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Asymmetric hydrogen transfer protocol for a synthesis of (+)-frontalin and (−)-malyngolide

Regina Mikie Kanada, Takahiko Taniguchi and Kunio Ogasawara *

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

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Abstract

An insect aggregate pheromone (+)-frontalin and a marine antibiotic (−)-malyngolide, both bearing a quaternary stereogenic center in their molecules, have been synthesized in diastereocontrolled manner by employing a catalytic asymmetric hydrogen transfer reaction as the key step. An inversion protocol allowing enantioconvergent use of the other enantiomeric resolved product has also been devised.

Keywords: asymmetric reaction; epoxides; natural products; radicals and radical compounds; ruthenium and compounds.

We recently found that the racemic tricyclic allyl alcohol (±)-**3b** and its oxygenated derivatives (R=CH_2OH, CH_2OTBS, CH_2OPiv) are well discriminated[1,2] in asymmetric hydrogen transfer reaction[3] in the presence of a ruthenium(II)–chiral amine complex[4] [Ru^{II}-(*S,S*)-or (*R,R*)-TsDPEN] to give the chiral enones, leaving the chiral alcohols both in acceptable enantiomeric purity, though the unsubstituted (±)-**3a** is not well discriminated.[2] On the contrary, the unsubstituted (±)-**3a** is well discriminated under the lipase-mediated asymmetric transesterification conditions[5] to give the enantiopure acetate, leaving the enantiopure alcohol **3a**, though the substituted (±)-**3b** does not react under the same conditions[6] (Scheme 1). We also found that the chiral enones **4a** and **b** may be inverted into the corresponding enantiomers in a three-step sequence of reactions involving the Wharton rearrangement[1,7] in an acceptable overall yield. On the basis of these findings, we planned enantio- and diastereocontrolled construction of two natural products bearing a quaternary stereogenic center in their molecules by utilizing an appropriate α-substituted chiral enone **4** obtained through the resolution by the catalytic asymmetric hydrogen transfer reaction. In this paper we wish to report a diastereocontrolled route to an insect aggregate pheromone (+)-frontalin[8] **12** isolated from the *Dendroctonus* pine beetle and a marine antibiotic (−)-malyngolide[9] **20** and a new molecular inversion method which enables the enantioconvergent synthesis of the latter.

To obtain (+)-frontalin **12**, the enone (+)-**4b**, $[\alpha]_D^{27}$ +83.8 (*c* 1.65, $CHCl_3$) (>99% ee), obtained from the tricyclic 1,2-enediol bis-trimethylsilyl ether[10] **1** via **2b** by employing a sequence of ring-expansion reaction,[1,11] reductive elimination, and the asymmetric hydrogen transfer reaction,[1–4] was treated with

* Corresponding author. Fax: +81-22-217-6845; e-mail: konol@mail.cc.tohoku.ac.jp (K. Ogasawara)

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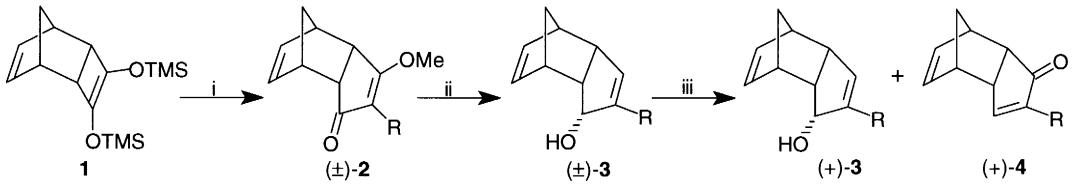
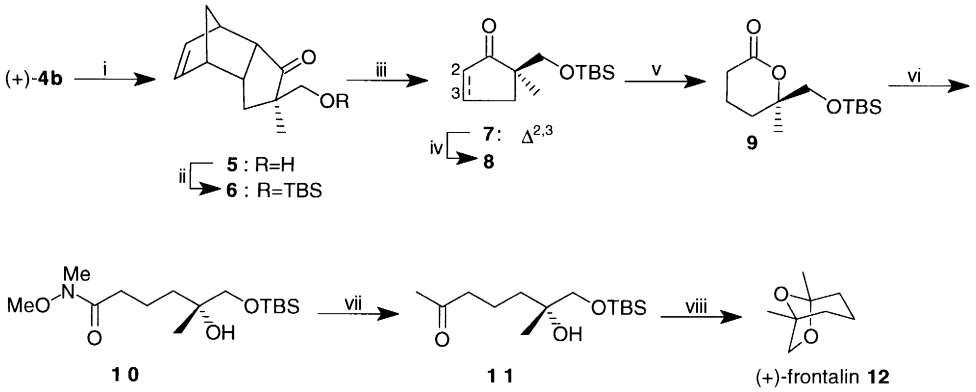


