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The SAMP-/RAMP-hydrazone methodology in asymmetric synthesis of 4S-ferrugineone and 4S,5S-ferrugineol: The pheromones of palm weevils

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Abstract

4S-ferrugineone and 4S,5S-ferrugineol as pheromones of palm weevils were synthesized in 3 and 4 steps, respectively, starting from nonane-5-one employing SAMP-/RAMP -hydrazone methodology. 5-Nonanone is transformed to its corresponding RAMP hydrazone by reaction with the enantiomerically pure hydrazine RAMP. Metalation with lithium diisopropylamide (LDA) in ether to form azaenolate, followed by methylation with methyl iodide, furnishes the product hydrazone. Finally, cleavage of the hydrazone moiety to regenerate the carbonyl functionality is possible by ozonolysis, leads to the 4S-ferrugineone. The crucial step would be the final diastereoselective reduction to the 4S, 5S-ferrugineol.

Keywords: Pheromone, 4S-ferrugineone, 4S,5S-ferrugineol, SAMP/RAMP hydrazone

Introduction

Asian palm weevils are major and important agricultural pest of worldwide distribution that damage a broad range of economically important plants, such as coconut and palm trees. There is a big problem with ferrugineus and vulneratus in Arabic and Mediterranean countries, which causes a lot of damages among the palm crops [1]. They produce (4S)-

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4-methyl-5-nonanone **1** and (4S,5S)-4-methyl-5-nonanol **2**. The trivial names of these pheromones are 4S-ferrugineone and 4S,5S-ferrugineol, respectively (Figure 1) [2].

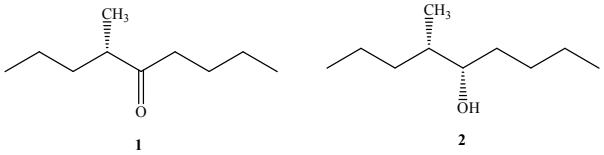
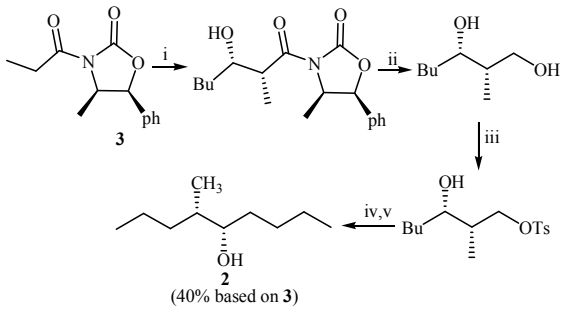


Figure 1. Structures of 4S-ferrugineone 1 and 4S, 5S-ferrugineol 2

Limited progress has been made for the preparation of title non-racemic pheromones. *Gil* carried out synthesis of 4S,5S-ferrugineol **2** starting from a chiral amide **3** as the source of chirality which allows an effective control of the relative and absolute stereochemistry of the aldol reaction (Scheme 1) [3].

The epoxide **4** has also been used for the preparation of 4S, 5S-ferrugineol (Scheme 2) [4]. Jones' oxidation of (4S,5R)-4-methyl-5-nonanol in a two-phase system (Et_2O:H_2O) gave corresponding ketone, 4S-ferrugineone **1**

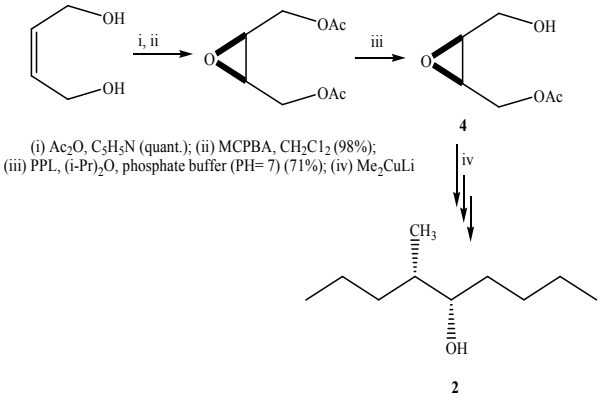


(40% based on **3**)

