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Total synthesis of an anticancer norsesquiterpene alkaloid isolated from the fungus Flammulina velutipes†

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First total synthesis of a norsesquiterpene alkaloid (R)-8-hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopenta[e]isoindole-1,3(2H,6H)-dione, isolated from the mushroom-forming fungus Flammulina velutipes, in both racemic and enantiomeric pure forms, is reported. The (+)-enantiomer of the natural product has been synthesized from D(-)-pantolactone chiral pool. The synthesis features a one-pot, three-step reaction sequence comprising an enyne RCM/Diels-Alder/aromatization to construct the desired indane skeleton present in the natural product. Our synthesis further confirms the assigned structure and absolute configuration of the natural product.

Introduction

The norsesquiterpene alkaloid (+)-1 was isolated from the solid culture of mushroom-forming fungus Flammulina velutipes fermented on rice by Kai-Shun Bi’s group from China.† The structure of (+)-1 was elucidated by spectroscopic methods and the absolute configuration was assigned by using the circular dichroism data of its [Rh2(OCOCF3)4] complex. Compound (+)-1 showed cytotoxicity against KB cells in vitro, with an IC50 value of 16.6 µM by the MTT method. Hence, alkaloid (+)-1 can be a good starting point for developing potential drugs for treating human oral cancers. Compound (+)-1 has a substituted phthalimide unit, fused with a five-membered ring, which is a privileged motif in medicinal chemistry with attractive biological activities. For example, M. Tao et al. reported compound 2 as a poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor with IC50 value of 40 nM.2b PARP inhibitors are very important compounds in drug discovery, as they are useful in treating various diseases, cancers and neurological disorders in particular. There are several candidates that target PARP, which are currently being tested in human clinical trials.2d Hence, we became interested in the synthesis of target compound 1 and its analogues because of the interesting biological activity and to confirm the absolute stereochemistry of the natural product. Herein, we report the first total synthesis of racemate (+)-1 and enantiomer (-)-1.

Results and Discussion

The retrosynthetic analysis of the target molecule is shown in Scheme 1. The target molecule is visualized from diene and maleimide via Diels-Alder reaction followed by aromatization. The diene could be prepared by ring-closing metathesis (RCM) of an enyne, which in turn could be synthesized from the known intermediate 3 or pantolactone.

![Scheme 1: Retrosynthetic analysis for target molecule.](image)

† Electronic Supplementary Information (ESI) available: 1H & 13C spectral data comparison tables of synthetic vs natural product. Copies of NMR spectra (1H & 13C) of all new compounds. See DOI: 10.1039/b000000x.
The synthesis of racemate (±)-1 commenced with a Grignard reaction of 1-propenyl magnesium bromide on a known aldehyde 3, followed by benzyl protection/TBS protection of alcohol furnished the enyne intermediate 4a/4b. The enyne 4a/4b, on ring-closing metathesis (RCM) with Grubbs' 1st generation catalyst, followed by Diels-Alder reaction 4,5 with maleimide, provided 6a/6b in good overall yields. We have not put much effort in analyzing the stereochemical outcome of the Diels-Alder product, as the resulting stereocenters will be destroyed in the next step (during aromatization). Aromatization followed by deprotection of the benzyl/TBS group in adduct 6a/6b should have provided the target molecule. However, all the efforts to aromatize 6a/6b were not successful (Scheme 2).6

At this stage, we changed the strategy to use one of our previously developed one-pot enyne RCM/Diels-Alder/aromatization sequence to construct the indane skeleton. The revised plan started from the previously synthesized intermediate 4a, which upon RCM using Grubbs' 1st generation catalyst followed by Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) and subsequent treatment with DDQ, provided the aromatized compound 7 in a moderate yield (~40%). The indane derivative 7 on ester hydrolysis using aq. KOH followed by heating with urea in ethylene glycol7 furnished the desired compound 8. The final step, deprotection of benzyl group, was performed using 10% Pd/C under the blanket of hydrogen atmosphere, which furnished the racemic norsesquiterpene alkaloid (±)-1 in 83% yield (Scheme 3). The spectral data (1H NMR, 13C NMR and MS) were compared with the isolated natural product and found to be identical.1

After the successful synthesis of racemate (±)-1, we turned our attention towards the synthesis of the natural product in enantiopure form. We have chosen pantolactone as the starting material to access both the enantiomers of the target alkaloid as both the antipodes are commercially available and it is also a favourite chiral pool from our group for total syntheses.4,8 The known lactol 9,8c prepared from D-(-)-pantolactone, on Wittig reaction,9 resulted in primary alcohol 10 in 92% yield. The alcohol 10 was subjected to Swern oxidation to give an aldehyde, which on homologation (methoxymethyl Wittig reaction followed by hydrolysis),10 produced the desired aldehyde 11 in good overall yield. The key enyne intermediate (+)-4 was prepared by using Ohira-Bestmann reagent11 in which the aldehyde arm of 11 was transformed to the corresponding alkyne. The spectral data (1H NMR & 13CNMR) and TLC analysis of compound (+)-4 were

Scheme 4: Enantiospecific total synthesis of (-)-1

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compared to that of the compound 4a and were found to be identical. The compound (+)-4 was transformed to the target compound (-)-1 by using the same protocol developed for the synthesis of the racemate (+)-1 through the intermediary of (-)-7 and (+)-8. The optical rotation of synthesized (-)-1 was found to be comparable but with the opposite sign. This exercise confirms the absolute configuration of the secondary alcohol present in the natural product as “S”. The natural isomer (+)-1 can be obtained starting from L-(-)-pantolactone by following the same route.

