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An improved total synthesis of (-)-Hyrtiosal from (-)-Sclareol

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ABSTRACT

An efficient total synthesis of (-)-hyrtiosal was accomplished in linear 10 steps from commercially available (-)-sclareol. An acid-catalyzed cyclization of α, β-unsaturated amide successfully constructed the key intermediate Weinreb amide 4b with bulky *N*, *O*-dimethylhydroxylamine group, which benefited the stereoselectivity in the epoxidation of 5. One-pot reaction involved the rearrangement of epoxide 5 and the thiol protection of aldehyde 6 catalyzed by $BF_3 \cdot Et_2O$ was developed to give a 74% yield. This practical synthetic route provided (-)-hyrtiosal on grams scale.

KEYWORDS

Total synthesis;
(-)-Hyrtiosal;
Acid-catalyzed cyclization;
Weinreb amide;
(-)-Sclareol.

INTRODUCTION

(-)-Hyrtiosal **1**, embodying the unique structure of hyrtiosane skeleton, was firstly isolated from the Okinawan Marine sponge *Hyrios erectus* by Iguchi *et. al*. in 1992[1]. It also existed in extracts of various sponges[2]. The stereochemistry of (-)-hyrtiosal was verified by X-ray crystallography[2d] and its absolute configuration was confirmed by the sample provided from total synthesis[3a].

Preliminary pharmacological studies demonstrated that (-)-hyrtiosal had significant cytotoxic activities against KB, Hela and PC12 cell lines[1, 2f]. Recently, (-)-hyrtiosal was reported to be a competitive inhibitor of PTP1B (IC_{50} = 42 μM)[4] and HIV-1 intergrase (IC_{50} = 9.6 μM)[5].

The first total synthesis of (-)-hyrtiosal reported 9 steps[3] from methyl isoanticopalate, which was synthesized from (-)-sclareol in 8 steps[6]. Lunardi group also succeeded in synthesizing (-)/(+)-hyrtiosal and their C-16 epimers starting from copalic acid, however, with low *ee* value[7].

In current research, we developed a concise route to synthesize (-)-hyrtiosal in linear 10 steps from (-)-sclareol. As a key intermediate, compound 4b was synthesized from (-)-sclareol in 4 steps which could be applied in the synthesis of various marine natural diterpene products with a broad spectrum of bioactivity.

Weinreb amide 4b acted as the key intermediate had several other reasons as well. The introduction of *N*, *O*-dimethylhydroxylamine group could improve the stereoselectivity of **5** in epoxidation as well as the Weinreb amide could be directly reduced to the corresponding aldehyde with lithium aluminum hydride (LAH) or diisobutylaluminum hydride (DIBAL-H). Compared with the classic method, this new developed synthetic route has the benefits of shorter reaction sequence as well as the better overall yields.

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EXPERIMENTAL SECTION

General information

Commercially available reagents were used without further purification unless otherwise noted. All the reactions were carried out in oven-dried glass flasks under N_2 atmosphere at room temperature unless otherwise noted. The following solvents were distilled before used: tetrahydrofuran (THF) was distilled from Na, dichloromethane and toluene were distilled from CaH_2. The reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. All yields refer to isolated products. NMR spectra were recorded for ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz using TMS as internal standard on a Bruker AVANCE 400 MHz spectrometer.

N-methoxyl-*N*-methyl-enantio-labdiene-8(9), 13, 15-saeure-amide (3b)