(i) nBu_2BOTf/DIPEA, -78°C, C_4H_9CHO (81%); (ii) $LiBH_4$, Et_2O, 0°C (87%); (iii) TsCl/Py, rt, 14 h (86%); (iv) DHP, rt, 4 h; (v) Et_2CuLi, then PPTS/MeOH

Scheme 1.

with an acceptable yield. The (4S,5R)-4-methyl-5-nonanol was also inverted through Mitsunobu reaction to 4S,5S-ferrugineol **2** [2].



(i) Ac_2O, C_5H_5N (quant.); (ii) MCPBA, CH_2C1_2 (98%); (iii) PPL, $(i\text{-}Pr)_2O$, phosphate buffer (PH= 7) (71%); (iv) Me_2CuLi

Scheme 2.

Because of very limited amount of the natural pheromones, their enantioselective or diastereoselective synthesis is required in order to study their stereochemistry-bioactivity relationships and industrial importance. Effective carbon-carbon or carbon-heteroatom bonds formations α to a carbonyl group in a region-, diastereo- and enantioselective manner is one of the most important procedures in organic synthesis. While the classical carbonyl enolate chemistry is usually accompanied by the problem of control of regiochemistry, side reactions of products, and lack of reactivity, the metalated hydrazones derivatives as reactive enolate equivalents give better yields and selectivities [6-11]. The combination of the useful hydrazone technique with a cyclic amino acid derivatives resulted in the now widely

used auxiliary [12], (S)- or (R)-1-amino-2-methoxymethylpyrrolidine (SAMP or RAMP), introduced in 1976 by our group (Figure 2) [13,14].

We now wish to describe an efficient asymmetric synthesis of 4S-ferrugineone and 4S,5S-ferrugineol in 3 and 4 steps respectively, with reaction of nonane-5-one and methyl iodide employing SAMP/RAMP hydrazone methodology. According to the general Scheme 3, 5-nonanone **5** is transformed to its corresponding RAMP hydrazone (R)-**6** by reaction with the enantiomerically pure hydrazine RAMP.

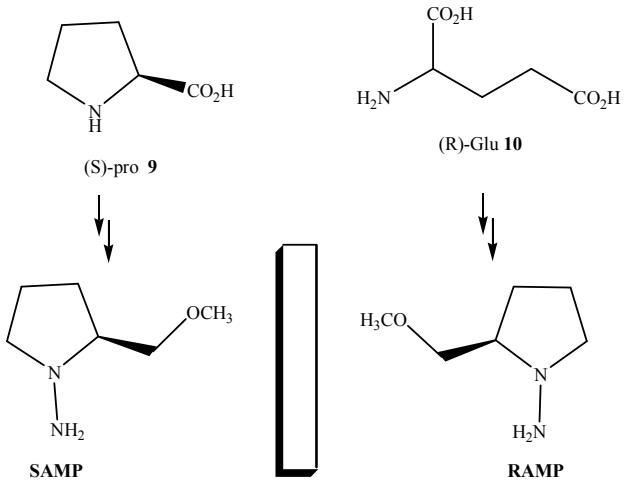


Figure 2. Structures of RAMP and SAMP.

Metalation with lithium diisopropylamide (LDA) in ether to form azaenolate (R)-**7**, followed by methylation with methyl iodide, furnishes the product hydrazone **8**. Finally, cleavage of the hydrazone moiety in order to regenerate the carbonyl functionality is possibly done by ozonolysis, and leads to the 4S-ferrugineone **1**. The crucial step would be the final diastereoselective reduction to the 4S,5S-ferrugineol **2**.