**Conclusion**

In summary, we have achieved the first total synthesis of norsesquiterpene alkaloid (1), an anticancer agent, isolated from the fungus *Flammulina velutipes*. The enantiospecific synthesis of unnatural enantiomer starting from D-(-)-pantolactone confirmed the previously assigned absolute configuration of the natural product. Another highlight of the present work is the use of the appropriately substituted indane skeleton. As the structure of the target alkaloid (1) is close to one of the known potent PARP-1 inhibitor (2), the synthesized compounds and the related one are expected to show interesting biological activities.

**Experimental**

**General:** All reactions were carried out in oven-dried glassware under argon or nitrogen unless otherwise specified, with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F 254). Visualization was accomplished with either UV light, iodine vapours, or by immersion in ethanolic solutions of phosphomolybdic acid, para-anisaldehyde, or KMnO 4 followed by heating with a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). High resolution mass spectra (HRMS, ESI) were recorded with an instrument. Samples were measured with electrospray ionization with an MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on an FT-IR spectrometer as thin films. Optical rotations were recorded on a Perkin Elmer 2410 polarimeter at 589 nm. Chemical nomenclature was generated using Chem Bio Draw Ultra 13.0. Melting points of solids were measured in a melting point apparatus.

**[(5,5-Dimethyloct-2-en-7-yn-4-yl)oxy]methylbenzene (4a):** To a solution of 2,2-dimethylpent-4-ynal (3.3 g, 18 mmol) in dry diethyl ether (50 mL) 1-propenyl magnesium bromide (0.5 M in THF, 44 mL, 22 mmol) was added slowly at 0 °C and stirred for 1 h. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (30 mL), organic layer was separated and the aqueous layer was extracted with diethyl ether (50 mL x 2). Combined organic layer was washed with brine solution (30 mL), dried over Na2SO4 and solvent was evaporated under reduced pressure to afford 2.2 g of crude 5,5-dimethyloct-2-en-7-yn-4-ol.

To a suspension of NaH (1.4 g, 36 mmol, 60% in mineral oil) in dry DMF (50 mL) was added above obtained alcohol in DMF (10 mL) at 0 °C. After being stirred at 0 °C for 30 min, BnBr (2.2 mL, 18 mmol) and TBAI (670 mg, 1.8 mmol) was added at 0 °C and the mixture was stirred at rt for 2 h. Water (30 mL) was added and extracted with diethyl ether (50 mL x 3). The organic layer was washed with brine solution (20 mL), dried over Na2SO4, evaporated in vacuo. The residue was purified by column chromatography (2% ethyl acetate in hexanes) to afford 4a (3.5 g, 79%, pale yellow liquid) as ~3:2 E, Z mixture. IRmax (film): 3306, 2968, 2938, 2359,1506 cm⁻¹; 1H NMR (400 MHz, CDCl3) (mixture of E, Z): δ 7.39 - 7.34 (m, 8H), 7.33 - 7.27 (m, 2H), 5.95 - 5.81 (m, 1H), 5.79 - 5.65 (m, 1H), 5.52 - 5.35 (m, 2H), 4.66 - 4.53 (m, 2H), 4.39 - 4.26 (m, 2H), 4.12 - 4.00 (m, 1H), 3.58 (d, J = 8.7 Hz, 1H), 2.43 - 2.30 (m, 2H), 2.26 - 2.17 (m, 2H), 2.05 - 1.91 (m, 2H), 1.81 (td, J = 6.8, 1.4 Hz, 3H), 1.71 (td, J = 7.1, 1.3 Hz, 3H), 1.08 - 1.03 (m, 6H), 1.03 - 0.97 (m, 6H); 13C NMR (100 MHz, CDCl3): δ 139.2, 139.1, 130.7, 129.6, 128.1, 128.0, 127.6, 127.5, 127.2, 127.1, 85.7, 82.6, 78.5, 70.1, 70.0, 69.8, 69.7, 38.2, 37.6, 29.0, 28.9, 23.5, 23.1, 22.4, 22.1, 17.9, 13.7; MS: 265 (M+Na)⁺; HRMS calculated for C12H22O2Na 265.1563, found 265.1561.