The solution of diethyl (*N*-methoxy-*N*-methylcarbamoyl-methyl) phosphonate (67.1 g, 286 mmol) in THF (150 mL) was added dropwise to the solution of NaH (12.6 g, 60 % in mineral oil, 315 mmol) in THF (300 mL) at 0 °C. After it was warmed to room temperature and stirred for 1 h, the reaction was cooled to 0 °C again and **2** (29.5 g, 113 mmol) in THF (100 mL) was added dropwise. The reaction was quenched with water (100 mL) after the starting material was consumed. Then, THF was removed under reduced pressure and the residue was extracted with EtOAc (3 × 100 mL). The organic layer was washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. Purification of the resulting dark yellow oil by flash chromatography gave **3** as a yellow oil (34.0 g, 92%). $[\alpha]^D_{26}$ = -73.1 (c 1.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δpm: 6.14 (s, 1H), 3.69 (s, 3H), 3.22 (s, 3H), 2.21-2.19 (m, 2H), 2.17 (d, *J* = 1.1 Hz, 3H), 2.16-2.14 (m, 1H), 2.09-2.02 (m, 2H), 1.99 (d, *J* = 6.4 Hz, 1H), 1.86-1.83 (dt, *J* = 2.5, 11.6 Hz, 1H), 1.69-1.64 (m, 2H), 1.60 (s, 3H), 1.53-1.48 (m, 1H), 1.45-1.40 (m, 2H), 1.19-1.12 (m, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δppm: 168.3, 139.7, 128.5, 122.6, 113.3, 61.3, 51.9, 41.9, 41.8, 39.1, 37.0, 33.6, 33.3, 26.5, 21.7, 20.1, 19.5, 19.0, 18.8; IR (KBr) νcm^{-1}: 2939, 1656, 1408, 1099, 997; HRMS m/z: calcd. for $C_{22}H_{38}NO_2$ $(M+1)^+$ 348.2903, found 348.2902.

N-methoxyl-N-methyl-isocopalamide (4b)

The solution of **3** (9.2 g, 2.65 mmol) in formic acid (100 mL) was heated to 80 °C and stirred for 6 h. Then, the formic acid was removed under reduced pressure and the residue was diluted with EtOAc (100 mL). The organic layer was washed with saturated $NaHCO_3$ and brine successively. It was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the resulting dark yellow oil by flash chromatography and recrystallized to give 4b as a white crystal (6.0 g, 65%). $[\alpha]^D_{25}$ = -29.7 (c 1.06, $CHCl_3$); mp: 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 5.52 (s, 1H), 3.70 (s, 3H), 3.50 (s, 1H), 3.21 (s, 3H), 1.97 (bs, 2H), 1.63 (m, 2H), 1.59 (s, 4H), 1.54 (m, 1H), 1.40-1.36 (m, 4H), 1.24 (t, *J* = 8.5 Hz, 1H), 1.17-1.09 (m, 1H), 1.04 (s, 3H), 0.92 (s, 3H), 0.87 (s, 4H), 0.82 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 174.1, 130.1, 123.7, 61.0, 56.7, 55.5, 54.8, 41.9, 41.1, 39.9, 37.7, 37.5, 33.5, 33.2, 31.9, 22.9, 21.7, 21.3, 18.6, 18.5, 15.7, 15.5; IR (KBr) νcm^{-1}: 2927, 1658, 1378, 1005, 863; HRMS m/z: calcd. for $C_{22}H_{38}NO_2$ $(M)^+$ 347.2824, found 347.2822.

N-methoxyl - *N* - methyl - 12*α*, 13*α* - epoxy - isoanticopal -15-amide (5)

m-CPBA (8.7 g, 80%, 40.3 mmol) was added to the solution of 4b (7.0 g, 20.2 mmol) in CH_2Cl_2 (250 mL) at 0 °C under N_2. The reaction was quenched with saturated $Na_2S_2O_3$ after the starting material was consumed. The mixture was extracted with CH_2Cl_2 (3 × 60 mL) and the organic layer was washed with saturated $NaHCO_3$ and brine successively. The organic layer was dried with Na_2SO_4 for 30 min, filtered and concentrated under reduced pressure. Further purification with flash chromatography gave **5** as a white solid (6.6 g, 90%). $[\alpha]^D_{26}$ = 5.4 (c 1.15, $CHCl_3$); mp: 70-72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 3.70 (s, 3H), 3.15 (s, 3H), 3.02 (s, 1H), 2.85 (s, 1H), 2.00 (dd, *J* = 15.0, 3.9 Hz, 1H), 1.70 (q, *J* = 12.5 Hz, 3H), 1.53 (t, *J* = 11.1 Hz, 2H), 1.40 (d, *J* = 13.2 Hz, 1H), 1.32 (t, *J* = 12.0 Hz, 3H), 1.23 (s, 3H), 1.12 (s, 3H), 1.05-1.01 (m, 2H), 0.95-0.90 (m, 2H), 0.85 (s, 3H),

