



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

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Abstract

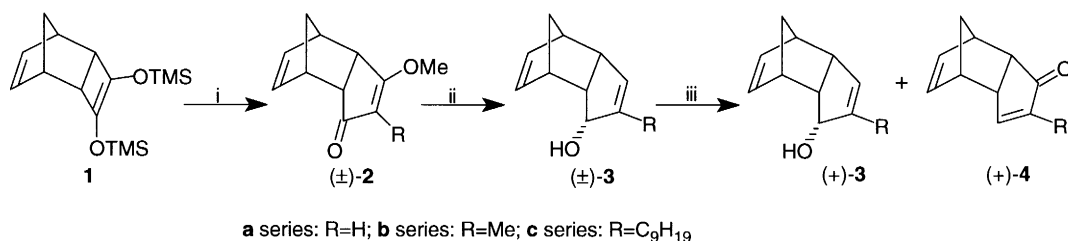
An insect aggregate pheromone (+)-frontalin and a marine antibiotic (–)-malyngolide, both bearing a quaternary stereogenic center in their molecules, have been synthesized in diastereocontrolled manner by employing a catalytic asymmetric hydrogen transfer reaction as the key step. An inversion protocol allowing enantioconvergent use of the other enantiomeric resolved product has also been devised. © 2000 Elsevier Science Ltd. All rights reserved.

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We recently found that the racemic tricyclic allyl alcohol ($\pm$)-**3b** and its oxygenated derivatives ($R=CH_2OH$, CH_2OTBS , CH_2OPiv) are well discriminated^{1,2} in asymmetric hydrogen transfer reaction³ in the presence of a ruthenium(II)–chiral amine complex⁴ $[Ru^{II}-(S,S)\text{-or } (R,R)\text{-TsDPEN}]$ to give the chiral enones, leaving the chiral alcohols both in acceptable enantiomeric purity, though the unsubstituted ($\pm$)-**3a** is not well discriminated.² On the contrary, the unsubstituted ($\pm$)-**3a** is well discriminated under the lipase-mediated asymmetric transesterification conditions⁵ to give the enantiopure acetate, leaving the enantiopure alcohol **3a**, though the substituted ($\pm$)-**3b** does not react under the same conditions⁶ (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 (+)-frontalin⁸ **12** isolated from the *Dendroctonus* pine beetle and a marine antibiotic (–)-malyngolide⁹ **20** and a new molecular inversion method which enables the enantioconvergent synthesis of the latter.

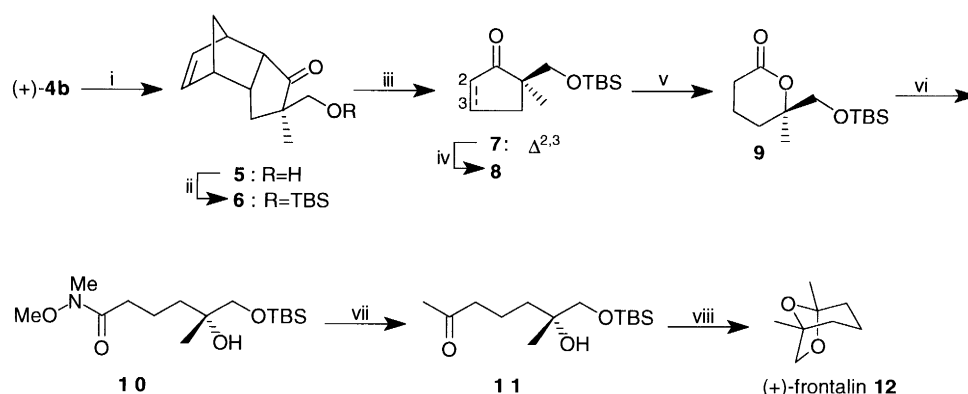
To obtain (+)-frontalin **12**, the enone (+)-**4b**, $[\alpha]_D^{27} +83.8$ (c 1.65, $CHCl_3$) (>99% ee), obtained from the tricyclic 1,2-enediol bis-trimethylsilyl ether¹⁰ **1** via **2b** by employing a sequence of ring-expansion reaction,^{1,11} reductive elimination, and the asymmetric hydrogen transfer reaction,^{1–4} was treated with

