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Asymmetric Synthesis of (+)-*trans*-Aerangis Lactone

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Asymmetric synthesis of (+)-*trans*-aerangis lactone was achieved from commercially available 1-hexanol or 1-hexanal in four steps *via* iridium-catalyzed diastereoselective and enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level, and ruthenium-catalyzed olefin metathesis.

Key Words : Aerangis lactone, Asymmetric, Catalytic, Crotylation, Metathesis

Introduction

Lactones are important flavor and aroma constituents that are extensively used as additives in food and perfume. Many lactones exhibit interesting biological activities as attractants for pollination and seed germination stimulants.[1] They also act as allergens,[2] pheromones,[3] antiseptics,[4] and cardiotonic agents.[5] In particular, δ-lactones appear as a ubiquitous structural motif in a number of natural products that display a wide range of biological activity.[6] As representative examples of δ-lactones, *trans*-aerangis lactones (**1a** and **1b**) and *cis*-aerangis lactones (**2a** and **2b**) were first reported by Kaiser in 1993 as the main odoriferous components of the African moth orchids *Aerangis confusa* and *Aerangis kirkii*.[7] Later, (–)-*cis*-aerangis lactone (**2a**) was found to be the sole stereoisomer present in the scent of living white flowering orchids (*Aerangis confusa*). All four stereoisomers were initially synthesized as a racemic mixture of *trans*- and *cis*-isomers through hydrogenation of dihydrojasmone and subsquent Bayer-Villiger oxidation of the cyclopentanone moiety.[8]

Due to their unique structural features and interesting biological activities, a few asymmetric synthetic approaches to aerangis lactones have been reported. In 2001, Brenna reported the first enantioselective synthesis of **1a** and **2a** from enantiopure (+)-*trans*-cognac lactone derived from Baker's yeast reduction of 1,4-keto acid.[9] A general enantioselective synthetic route to the *cis*-aerangis lactones (**2a** and **2b**) using a $TiCl_4$-mediated Evans asymmetric aldol reaction was also described.[10] Yadav reported a concise stereoselective synthesis of **2a** using Sharpless asymmetric epoxidation of a primary allylic alcohol and TBSOTf-mediated intramolecular hydride transfer of a chiral epoxy alcohol as the key steps.[11] Recently, Christmann demonstrated the 1,2-epoxidation of a chiral 2-chloroalcohol, prepared from (+)-citronellal, using MacMillan's organocatalytic α-chlorination methodology[12] and its application to the synthesis of the (–)-*cis*-enantiomer **2a**.[13]

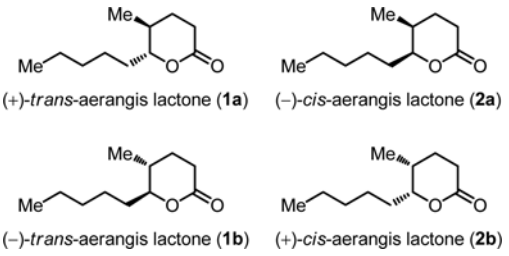


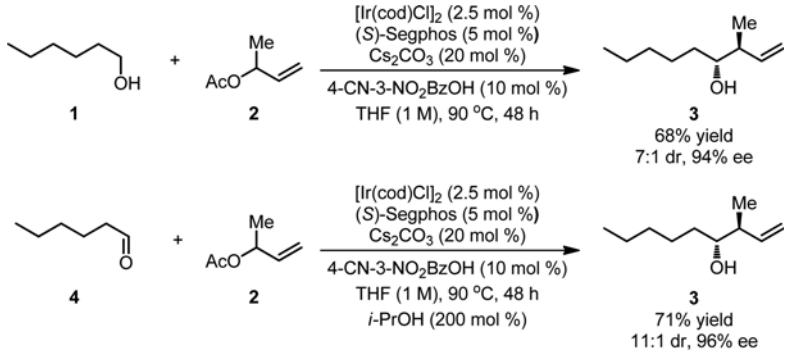
Figure 1. Structure of aerangis lactone isomers.