0.78 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 173.4, 61.6, 60.5, 57.7, 56.4, 55.6, 51.3, 41.8, 39.5, 39.2, 37.2, 36.7, 33.4, 33.1, 31.9, 22.3, 21.8, 21.7, 18.3, 18.2, 15.7, 15.4; IR (KBr) νcm^{-1}: 2947, 1662, 1408, 1176, 1003; HRMS m/z: calcd. for $C_{22}H_{38}NO_3$ $(M+1)^+$ 364.2852, found 364.2853.

N-methoxyl-*N*-methyl-13S-11(12→13)-*abeo*-12-ethylenedithiaisoanticopal-15-amide (7)

$BF_3{\cdot}Et_2O$ (10 mL) was added to the solution of 5 (1.37 g, 3.77 mmol) in toluene (50 mL) dropwise at 0 °C under N_2. Then the mixture was warmed to 60 °C and stirred for 2 h. Upon cooling, 1,2-ethanedithiol (0.47 mL, 5.50 mmol) was added to the mixture. After the solution was stirred for 12 h at room temperature, aqueous $NaHCO_3$ was added to quench the reaction and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to gain yellow oil. Further purification with flash chromatography gave **7** as a yellow oil (1.22 g, 74%). $[\alpha]^D_{26}$ = -8.9 (c 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 4.77 (s, 1H), 3.72 (s, 3H), 3.28-3.16 (m, 8H), 1.76 (dd, *J* = 11.2, 5.2 Hz, 1H), 1.69 (m, 1H), 1.63 (m, 1H), 1.58 (d, *J* = 3.6 Hz, 1H), 1.55 (d, *J* = 4.6 Hz, 1H), 1.51 (m, 1H), 1.40 (s, 3H), 1.36 (m, 2H), 1.33-1.25 (m, 2H), 1.20-1.15 (m, 2H), 1.07 (s, 3H), 1.99-0.89 (m, 2H), 0.86 (s, 6H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 173.8, 68.8, 61.2, 60.4, 57.6, 56.9, 49.5, 47.8, 42.5, 41.3, 40.3, 39.0, 38.6, 37.0, 36.7, 33.5, 33.1, 27.1, 21.3, 19.1, 18.3, 17.3, 15.8; HRMS m/z: calcd. for $C_{24}H_{42}NO_2S_2$ $(M+1)^+$ 440.2657, found 440.2661.

13*S*-11(12→13)-*abeo*-12-ethylenedithia-15-isoanticopalal (8)

The solution of $LiAlH_4$ (192 mg, 5.05 mmol) in THF (15 mL) was added to the solution of **7** (1.1 g, 2.51 mmol) in THF (10 mL) at -10 °C. The mixture was warmed to room temperature and stirred until the starting material disappeared. Quenching the reaction with EtOAc (10 mL) and the solid substance was removed by filtration. The filtrate was concentrated and purified by flash chromatography to give 8 as a white solid (644 mg, 67%). $[\alpha]^D_{26}$ = + 22.3 (c 1.13, $CHCl_3$); mp: 129-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.95 (d, *J* = 3.2 Hz, 1H), 4.80 (s, 1H), 3.28-3.17 (m, 4H), 2.23 (d, *J* = 3.1 Hz, 1H), 1.94-1.91 (m, 1H), 1.73 (q, *J* = 6.0 Hz, 1H), 1.66-1.62 (m, 2H), 1.57 (s, 3H), 1.53-1.48 (m, 2H), 1.43-1.39 (m, 5H), 1.07 (s, 3H), 1.00-0.90 (m, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 205.9, 68.1, 67.9, 59.7, 57.3, 47.9, 47.8, 42.4, 40.7, 40.1, 39.2, 38.7, 37.8, 37.0, 33.5, 33.1, 26.1, 21.3, 18.5, 18.2, 17.6, 15.8; IR (KBr) νcm^{-1}: 2924, 1711, 1449, 1388; HRMS m/z: calcd. for $C_{22}H_{37}OS_2$ $(M+1)^+$ 381.2286, found 381.2290.