Experimental

Generel

All the chemicals required for the synthesis of 4S-ferrugineone and 4S,5S-ferrugineol were purchased from Sigma-Aldrich (St. Louis, MO, USA), Fluka (Neu-Ulm, Germany) and Merck (Darmstadt, Germany) companies and were used as received. A Bruker (DRX-400 Avance) NMR instrument was used to record the ^{1}H NMR and ^{13}C NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature; chemical shifts have been expressed in ppm. Silica gel and diethyl ether and ethyl acetate are used for column chromatography.

Synthesis of hydrazone (R)-6: A mixture of 2.6 g (20 mmol) (R)-1-amino-2-methoxymethylpyrrolidine (RAMP), and 3.62 mL (21 mmol) nonane-5-one **5** is stirred for 20 hr at 60 °C in a round bottom flask topped by a reflux condenser. After the reaction is com-

plete (determined by TLC), 5 mL CH_2Cl_2-H_2O (6:1) is added to the mixture. The organic layer is separated, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by distillation yielded 3.90 g pure hydrazone **(R)-6** as light yellow oil (73%). The hydrazone is stored in a refrigerator; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 0.80-1.08 (m, 6H, CH_3), 1.35-1.51 (m, 8H), 1.65 (m, 1H) 1.8 (m, 2H), 2.0 (m, 1H), 2.1-2.55 (m, 5H), 3.02-3-20 (m, 3H), 3.32 (s, 3H, OCH_3), 3.37 (dd, J_1 = 3.9 Hz, J_2 = 9.2 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 14.0 (CH_3), 21.9 (CH_2), 21.9 (CH_2), 23.0 (CH_2), 26.7 (CH_2), 28.5 (CH_2), 29.5 (CH_2), 30.2 (CH_2), 35.8 (CH_2), 54.9 (CH_2), 59.0 (CH_3), 65.9 (CH), 75.5 (CH_2), 171.6 (C=N).

Synthesis of hydrazone 8: To a 5.3 mL (8.5 mmol, 1.6 M in hexane) n-BuLi and 40 mL anhydrous ether in a round bottom flask is added dropwise via syringe 1.2 mL (8.5 mmol) diisopropylamine under Argon at 0 °C, and stirred for 15 min to generate a solution of LDA. After dropwise addition of 2.03 g (8 mmol) hydrazone **(R)-6**, the mixture is stirred at 0 °C for 4 hr to preparation of azaenolate **(R)-7**, cooled to -110 °C, and 0.55 mL (8.5 mmol) methyl iodide (dissolved in 3 mL ether) is added. The mixture is stirred at this temperature for 3 hr, is allowed to warm up to room temperature within 12 hr, after which the reaction is quenched with ether/H_2O (2:1) and the inorganic salts are thoroughly washed out with water. The organic layer is separated, dried over Na_2SO_4. Concentrating *in vacuo* afforded oily hydrazone **8**, which is used at ozonolysis step without further purification; ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.85-0.90 (m, 9H, CH_3), 1.20-1.40 (m, 6H), 1.50-2.20 (m, 8H), 2.48 (m, 1H), 2.90-3.38 (m, 2H), 3.20 (m, 1H), 3.30-3-33 (m, 4H), 3.32 (m, 1H), ^{13}CNMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 14.3 (CH_3), 17.7 (CH_3), 21.2 (CH_2), 21.7 (CH_2), 23.0 (CH_2), 26.4 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 34.6 (CH), 36.3 (CH_2), 55.3 (CH_2), 59.1 (CH_3), 65.8 (CH), 75.2 (CH_2), 177.4 (C=N).