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Scheme 1. Reagents and conditions: (i) for **1b**: (a) MeCH(OMe)₂, BF₃·OEt₂, CH₂Cl₂, −78°C, then TFA reflux. (b) Me₂SO₄, NaH, DMF–THF (1:1) (56%). For **1c**: (a) Me(CH₂)₈CH(OMe)₂, BF₃·OEt₂, CH₂Cl₂, −78°C, then TFA rt. (b) (i) CH₂N₂, Et₂O, 0°C (47%). (ii) LAH, Et₂O, reflux (for **3b**: 65%, for **3c**: 61%). (iii) For **3b**: [Ru^{II}(η⁶-mesitylene)](1*S*,2*S*)-TsDPEN (1 mol%), acetone, rt [(+)-**3b** (47%:59% ee) and (+)-**4b** (30%:>99% ee)]; for **3c**: [Ru^{II}(η⁶-*p*-cymene)](1*S*,2*S*)-TsDPEN (2 mol%), acetone, rt [(+)-**3c** (44%:>99% ee) and (+)-**4c** (52%:85% ee)]

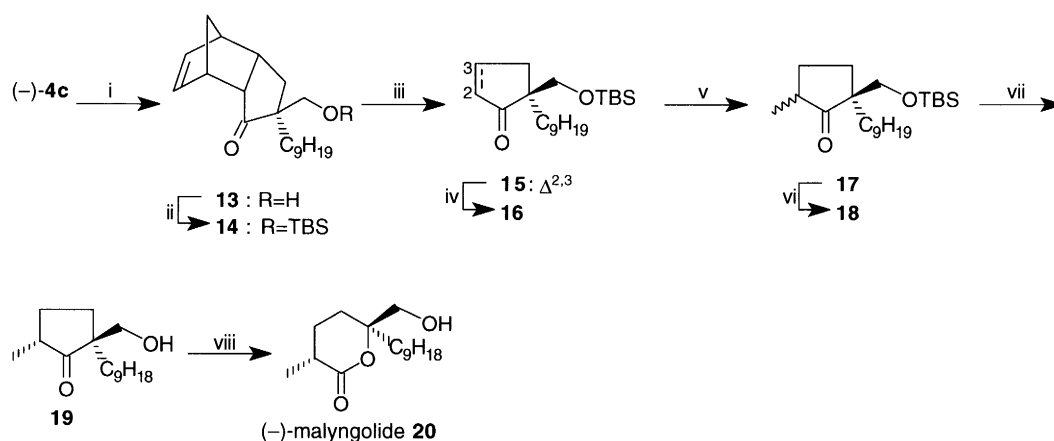
diisobutylaluminum hydride (DIBAL) and copper(I) iodide, followed by gaseous formaldehyde in the same flask¹² to construct the quaternary stereogenic center adjacent to the ketone functionality, giving rise to the single hydroxyketone **5** [α]_D²⁸ +205.9 (*c* 1.15, CHCl₃), diastereoselectively. After *O*-silylation, the resulting TBS ether **6**, [α]_D²⁹ +144.7 (*c* 0.90, CHCl₃), was heated in diphenyl ether¹³ at 280°C to give the cyclopentenone **7** [α]_D²⁸ +53.1 (*c* 0.59, CHCl₃), by retro-Diels–Alder reaction, which gave the cyclopentanone **8** [α]_D²⁸ +53.8 (*c* 0.64, CHCl₃), on catalytic hydrogenation. Baeyer–Villiger reaction of **8** with *m*-chloroperbenzoic acid proceeded regioselectively to give the δ -lactone **9** [α]_D²⁹ +10.7 (*c* 0.67, CHCl₃), as the single product. Treatment of **9** with *N*-methylhydroxylamine methyl ether hydrochloride in the presence of trimethylaluminum¹⁴ afforded the methyl hydroxamate **10** [α]_D³¹ +2.6 (*c* 0.66, CHCl₃), which gave the methyl ketone **11** [α]_D²⁹ +1.5 (*c* 0.94, CHCl₃), on reaction with methyllithium. On exposure to methanolic hydrochloric acid, **11** furnished (+)-frontalin **12** [α]_D²⁷ +53.4 (*c* 0.37, Et₂O) [lit.^{8a}: [α]_D²² +53.8 (*c* 0.8, Et₂O)], 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, Et₃N, DMAP, CH₂Cl₂, rt (100%). (iii) PhOPh, 280°C, 30 min (97%). (iv) H₂, 10% Pd–C, AcOEt, overnight, rt (96%). (v) *m*-CPBA, NaHCO₃, CH₂Cl₂, rt, 3 days (75%). (vi) MeONHMe·HCl, Me₃Al, 0°C, 3 h (77%). (vii) MeLi, CH₂Cl₂, −78°C, 1 h (90%). (viii) concd HCl (cat.), pentane (80%)

