (natural form, **1a**)¹¹⁾ and (17*R*)-ambrein (a 1:1 ratio, estimated from the foregoing synthetic method) in a

93% yield. Recrystallization of the mixture by seedling with natural **1a** (1%) gave (+)-**1a**, mp 81–82°C (from MeOH), $[\alpha]_D^{20} +14.5^\circ$ ($c=0.5$, benzene), ref.¹⁾ $[\alpha]_D +15.0^\circ$ (benzene). ¹H-NMR (CDCl₃) δ : 0.79 (6H, s), 0.84 (3H, s), 0.87 (3H, s), 0.91 (3H, s), 1.13 (3H, s), 1.61 (3H, s), 1.25–2.20 (27H), 4.52–4.55 and 4.73–4.76 (each 1H, =CH₂), 5.16 (1H, t, $J=7$ Hz). The ¹H-NMR spectrum of synthetic (+)-**1a** was identical with that of natural (+)-**1a**, this result confirming the (*E*)-configuration⁵⁾ of (+)-ambrein (**1a**). Now, the synthesis of chiral γ -cyclogeraniol (**10**) is under further study to fulfill the synthesis of (+)-**1a** as a purely diastereomeric product.

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