Cleavage the hydrazone 8 to form 4S-ferrugineone 1: The oily crude hydrazone **8** is dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. A gentle stream of O_3 is flushed through the solution. The color of the solution turns green to blue (indicating excess O_3), when the reaction has run to completion (~ 30 min). Argon is then flushed through the solution as it warms up to room temperature. The solution concentrated *in vacuo*, and the 4S-ferrugineone **1** is separated by column chromatography as light yellow liquid (Silica gel, Et_2O); Yield: 1.22 g (57%, two steps); ee 96%

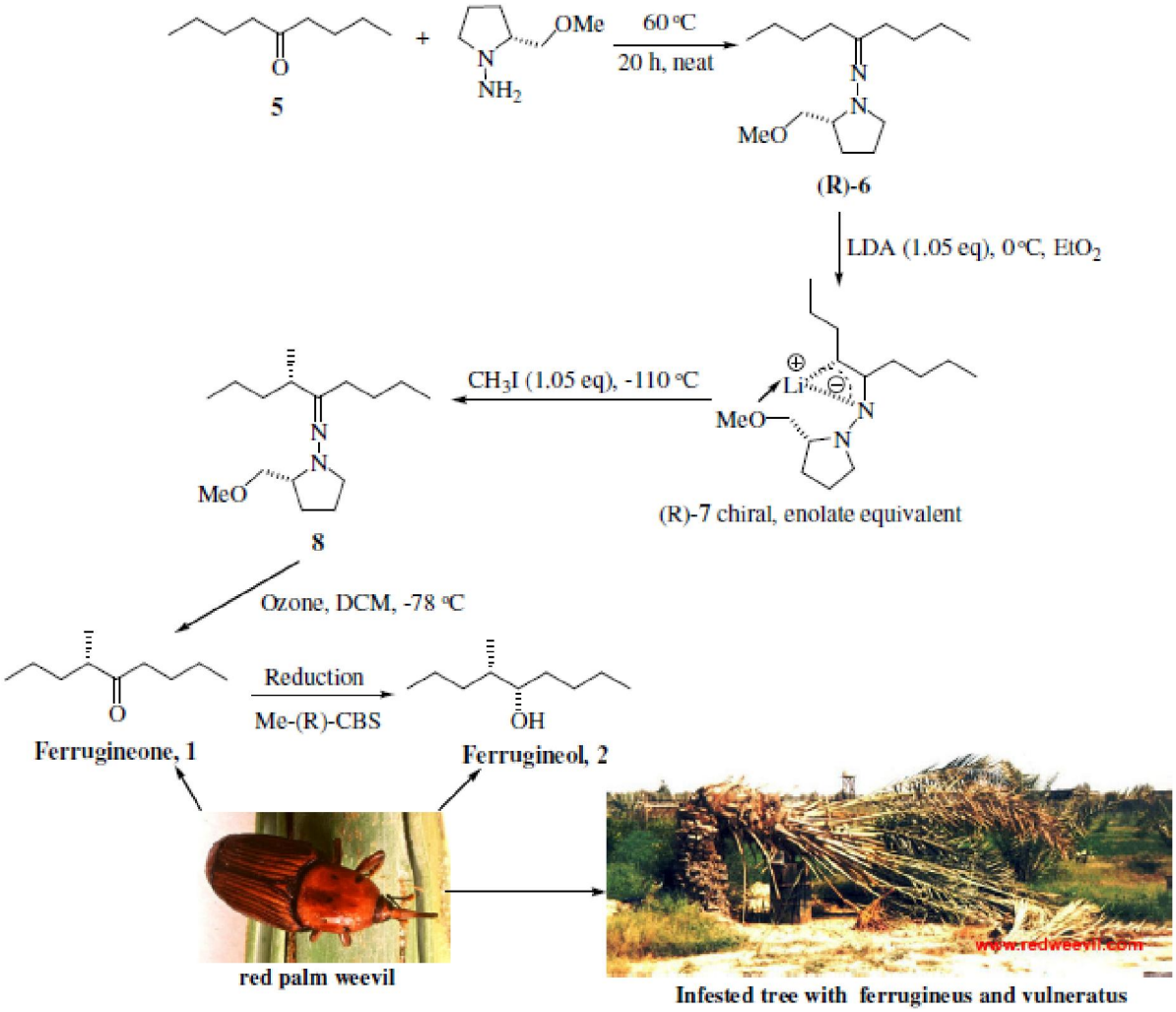
(GC); ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 6H, CH_3), 1.05 (d, *J* = 6.9 Hz, 3H), 1.35 (m, 5H), 1.06 (m, 3H), 2.42 (t, *J* = 7.5 Hz, 2H, $C(O)CH_2$), 2.53 (m, 1H, $CH(CH_3)$), ^{13}CNMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 14.1 (CH_3), 16.3 (CH_3), 20.5 (CH_2), 22.4 (CH_2), 25.8 (CH_2), 35.2 (CH_2), 40.9 (CH_2), 46.1 (CH), 215.1 (C=O).

