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 BF₃•Et₂O was developed to give a 74% yield. This practical synthetic route provided (-)-hyrtiosal on grams scale.

INTRODUCTION
(-)-Hyrtiosal 1, embodying the unique structure of hyrtiosane skeleton, was firstly isolated from the Okinawan Marine sponge Hyrtios 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[3] 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[4, 20]. Recently, (-)-hyrtiosal was reported to be a competitive inhibitor of PTP1B (IC₅₀ = 42 μM)[4] and HIV-1 integrase (IC₅₀ = 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 disobutylaluminum 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.
**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 N₂ atmosphere at room temperature unless otherwise noted. The following solvents were distilled before use: tetrahydrofuran (THF) was distilled from Na, dichloromethane and toluene were distilled from CaH₂. 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 ¹H NMR at 400 MHz and ¹³C 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 × 60 mL) and the organic layer was washed with saturated NaHCO₃ and brine successively. The organic layer was dried with Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the resulting dark yellow oil by flash chromatography gave 4b as a yellow oil (34.0 g, 92%). [α]D³⁷ = -29.7 (c 1.06, CHCl₃); mp: 111-113 °C; ¹H NMR (400 MHz, CDCl₃) 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, 3H); ¹³C NMR (100 MHz, CDCl₃) 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) vcm⁻¹: 2927, 1658, 1378, 1005, 863; HRMS m/z: calcd. for C₃₄H₃₈NO₂ (M)⁺ 347.2824, found 347.2822.

**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 NaHCO₃ and brine successively. It was then dried over Na₂SO₄, 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%). [α]D³⁷ = -73.1 (c 1.88, CHCl₃); mp: 70-72 °C; ¹H NMR (400 MHz, CDCl₃) 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), 0.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 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) vcm⁻¹: 2939, 1656, 1408, 1099, 997; HRMS m/z: calcd. for C₂₂H₃₈NO₂ (M+1)⁺ 348.2903, found 348.2902.

**N-methoxyl - N - methyl - 12a, 13a - 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 CH₂Cl₂ (250 mL) at 0 °C under N₂. The reaction was quenched with saturated Na₂SO₄ after the starting material was consumed. The mixture was extracted with CH₂Cl₂ (3 × 60 mL) and the organic layer was washed with saturated NaHCO₃ and brine successively. The organic layer was dried with Na₂SO₄ for 30 min, filtered and concentrated under reduced pressure. Further purification with flash chromatography gave 5 as a white solid (6.6 g, 90%). [α]D³⁷ = 5.4 (c 1.15, CHCl₃); mp: 70-72 °C; ¹H NMR (400 MHz, CDCl₃) 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), 0.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 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) vcm⁻¹: 2939, 1656, 1408, 1099, 997; HRMS m/z: calcd. for C₂₂H₃₈NO₂ (M+1)⁺ 348.2903, found 348.2902.
The organic layer was washed with brine, dried over Na$_2$O.

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%). $\alpha D_{26}^{\text{p}} = +22.3$ (c 1.13, CHCl$_3$); mp: 129-130°C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ppm: 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$_3$) $\delta$ppm: 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) vcm$^{-1}$: 2924, 1711, 1449, 1388; HRMS m/z: calcd. for C$_{22}$H$_{38}$NO$_3$ (M+1)$^+$ 381.2286, found 381.2290.

**Full Paper**

15α-homo-13S-11(12→13)-abeo-12-ethylenedithioisoanticopal-15-amide (9)

The solution of LiHMDS (28.8 mmol) in THF (20 mL) was added to the suspension of methoxy 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$_4$Cl 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$_2$SO$_4$ 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%). $\alpha D_{26}^{\text{p}} = -27.3$ (c 1.15, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ppm: 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 (ddd, $J = 12.3$ 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 (ddd, $J = 12.4$, 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$_3$) $\delta$ppm: 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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**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. Therefore, a modified strategy was applied to obtain 4b starting from 2. The Emmon-Horner Wittig reaction of 2 with diethyl (N-methoxy-N-methylcarbamoylmethyl) phosphonate 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.

(Scheme 1, Figure 1)
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 hydroxy-lamine group, epoxidation of Weinreb amide 4b only occurred from the less-hindered \textit{endo} face to furnish the sole compound 5 as a waxy solid. The next rearrangement of epoxide 5, catalyzed by BF$_3$·Et$_2$O, 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$_3$·Et$_2$O, one-pot method was developed to directly gain compound 7 from 5 in 74% yield as an oil. The reduction 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 \textit{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 (sep-
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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...

REFERENCES AND NOTES

[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.