As part of an ongoing research program directed toward the development of transition metal-catalyzed carbon-carbon bond forming reactions,[14] we have been interested in developing efficient routes to the asymmetric synthesis of biologically active natural products. In this paper, we present a new catalytic strategy for the asymmetric total synthesis of (+)-*trans*-aerangis lactone (**1a**), including two catalytic carbon-carbon bond formations, *i.e.*, iridium-catalyzed diastereoselective and enantioselective carbonyl crotylation, and ruthenium-catalyzed intermolecular metathesis.

For the total synthesis of (+)-*trans*-aerangis lactone (**1a**), we first investigated diastereoselective and enantioselective iridium-catalyzed carbonyl crotylation from the alcohol or aldehyde oxidation level, as described by Krische and coworkers,[15] to obtain the chiral homoallylic alcohol **3** (Scheme 1). Reaction of 1-hexanol (**1**) with 3-buten-2-yl acetate (**2**) in the presence of $[Ir(cod)Cl]_2$ (2.5 mol %), (*S*)-SEGPHOS (5 mol %), Cs_2CO_3 (20 mol %) and 4-CN-3-NO_2BzOH (10 mol %) in THF (1 M) produced **3** in 68% yield with 7:1 of *anti*-diastereoselectivity and 94% of enantiomeric excess (ee). Carbonyl crotylation from the aldehyde oxidation level using isopropanol as a terminal reductant was also explored. Under identical reaction conditions, but in the presence of isopropanol (200 mol %), aldehyde **4** was converted to the crotylation product **3** in high yield (71%) with a high level of *anti*-diastereoselectivity (11:1 dr) and an exceptional level of enantioselectivity (96% ee).

Next, we focused on the preparation of α,β-unsaturated ester **7** *via* intermolecular olefin metathesis using the Grubbs (**6a** and **6b**)[16] and Hoveyda-Grubbs (**6c** and **6d**)[17] ruthenium catalysts, as shown in Figure 2.

Based on previous reports, the first- and second-generation Grubbs catalysts (**6a** and **6b**) and the first- generation Hoveyda-Grubbs catalyst (**6c**) were first evaluated for the coupling of homoallylic alcohol **3** with methyl acrylate (**5**) under a range of reaction conditions to afford the corresponding product **7**. However, these attempts were un-



Scheme 1. Diastereoselective and enantioselective Ir-catalyzed carbonyl crotylation from the alcohol or aldehyde oxidation level.

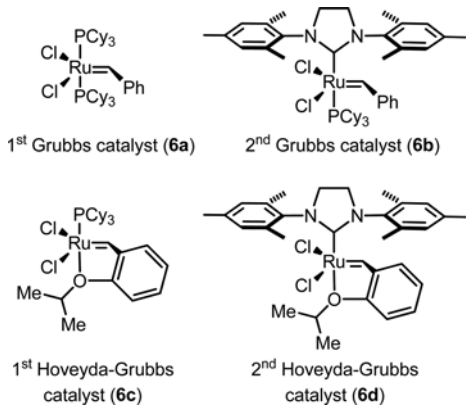


Figure 2. Structures of the Grubbs and Hoveyda-Grubbs catalysts.

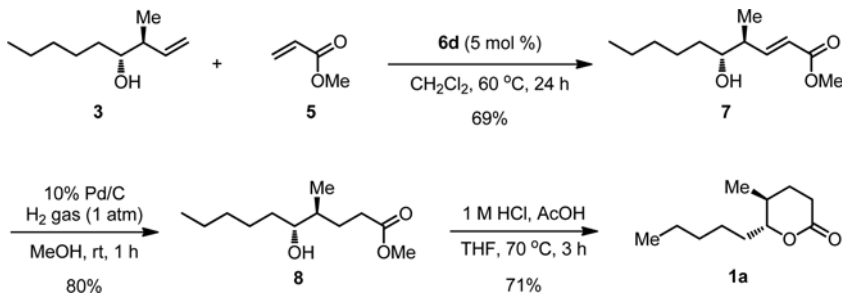
successful and led to the recovery of starting material. The best result was obtained when compound **3** was treated with the second-generation Hoveyda-Grubbs catalyst (**6d**, 1,3-bis(mesityl)-2-imidazolidinylidene ruthenium) in dichloromethane at 60 °C for 24 h, which provided the desired product **7** in 69% yield with high stereoselectivity (*trans*:*cis* 20:1). Hydrogenation of olefin **7** under palladium catalysis followed by lactonization under acidic conditions furnished (+)-*trans*-aerangis lactone (**1a**) in high yield. The spectral properties (^{1}H and ^{13}C NMR) and specific rotation of **1a** were in full agreement with reported literature values.[9]