Reduction of 4S-ferrugineone 1 to 4S,5S-ferrugineol using L-selectride as reduction reagent: 78 mg (0.5 mmol) 4S-ferrugineone **1** is added to 5 mL anhydrous THF in a round bottom flask. 0.5 mL L-selectride (1 M in THF) is added dropwise via syringe to the solution at -78 °C under Argon. After 1 hr the reaction is quenched with saturated NH_4Cl. The organic layer is separated, dried over Na_2SO_4. The solvent evaporated and the ferrugineol is separated by column chromatography (Silica gel, Et_2O). Yield: 61 mg (77%); de 10% (GC).

Reduction of 4S-ferrugineone 1 to 4S,5S-ferrugineol using Me-(R)-CBS as reduction reagent: 0.5 mL Me-(R)-CBS (1 M in THF) and 0.6 mL BH_3.THF (1 M in THF) are added to a round bottom flask at room temperature under Argon. The solution is stirred for 15 min at this temperature. Then 78 mg (0.5 mmol) 4S-ferrugineone **1** is added to solution at -78 °C. After 1 hr the reaction is quenched with saturated NH_4Cl. The organic layer is separated, is dried over Na_2SO_4. The solvent evaporated and the ferrugineol is separated by column chromatography (Silica gel, Et_2O). Yield: 56 mg (71%); de 40% (GC).

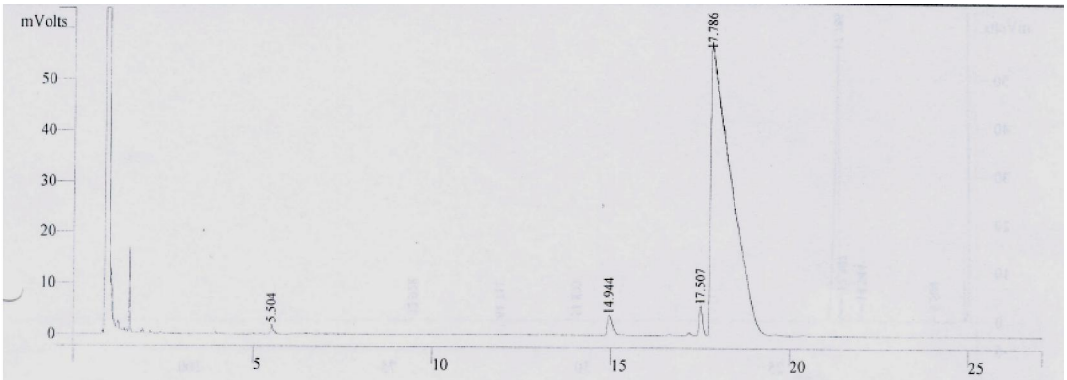
Results and discussion

The RAMP-hydrazone (R)**-6** is prepared in excellent yield by simply mixing the ketone and RAMP, stirring at 60 °C for 20 hr. Distillation of the crude yielded the pure hydrazone (R)**-6** as light yellow oil (73 %). Deprotonation of **6** by means of LDA in dry ether at 0 °C resulted in azaenolate (R)**-7**. Trapping of azaenolate by methyl iodide at -110 °C afforded hydrazone **8**. The crude **8** is clean enough to be cleaved in the ozonolysis step without further purification. To regenerate the original carbonyl functionality in the final product **8**, it is necessary to cleave the hydrazone **8**. 4S-ferrugineone **1** is liberated by oxidatively ozonolysis in dichloromethane at -78 °C without any epimerization and/or racemization at the newly generated chiral center.