15α-homo-13*S*-11(12→13)-*abeo*-12-ethylenedithia-15-isoanticopalal (9)

The solution of LiHMDS (28.8 mmol) in THF (20 mL) was added to the suspension of metheoxy methyltriphenyl-phosphonium chloride (6.57g, 19.2 mmol) in THF (50 mL) at -78 °C under N_2. After stirring for 15 min at -78 °C the solution of **8** (2.23 g, 5.87 mmol) in THF (15 mL) was added. Stirring for another 2 h and aqueous NH_4Cl was added to quench the reaction. After the THF was removed under reduced pressure, it was diluted with EtOAc (80 mL). Extraction and concentration of the organic layer gave a yellow oil. To the solution of the yellow oil in acetone (50 mL) was added *p*-TsOH (300 mg). After stirring for 6 h at room temperature, aqueous $NaHCO_3$ was added to quench the reaction. After the acetone was removed, the residue was diluted with EtOAc (50 mL). Upon separation, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give a white gel. Further purification of the gel by flash chromatography gave **9** as a white solid (2.20 g, 96%). $[\alpha]^D_{26}$ = -27.3 (c 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.73 (dd, *J* = 3.8, 1.2 Hz, 1H), 4.79 (s, 1H), 3.28-3.15 (m, 4H), 2.66 (ddd, *J* = 15.7, 5.0, 1.1 Hz, 1H), 2.45-2.38 (m, 1H), 2.07 (q, *J* = 5.0 Hz, 1H), 1.76 (dd, *J* = 12.3 Hz, 5.8, 1H), 1.63 (dt, *J* = 10.9, 3.1 Hz, 1H), 1.58-1.54 (m, 3H), 1.48 (m, 1H), 1.41 (s, 2H), 1.38 (s, 2H), 1.20 (m, 1H), 1.14 (s, 4H), 0.98 (d, *J* = 12.8 Hz, 1H), 0.90 (dd, *J* = 12.4, 2.2 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 203.3, 68.1, 59.4, 57.5, 53.7, 64.4, 45.5, 42.5, 42.4, 40.9, 40.1, 39.1, 38.4, 36.7, 36.4, 33.4, 33.1, 24.2, 21.2, 18.8,

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18.3, 16.4, 15.9; IR (KBr) νcm^{-1}: 2922, 1721, 1460, 1387; HRMS m/z: calcd. for $C_{23}H_{38}OS_2$ $(M)^+$ 394.2364, found 394.2360.

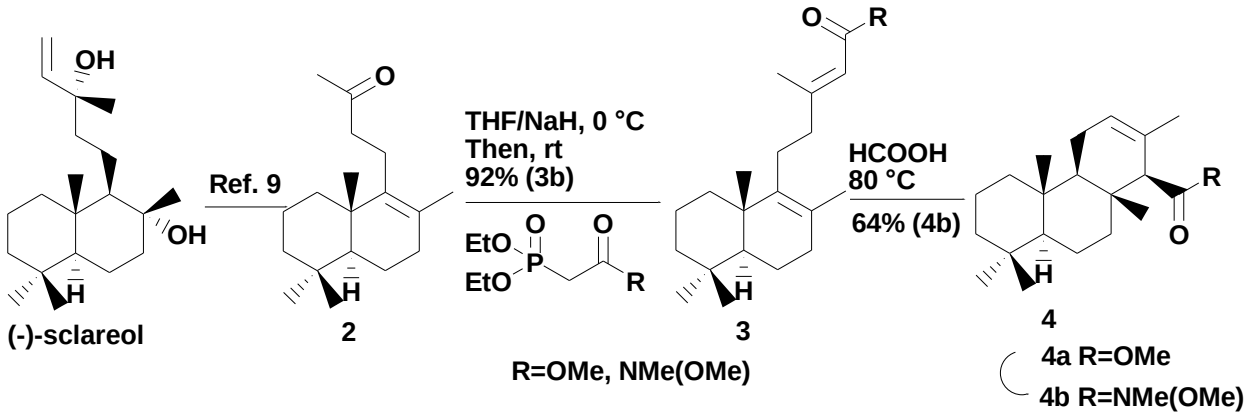
13*S*, 16*R*-19, 25-epoxy-17(25), 18-diene-16-hydroxyhyrtiosan-12-al (1) and 13*S*, 16*S*-19, 25-epoxy-17(25), 18-diene-16-hydroxyhyrtiosan-12-al (10)