Next, our strategy for the synthesis of (–)-*cis*-aerangis lactone (**2a**) focused on either a intermolecular Mitsunobu inversion of **7** with acrylic acid followed by intramolecular ring-closing metathesis to afford α,β-unsaturated lactone compound, or the mesylation of **8** followed by intramolecular S_N2 inversion under hydrolysis conditions to provide (–)-*cis*-aerangis lactone (**2a**). However, these attempts were unsuccessful and led to the formation of undesired byproducts.

In summary, we have described a catalytic approach to the asymmetric total synthesis of (+)-*trans*-aerangis lactone starting from readily available 1-hexanol or 1-hexanal *via* iridium-catalyzed diastereoselective and enantioselective carbonyl crotylation, and ruthenium-catalyzed intermolecular metathesis as key steps. This synthetic strategy could be applied to the synthesis of a broad range of biologically active natural products with a lactone framework.

Experiments

General Methods. Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH_2, P_2O_5 or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230-400 mesh) was used. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a Bruker Unity 300 MHz spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26) and $CDCl_3$ δ_C (77.2) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*)



Scheme 2. Total synthesis of (+)-*trans*-aerangis lactone (**1a**).

are reported in hertz (Hz). IR spectra were recorded on a Varian 2000 Infrared spectrophotometer and are reported as cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 spectrometer.

(3*S*,4*R*)-3-Methylnon-1-en-4-ol (3). To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (168 mg, 0.25 mmol, 2.5 mol %), (*S*)-SEGPHOS (305 mg, 0.5 mmol, 5 mol %), Cs_2CO_3 (650 mg, 1.99 mmol, 20 mol %) and 4-cyano-3-nitrobenzoic acid (192 mg, 0.998 mmol, 10 mol %) was added THF (5 mL) followed by acetic acid 3-buten-2-yl ester (**2**) (2.5 mL, 19.96 mmol, 200 mol %). The reaction mixture was allowed to stir at 90 °C for 0.5 h and cooled to room temperature. 1-Hexanal (**4**) (1.2 mL, 9.98 mmol, 100 mol %) in THF (5 mL) and isopropanol (1.5 mL, 19.96 mmol, 200 mol %) were added to the reaction mixture and the reaction mixture was allowed to stir at 90 °C for 48 h, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2:pentane: diethyl ether = 50:1) afforded **3** (1.11 g, 7.103 mmol, 11:1 dr) as a colorless oil in 71% yield. R_f = 0.43 (pentane:diethyl ether = 6:1); $[\alpha]_D^{28}$ +22.2 (*c* 0.3, CH_2Cl_2); IR (CH_2Cl_2) ν 3398, 3075, 2930, 1639, 1459, 1320, 1121, 1002, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.21-1.52 (m, 8H), 2.12-2.26 (m, 1H), 3.35-3.47 (m, 1H), 5.05-5.11 (m, 2H), 5.73 (ddd, *J* = 16.2, 11.1, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 16.3, 22.7, 25.4, 32.0, 34.2, 44.1, 74.7, 116.3, 140.4; HRMS (EI) Calcd for $C_{10}H_{20}O$ $[M]^+$ 156.1514, found 156.1516; HPLC (Chiralcel AD-H column, *n*-hexane:*i*-PrOH = 99:1, 0.5 mL/min, 254 nm): t_{minor} = 10.28 min, t_{major} = 12.05 min; ee = 96%.