a series: R=H; **b** series: R=Me; **c** series: R=C_9H_{19}

Scheme 1. Reagents and conditions: (i) for **1b**: (a) MeCH $(OMe)_2$, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78°C, then TFA reflux. (b) Me_2SO_4, NaH, DMF–THF (1:1) (56%). For **1c**: (a) $Me(CH_2)_8CH(OMe)_2$, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78°C, then TFA rt. (b) (i) CH_2N_2, Et_2O, 0°C (47%). (ii) LAH, Et_2O, reflux (for **3b**: 65%, for **3c**: 61%). (iii) For **3b**: [Ru^{II} (η^6-mesitylene)](1*S*,2*S*)-TsDPEN (1 mol%), acetone, rt [(+)-**3b** (47%:59% ee) and (+)-**4b** (30%:>99% ee)]; for **3c**: [Ru^{II} (η^6-*p*-cymene)](1*S*,2*S*)-TsDPEN (2 mol%), acetone, rt [(+)-**3c** (44%:>99% ee) and (+)-**4c** (52%:85% ee)]

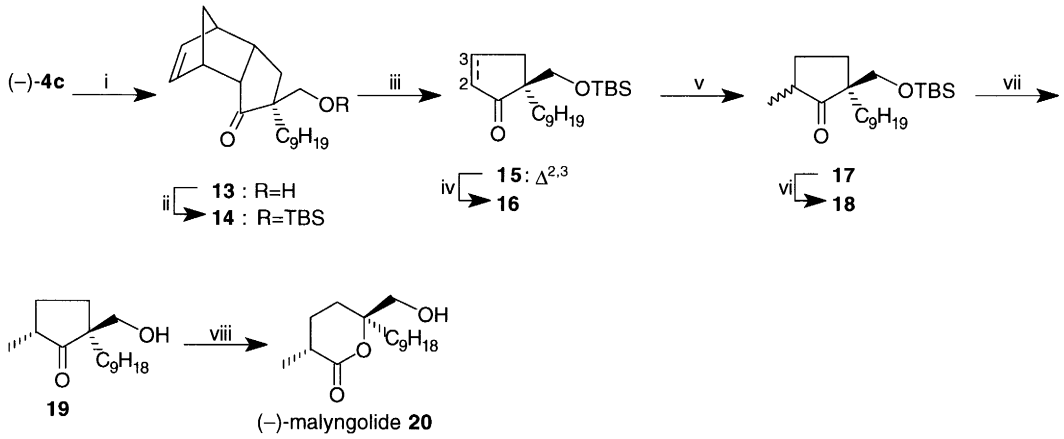
diisobutylaluminum hydride (DIBAL) and copper(I) iodide, followed by gaseous formaldehyde in the same flask[12] to construct the quaternary stereogenic center adjacent to the ketone functionality, giving rise to the single hydroxyketone **5** $[\alpha]_D^{28}$ +205.9 (*c* 1.15, $CHCl_3$), diastereoselectively. After *O*-silylation, the resulting TBS ether **6**, $[\alpha]_D^{29}$ +144.7 (*c* 0.90, $CHCl_3$), was heated in diphenyl ether[13] at 280°C to give the cyclopentenone **7** $[\alpha]_D^{28}$ +53.1 (*c* 0.59, $CHCl_3$), by retro-Diels–Alder reaction, which gave the cyclopentanone **8** $[\alpha]_D^{28}$ +53.8 (*c* 0.64, $CHCl_3$), on catalytic hydrogenation. Baeyer–Villiger reaction of **8** with *m*-chloroperbenzoic acid proceeded regioselectively to give the δ-lactone **9** $[\alpha]_D^{29}$ +10.7 (*c* 0.67, $CHCl_3$), as the single product. Treatment of **9** with *N*-methylhydroxylamine methyl ether hydrochloride in the presence of trimethylaluminum[14] afforded the methyl hydroxamate **10** $[\alpha]_D^{31}$ +2.6 (*c* 0.66, $CHCl_3$), which gave the methyl ketone **11** $[\alpha]_D^{29}$ +1.5 (*c* 0.94, $CHCl_3$), on reaction with methyllithium. On exposure to methanolic hydrochloric acid, **11** furnished (+)-frontalin **12** $[\alpha]_D^{27}$ +53.4 (*c* 0.37, Et_2O) [lit.[8a]: $[\alpha]_D^{22}$ +53.8 (*c* 0.8, Et_2O)], by concurrent desilylation and intramolecular ketalization (Scheme 2).