To a solution of 3-bromofuran (0.22 mL, 2.45 mmol) in THF (15 mL) was added *n*-BuLi (0.90 mL, 2.5M in hexane, 2.25 mmol) at -78 °C under N_2. After stirring for 15 min, the solution of 9 (590 mg, 1.50 mmol) in THF (10 mL) was added to the mixture. The reaction was stirred for another 2 h before quenching with aqueous NH_4Cl. THF was removed under reduced pressure and the residue was diluted with EtOAc (20 mL). Extraction and concentration to get a yellow oil. The yellow oil was resolved with THF at room temperature and $CaCO_3$ (179 mg, 1.79 mmol) with $HgClO_4.3H_2O$ (1.02 g, 2.25 mmol) was added successively. After stirred for 15 min, the mixture was filtered through a short pad of silica gel. Concentration and further purification with flash chromatography gave (-)-hyrtiosal 1 (150 mg, 26%) and its epimer **10** (180 mg, 31%) as white solid. $[\alpha]^D_{26}$ = -73.1 (c 1.14, $CHCl_3$); mp: 143-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.49 (s, 1H), 7.39 (s, 2H), 6.39 (s, 1H), 4.45 (t, *J* = 6.6 Hz, 1H), 2.01 (t, *J* = 7.0 Hz, 1H), 1.92 (q, *J* = 6.2 Hz, 1H), 1.75 (d, *J* = 12.4 Hz, 1H), 1.65 (m, 4H), 1.42-1.38 (m, 7H), 1.21(s, 3H), 1.17-1.10 (m, 4H), 0.89 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 205.8, 143.2, 138.8, 108.5, 64.3, 60.4, 57.5, 52.9, 48.1, 44.6, 42.4, 40.3, 40.2, 36.8, 33.7, 33.6, 33.5, 33.1, 21.2, 19.2, 18.8, 18.3, 16.6, 15.7; IR (KBr) νcm^{-1}: 3540, 3447, 3129, 2918, 2864, 1708, 1387, 1022, 874; HRMS m/z: calcd. for $C_{25}H_{38}O_3$ $(M + Na)^+$ 409.2719, found 409.2714.