Scheme 3.

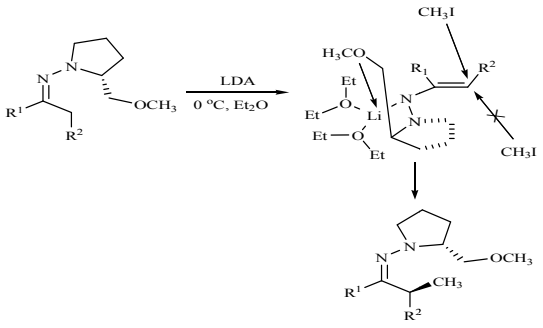
This reaction is very clean, and the ferrugineone formed in good overall yield (two steps) of 57 % and enantiomeric excess up to 96% ee by gas chromatography (GC) with chiral column (Figure 3).



Peak No	Peak Name	Ret Time (min)	Result ()	Peak Area (counts)	Sep. Code	Peak Height (counts)	Width 1/2 (sec)
1		5.50	0.31	7288	BV	1967	3.48
2		14.94	1.52	36202	BB	3897	8.87
3		17.51	1.77	42202	VV	5821	6.80
4		17.79	95.29	2265856	VB	57671	37.58
5		51.83	0.57	13625	VB	360	0.00
6		61.71	0.32	7512	BB	320	19.61
7		72.93	0.21	5086	VB	807	5.50
	Totals		**99.99**	**2377771**		**70843**	

Figure 3. Calculation of enantiomeric excess (ee) of ferrugineone **1** by GC with chiral column.

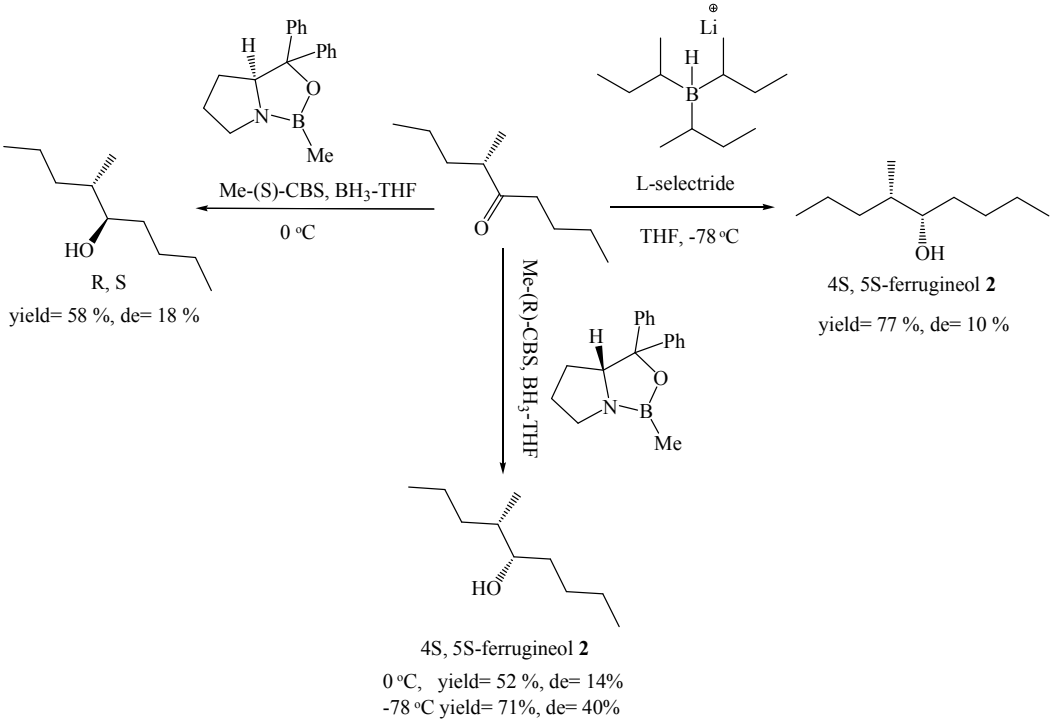
It should be mentioned that the addition of methyl iodide as a small tiny electrophile with high enantiomeric excess at α position to the CO group of 5-nonanone **5** is due to the existence of the hitherto intramolecular chelation of Li by the OMe group which preferably methylated from a side of the molecule (Scheme 4)[15].