(4*S*,5*R*,*E*)-Methyl 5-hydroxy-4-methyldec-2-enoate (7). To a stirred solution of **3** (386 mg, 2.47 mmol, 100 mol %) in anhydrous CH_2Cl_2 (12 mL, 0.2 M) was added methyl acrylate (**5**) (1.1 mL, 12.35 mmol, 500 mol %) and second generation Hoveyda-Grubbs catalyst **6d** (75 mg, 0.12 mmol, 5 mol %) under N_2 atmosphere. The reaction mixture was stirred for 24 h at 60 °C and concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2: *n*-hexane:EtOAc = 5:1) afforded **7** (365 mg, 1.704 mmol) as a colorless oil in 69% yield. R_f = 0.15 (*n*-hexane:EtOAc = 6:1); $[\alpha]_D^{28}$ –2.7 (*c* 0.3, CH_2Cl_2); IR (CH_2Cl_2) ν 3458, 2933, 2359, 1724, 1440, 1287, 1183, 999, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.15-1.49 (m, 8H), 1.68 (br s, 1H), 2.33-2.38 (m, 1H), 3.46-3.53 (m, 1H), 3.69 (s, 3H), 5.83 (d, *J* = 15.9 Hz, 1H), 6.93 (dd, *J* = 15.9, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 15.8, 22.6, 25.4, 31.8, 34.6, 42.6, 51.5, 74.8, 121.7, 150.7, 167.0; HRMS (CI) Calcd for $C_{12}H_{23}O_3$ $[M+H]^+$ 215.1647, found 215.1651.

(4*S*,5*R*)-Methyl 5-hydroxy-4-methyldecanoate (8). To a stirred solution of **7** (245 mg, 1.14 mmol, 100 mol %) in methanol (11.4 mL, 0.1 M) was added 10% Pd/C (245 mg). The reaction mixture was stirred for 1 h under H_2 balloon (1 atm) at room temperature and concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2: *n*-hexane:EtOAc = 5:1) afforded **8** (197 mg, 0.911 mmol) as a colorless oil in 80% yield. R_f = 0.19 (*n*-hexane:EtOAc = 5:1); $[\alpha]_D^{28}$ +47.5 (*c* 0.3, CH_2Cl_2); IR (CH_2Cl_2) ν 3490, 2933, 2361, 1737, 1462, 1344, 1207, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83-0.90 (m, 6H), 1.21-1.59 (m, 10H), 1.78-1.87 (m, 1H), 2.22-2.45 (m, 2H), 3.38-3.43 (m, 1H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.2, 22.7, 25.7, 27.0, 31.8, 31.9, 33.6, 38.3, 51.6, 75.6, 174.6; HRMS (CI) Calcd for $C_{12}H_{25}O_3$ $[M+H]^+$ 217.1804, found 217.1803.

(5*S*,6*R*)-5-Methyl-6-pentyltetrahydro-2*H*-pyran-2-one (1a). To a stirred solution of **8** (30.2 mg, 0.14 mmol, 100 mol %) in THF (0.47 mL, 0.3 M) was added 1 M HCl (0.47 mL) and AcOH (0.47 mL) under N_2 atmosphere. The reaction mixture was stirred for 3 h at 70 °C, and the reaction mixture was quenched with *s*-$NaHCO_3$ (1 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with H_2O (3 mL) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2: *n*-hexane:EtOAc = 3:1) afforded **1a** (18.3 mg, 0.099 mmol) as a colorless oil in 71% yield. R_f = 0.22 (*n*-hexane:EtOAc = 3:1); $[\alpha]_D^{28}$ +45.7 (*c* 0.3, CH_2Cl_2); IR (CH_2Cl_2) ν 2929, 1738, 1462, 1344, 1247, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.20-1.39 (m, 5H), 1.43-1.61 (m, 3H), 1.62-1.74 (m, 2H), 1.81-1.91 (m, 1H), 2.35-2.64 (m, 2H), 3.87-3.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 17.5, 22.6, 24.1, 27.8, 29.5, 31.7, 32.2, 33.4, 85.9, 172.0; HRMS (CI) Calcd for $C_{11}H_{21}O_2$ $[M+H]^+$ 185.1542, found 185.1542.

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