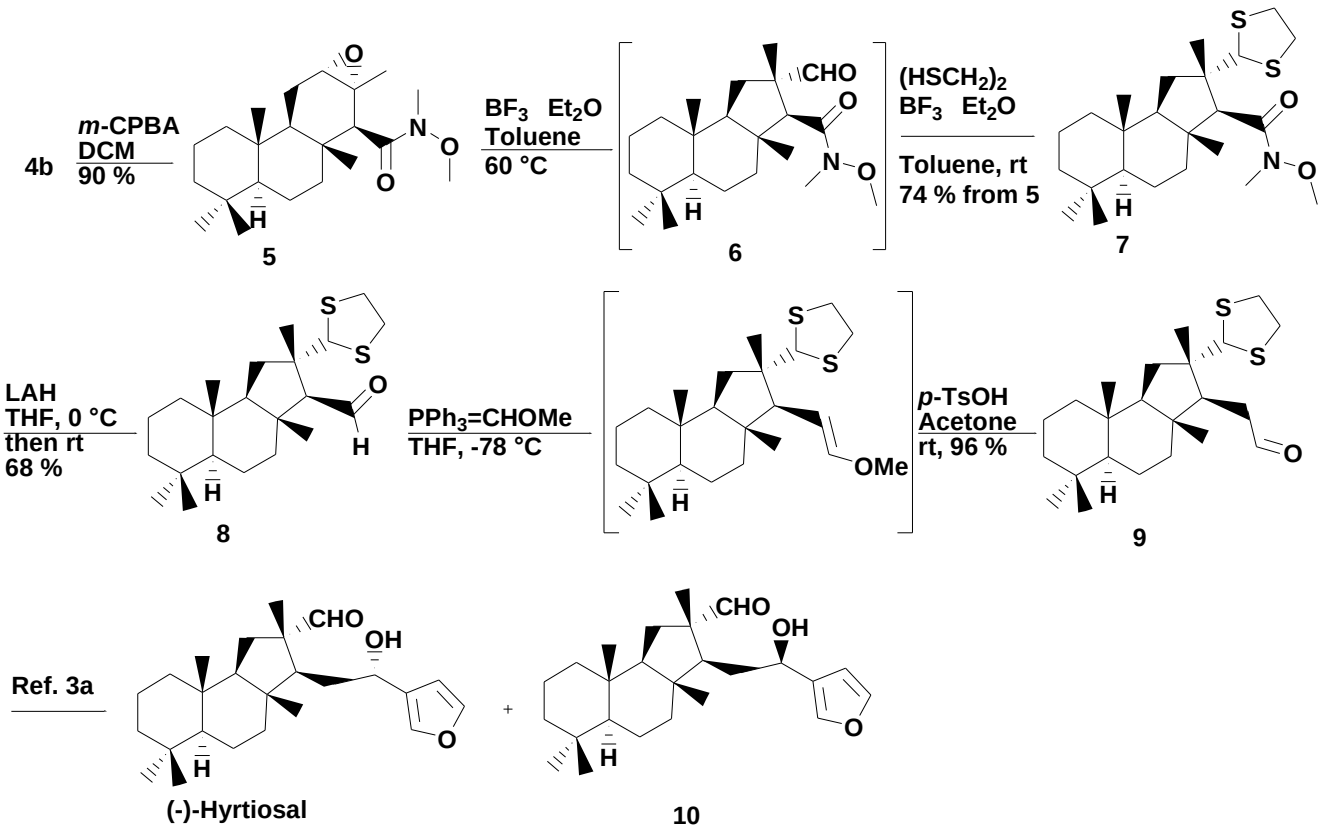
^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.34 (s, 1H), 7.41 (s, 1H), 7.36 (s, 1H), 6.42 (s, 1H), 4.51 (dd, *J* = 8.0, 6.0 Hz, 1H), 1.86-1.78 (m, 2H), 1.74-1.70 (m, 2H), 1.69-1.65 (m, 2H), 1.61-1.57 (m, 2H), 1.48-1.36 (m, 7H), 1.28 (t, *J* = 6.8 Hz, 1H), 1.23 (s, 3H), 1.18-1.14 (m, 1H), 1.06 (q, *J* = 6.0 Hz, 1H), 0.88 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 205.0, 143.6, 140.1, 108.0, 65.5, 60.4, 57.4, 52.3, 50.4, 44.7, 42.4, 41.2, 36.8, 33.8, 33.5, 33.4, 33.1, 21.2, 19.0, 18.8, 18.3, 16.5, 15.7.

RESULTS/DISCUSSION

Using the reported process, 4a was synthesized first. However, all tentative efforts failed to directly transform 4a to amide 4b with known procedures[8]. Therefore, a modified strategy was applied to obtain 4b starting from 2. The Emmon-Horner Wittig reaction of 2 with diethyl (N-methoxy- N – methylcarbamoylmethy l) phosphonate[10]. using sodium hydride as base offered the expected α,β-unsaturated amide 3 in excellent yield. Because of the high stereoselectivity of 3 (E/Z =15:1) the cyclization in anhydrous formic acid lead to 4b (mp. 111.0 - 113.0 C) as a single conformation with moderate yield. The configuration of 4b was further confirmed by the X-ray crystallographic analysis[11]. (Scheme 1, Figure 1)