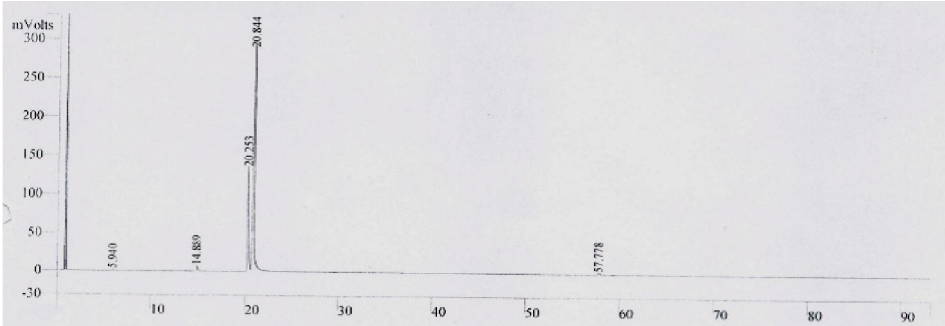
Scheme 4.

Diastereoselective reduction of ferrugineone **1** to the 4S, 5S-ferrugineol **2** would be the final step. A great amount of attention has been paid to asymmetric reduction of aromatic alkyl ketones [16-21]. Unfortunately when both substituents are aliphatic groups none of the reported chemical catalysts can clearly differentiate between two groups. Less attention has been paid to asymmetric reduction of such ketones [22-24]. Using L-selectride as reduction reagent gave the 4S, 5S-ferrugineol **2** with 77% yield and diastereomeric excess 10% de (Scheme 5). Asymmetric borane reductions of prochiral ketones catalyzed by oxazaborolidines (CBS reagents) have been reported by Corey, Bakshi, and Shibata [25]. The asymme

tric reduction of prochiral ketones with borane-tetrahydrofuran complex (BTHF) catalyzed by the CBS reagents is an excellent tool for the synthesis of alcohols in high enantiomeric excess [26]. As shown in Scheme 4, diastereoselective reduction of ferrugineone **1** by Me-(*R*)-CBS and Me-(*S*)-CBS reagents at 0 °C afforded the 4S, 5S-ferrugineol **2** and its diastereomer with diastereomeric excesses 14% and 18% de respectively. The 4S,5S-ferrugineol **2** has been obtained with better yield (71%) and good diastereomeric excess 40% de at -78 °C (Figure 4).



Scheme 5.



Peak No	Peak Name	Ret Time (min)	Result ()	Peak Area (counts)	Sep. Code	Peak Height (counts)	Width 1/2 (sec)
1		5.94	0.19	9473	BB	1469	5.32
2		14.89	1.39	69079	BB	6926	8.56
3		20.25	29.57	1471290	BV	135963	9.89
4		20.84	68.13	3389496	VB	299272	9.99
5		57.78	0.72	35610	BB	2506	13.01
	Totals		**100.00**	**4974948**		**446136**	

Figure 4. Calculation of diastereomeric excess (de) of 4S, 5S-ferrugineol **2** by GC.

Conclusion

In summary, an efficient synthesis of 4S-ferrugineone and 4S, 5S-ferrugineol has been achieved from nonane-5-one, employing the SAMP/RAMP hydrazone methodology in key steps.

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR of synthesized compounds. This material is available free of charge via the Internet at**:**

http://icc.journals.pnu.ac.ir

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