Scheme 2. Reagents and conditions: (i) DIBAL, CuI, THF–HMPA (4:1), −50°C, 1 h then HCHO (gas) (74%). (ii) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt (100%). (iii) PhOPh, 280°C, 30 min (97%). (iv) H_2,10% Pd–C, AcOEt, overnight, rt (96%). (v) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 3 days (75%). (vi) MeONHMe·HCl, Me_3Al, 0°C, 3 h (77%). (vii) MeLi, CH_2Cl_2, −78°C, 1 h (90%). (viii) concd HCl (cat.), pentane (80%)

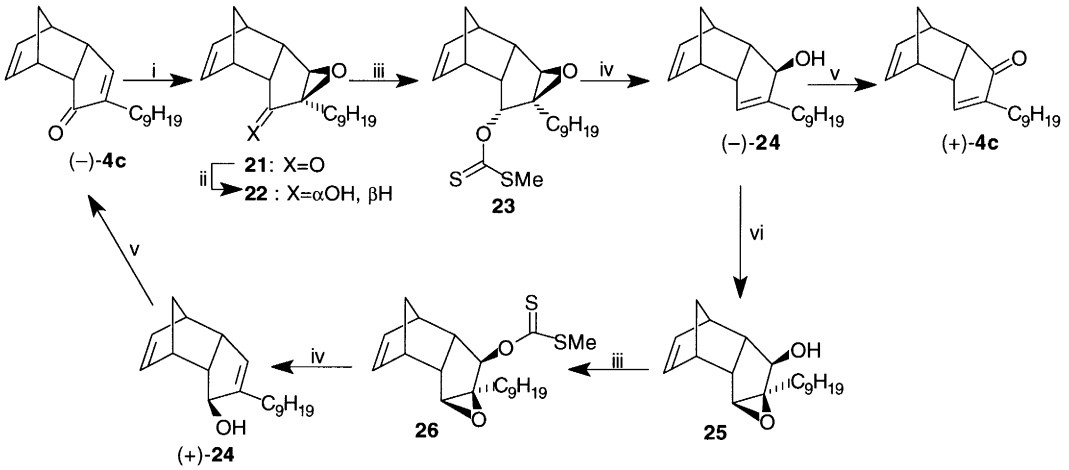
On the other hand, to obtain (−)-malyngolide **20**, the asymmetric hydrogen transfer reaction of (±)-**3c** having an α-C_9H_{19} substituent was first examined chain as only the substrates having a one-carbon 2-substituent were so far examined and as (±)-**3c** was found to be completely inert under lipase-mediated resolution conditions. Thus, (±)-**3c** was stirred with (1*S*,2*S*)-TsDPEN (2 mol%) in acetone (1 M) at room temperature to give the enantioenriched enone (+)-**4c** $[\alpha]_D^{27}$ +17.0 (*c* 0.45, $CHCl_3$) (85% ee),

in 52% yield, leaving the enantiopure alcohol (+)-**3c** $[\alpha]_D^{30}$ +114.9 (*c* 0.58, $CHCl_3$) (>99% ee), in 44% recovery yield. Although the absolute configuration could not be determined at this stage, the alcohol (+)-**3c**, supposed to have the same configuration as (+)-**3a** and **b**, was oxidized with manganese(IV) oxide to give the enone (−)-**4c** $[\alpha]_D^{29}$ −17.1 (*c* 1.30, $CHCl_3$) (>99% ee), in 89% yield. The enone (−)-**4c**, thus obtained, was transformed into the hydroxyketone **13** $[\alpha]_D^{27}$ −125.1 (*c* 0.96, $CHCl_3$), on the same reductive aldolization as above, which was then transformed into the silyl ether **14** $[\alpha]_D^{27}$ −103.6 (*c* 1.03, $CHCl_3$). Thermolysis of **14** afforded cyclopentenone **15** $[\alpha]_D^{27}$ −17.9 (*c* 1.07, $CHCl_3$), which was hydrogenated to give the cyclopentanone **16**, −10.1 (*c* 0.98, $CHCl_3$). Methylation of **16** under kinetic conditions gave the monomethylated ketone **17** as a diastereomeric mixture, which was desilylated to give the hydroxyketone **18** as a mixture of epimers. The mixture, on treatment with LDA followed by exposure to diluted acetic acid, afforded the single hydroxyketone **19** $[\alpha]_D^{29}$ −19.3 (*c* 1.13, $CHCl_3$), by kinetic protonation.[15] Finally, **19** was subjected to the Baeyer–Villiger oxidation to give natural (−)-malyngolide **20** $[\alpha]_D^{31}$ −13.7 (*c* 0.69, $CHCl_3$) [lit.[9a]: $[\alpha]_D^{28}$ −13.4 (*c* 0.3, $CHCl_3$)], regioselectively. This confirmed the stereochemistry of the products (+)-**4c** and (−)-**3c** obtained by the catalytic asymmetric hydrogenation transfer reaction (Scheme 3).