Scheme 1 : Synthesis of key intermediate 4b



Scheme 2 : Synthesis of (-)-Hyrtiosal

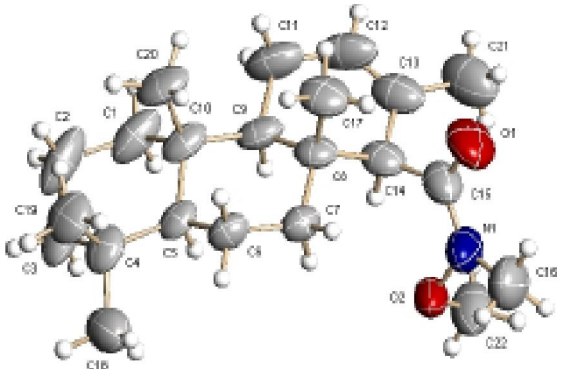


Figure 1 : X-ray structure of compound 4b.

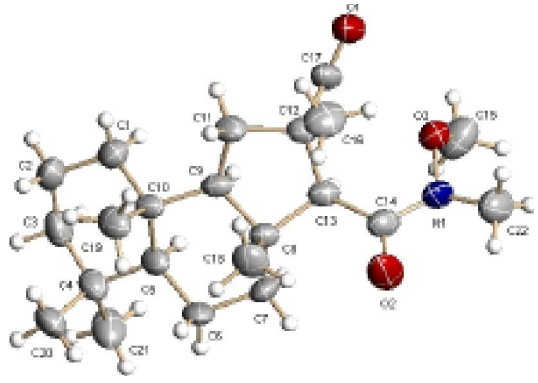


Figure 2 : X-ray structure of compound 6.

After 4b was obtained, the synthesis of aldehydes 8 and 9 were performed as shown in Scheme 2. Owing to the existence of the bulky *N*, *O*-dimethyl hydroxylamine group, epoxidation of Weinreb amide 4b only occurred from the less-hindered *endo* face to furnish the sole compound 5 as a waxy solid. The next rearrangement of epoxide 5, catalyzed by $BF_3 \cdot Et_2O$, successfully provided compound 6 and its configuration of C-13 was determined by X-ray study (Figure 2)[11]. As the thiol protection could also be promoted by $BF_3 \cdot Et_2O$, one-pot method was developed to directly gain compound 7 from 5 in 74% yield as an oil. The redection of amide 7 with LAH directly gave aldehyde 8 with 68% isolated yield. The aldehyde 8 was then treated with (methoxymethyl)-triphenylphosphonium chloride using LiHMDS as base to give the corresponding enol ether, which could be transformed to aldehyde 9 in the presence of catalytic amount of *p*-toluenesulfonic acid (Scheme 2).

With aldehyde 9 in hand, Urones' procedure was used to gain (-)-hyrtiosal in 26% yield as a white solid and its C-16 epimer in 31% yield as white solid (sepa-

rated by flash column chromatography)[3a]. The NMR date of 1 and 10 were identical to those previously reported, as well as the optical rotation data and X-ray of 1[11].

CONCLUSION

In summary, a practical total synthesis of (-)-hyrtiosal involving the construction of amide 4b, which has the advantages of improving the stereoselectivity in epoxidation and reducing the reaction steps, together with the Lewis-acid mediated rearrangement of epoxide **5** as key steps has been achieved over 10 steps from commercially available (-)-sclareol. This synthetic strategy can provide gram scale of (-)-hyrtiosal which can be used in the biological studies.

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SUPPLEMENTARY DATE

Copies of ^{1}H and ^{13}C NMR spectra for compound 1, 4b, 5, 6, 8, 9, 10, 11 and the X-ray of compound 1, 4b and 6 can be found in online version at…

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[11] Crystallographic Dates (Excluding Structures Factors) for The Structures in This Paper Have Been Deposited with The Cambridge Crystallographic Date Center as Supplementary Publication No.CCDC 789808, CCDC 789809, CCDC 789810. Copies of The Date Can be Obtained, Free of Charge, on Application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.