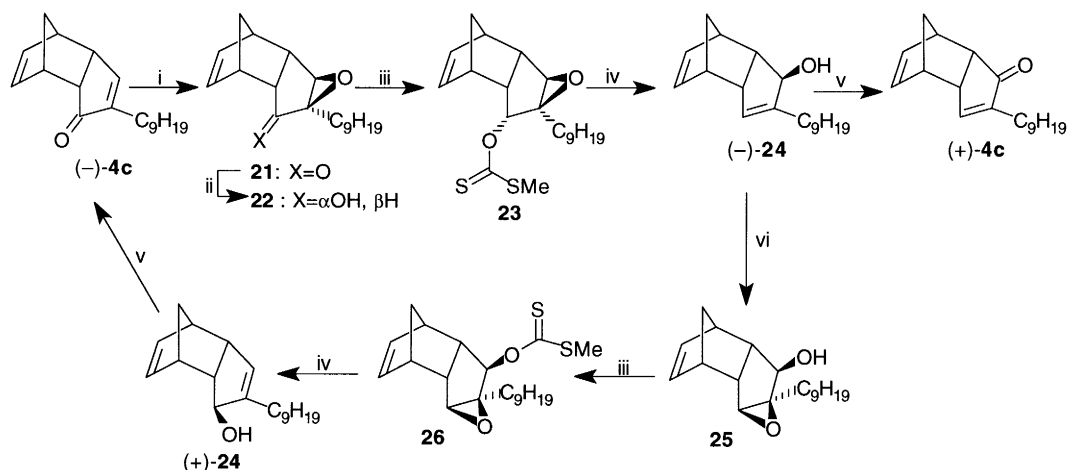
On the other hand, to obtain (−)-malyngolide **20**, the asymmetric hydrogen transfer reaction of (±)-**3c** having an α-C₉H₁₉ substituent was first examined chain as only the substrates having a one-carbon 2-substituent were so far examined and as (±)-**3c** was found to be completely inert under lipase-mediated 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** [α]_D²⁷ +17.0 (*c* 0.45, CHCl₃) (85% ee),

in 52% yield, leaving the enantiopure alcohol (+)-**3c** [α]_D³⁰ +114.9 (*c* 0.58, CHCl₃) (>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** [α]_D²⁹ –17.1 (*c* 1.30, CHCl₃) (>99% ee), in 89% yield. The enone (–)-**4c**, thus obtained, was transformed into the hydroxyketone **13** [α]_D²⁷ –125.1 (*c* 0.96, CHCl₃), on the same reductive aldolization as above, which was then transformed into the silyl ether **14** [α]_D²⁷ –103.6 (*c* 1.03, CHCl₃). Thermolysis of **14** afforded cyclopentenone **15** [α]_D²⁷ –17.9 (*c* 1.07, CHCl₃), which was hydrogenated to give the cyclopentanone **16**, –10.1 (*c* 0.98, CHCl₃). 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** [α]_D²⁹ –19.3 (*c* 1.13, CHCl₃), by kinetic protonation.¹⁵ Finally, **19** was subjected to the Baeyer–Villiger oxidation to give natural (–)-malyngolide **20** [α]_D³¹ –13.7 (*c* 0.69, CHCl₃) [lit.^{9a}: [α]_D²⁸ –13.4 (*c* 0.3, CHCl₃)], 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, Et₃N, DMAP, CH₂Cl₂, rt (83%). (iii) PhOPh, 280°C, 40 min (94%). (iv) H₂, 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, NaHCO₃, 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** [α]_D²⁷ –105.9 (*c* 0.61, CHCl₃), 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** [α]_D²⁵ –99.4 (*c* 0.49, CHCl₃), via the *endo*-alcohol **22** [α]_D²⁸ –1.48 (*c* 0.74, CHCl₃). On reaction with triethylsilane¹⁷ in the presence of AIBN, **23** yielded the desired *exo*-alcohol **24** [α]_D²⁹ –15.8 (*c* 0.30, CHCl₃), which afforded the enantiomeric enone (+)-**4c**, [α]_D²⁵ +17.0 (*c* 0.21, CHCl₃), 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**, [α]_D²⁸ +18.6 (*c* 0.15, CHCl₃), 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 $\sim\text{rt}$; 1 h (95%). (ii) $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, 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 , $85\text{--}90^\circ\text{C}$, 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) $\text{VO}(\text{acac})_2$, *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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