Scheme 3. Reagents and conditions: (i) DIBAL, CuI, THF–HMPA (4:1), −50°C then HCHO (gas) (98%). (ii) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt (83%). (iii) PhOPh, 280°C, 40 min (94%). (iv) H_2, 10% Pd–C, AcOEt, overnight, rt (100%). (v) LDA, HMPA, −78°C, 1 h, then MeI, −30°C, 1 h (91%). (vi) LDA, −78°C 1 h (76%). (vii) concd HCl, THF, rt, 2 h (100%). (viii) *m*-CPBA, $NaHCO_3$, rt, 4.5 days (52%)

In order to allow enantioconvergent utilization of the other enantiomer, we first examined the Wharton rearrangement on the epoxide **21** $[\alpha]_D^{27}$ −105.9 (*c* 0.61, $CHCl_3$), obtained from the enantiopure enone (−)-**4c**, to obtain the *exo*-allylic alcohol (−)-**24** by following the procedure established for the inversion of the enones, **4a**[16] and **b**.[1] However, the reaction of **21** did not proceed in the desired way and gave instead a complex mixture containing a trace of the allyl alcohol **24** under the same conditions. We, therefore, converted the epoxide **21** first into the xanthate **23** $[\alpha]_D^{25}$ −99.4 (*c* 0.49, $CHCl_3$), via the *endo*-alcohol **22** $[\alpha]_D^{28}$ −1.48 (*c* 0.74, $CHCl_3$). On reaction with triethylsilane[17] in the presence of AIBN, **23** yielded the desired *exo*-alcohol **24** $[\alpha]_D^{29}$ −15.8 (*c* 0.30, $CHCl_3$), which afforded the enantiomeric enone (+)-**4c**, $[\alpha]_D^{25}$ +17.0 (*c* 0.21, $CHCl_3$), on oxidation. Overall yield of (+)-**4c** from (−)-**4c** was 45% in five steps. The xanthate-mediated reaction was found to proceed with the *exo*-alcohol (−)-**24**. Thus, the *exo*-xanthate **26**, obtained from (−)-**24** via the epoxide **25**, $[\alpha]_D^{28}$ +18.6 (*c* 0.15, $CHCl_3$), furnished, under the same conditions, the inverted alcohol (+)-**24** which was further transformed into the enone (−)-**4** on oxidation (Scheme 4).



Scheme 4. Reagents and conditions: (i) 30% H_2O_2, 0.5N NaOH, MeOH, 0°C to ~rt; 1 h (95%). (ii) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0°C, 15 min (90%). (iii) NaH, CS_2, MeI, THF (for **23**: 100%, for **26**: 79%). (iv) AIBN (0.6 equiv.), Et_3SiH, 85–90°C, 1.5 h, evaporation, TBAF, THF, rt, 1 h (for (−)-**24**: 72%, for (+)-**24**: 65%). (v) cat. TPAP, NMO, 4 Å sieves, CH_2Cl_2 (74%). (vi) $VO(acac)_2$, *t*-BuOOH, 2,6-lutidine, toluene–benzene (3:2), rt (66%)

In summary, we have devised an enantioconvergent utilization of both enantiomeric α-substituted enones, resolved through asymmetric hydrogen transfer reaction, for an alternative synthesis of two natural products bearing a quaternary stereogenic center, an insect pheromone (+)-frontalin and a marine antibiotic (−)-malyngolide. A cyclopentenone inversion method involving radical reaction of a xanthate intermediate has also been established during the present study.

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