**Tert-butyli((5,5-dimethylcot-2-en-7-yn-4-yl)oxy)dimethylsilane (4b):** To a solution of above synthesized 5,5-dimethylcot-2-en-7-yn-4-ol (500 mg, 3.3 mmol) in dry DCM (20 mL) were added imidazole (671 mg, 9.9 mmol) and TBSCI (1.5g, 9.9 mmol) at 0 °C. After being stirred at 0 °C for 1h reaction mixture was allowed to rt and stirred for overnight. Water (20 mL) was added and extracted with diethyl ether (50 mL x 2). The organic layer was washed with brine solution (20 mL), dried over Na2SO4, evaporated in vacuo. The residue was purified by column chromatography (hexanes) to afford 4b (720 mg, 83%, pale yellow liquid) as ~1:1 E, Z mixture. IRmax (film): 3310, 2957, 2886, 2117, 1719 cm⁻¹; 1H NMR (200 MHz, CDCl3) (mixture of E, Z): δ 5.68 - 5.25 (m, 4H), 4.29 (d, J = 9.3 Hz, 1H), 3.83 (d, J = 7.7 Hz, 1H), 2.33 - 2.00 (m, 4H), 1.96 (q, J = 2.8 Hz, 2H, 1.71 - 1.62 (m, 6H), 0.95 - 0.86 (m, 30H), 0.04 (d, J = 3.0 Hz, 6H), 0.00 - 0.05 (m, 6H); 13C NMR (100MHz, CDCl3): δ 131.3, 127.6, 125.5, 82.9, 79.5, 77.3, 77.0, 76.7, 72.8, 69.7, 39.1, 38.4, 28.6, 28.5, 25.9, 25.8, 25.7, 23.1, 22.7, 22.2, 21.8, 18.1, 17.7, -3.8, -4.2, -5.0, -5.1; MS: 289 (M+Na)⁺; HRMS calculated for C21H33NO2Na 288.2337, found 288.2340.

8-(Benzyloxy)-4,7,7-trimethyl-4,6,7,8,8a,8b-hexahydrocyclopenta[e]isindole-1,3-(2H,3aH)-dione (6a): A solution of compound 4a (1.0 g, 4.1 mmol) in toluene (5 mL) was degassed for 10 min in a stream of argon and then treated with Grubbs’ Ird generation catalyst (170 mg, 5 mol%) in one portion. After being stirred at 50 °C for 12 h, the reaction mixture was cooled to room temperature and maleimide (481 mg, 4.9 mmol) was added and heated at 120 °C for 10 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (20% ethyl acetate in hexanes) to furnish 6a (0.770 g, 55% for two steps). mp 132-134 °C; IRmax (film): 3162, 3065, 2929, 1761, 1691, 1468, 1454 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 8.07 (bs, 1H), 7.46 - 7.40 (m, 2H), 7.36 (t, J = 7.3 Hz, 2H), 7.30 (d, J = 7.1 Hz, 1H), 5.41 (bs, 1H), 4.82 (q, J = 11.5 Hz, 2H), 4.45 (d, J = 8.8 Hz, 1H), 3.24 (t, J = 7.9 Hz, 1H), 3.02 (t, J = 7.6 Hz, 1H), 2.53 (t, J = 6.6 Hz, 1H), 2.36 (bs, 1H), 2.10 (bs, 2H), 1.41 (d, J = 7.3 Hz, 3H), 1.16 (s, 3H), 0.95 (s, 3H);
$^{15}$C NMR (100 MHz, CDCl$_3$): δ 178.0, 177.7, 142.2, 139.4, 128.3, 127.6, 127.5, 124.1, 86.4, 73.8, 47.7, 45.6, 43.3, 43.2, 42.3, 31.7, 27.1, 20.7, 16.9; MS: 338 (M-H); HRMS calculated for $C_{39}H_{38}ONaNa$: 338.2982, found 338.2984.

8-((Tert-butyldimethylsilyl)oxy)-4,7,7-trimethyl-7,8-dihydrocyclopent[a] [e]isoindole-1,3(2H,3aH)-dione (6b): The compound 6b was synthesized from 4b in 59% yield, following the procedure used for the synthesis of 6a. mp 204–206 °C; IR max(film): cm$^{-1}$ 2925, 1732, 1435, 1267; 1H NMR (400 MHz, CDCl$_3$): δ 7.86 - 7.79 (m, 5H), 7.19 (s, 1H), 4.86 - 4.75 (m, 2H), 4.75 - 4.58 (m, 1H), 3.08 - 2.97 (m, 2H), 2.97 - 2.86 (m, 3H), 2.86 - 2.75 (m, 2H), 2.69 - 2.58 (m, 3H), 2.45 - 2.35 (m, 1H), 2.35 - 2.24 (m, 1H), 2.18 - 2.07 (m, 1H), 1.47 - 1.37 (m, 1H), 1.37 - 1.27 (m, 1H), 0.99 (s, 3H); 13C NMR (100 MHz, CDCl$_3$): δ 169.1, 168.5, 153.2, 139.1, 138.9, 138.8, 133.2, 129.7, 128.1, 127.7, 127.5, 126.0, 72.6, 44.9, 27.3, 22.4, 17.8; MS: 358 (M+Na$^+$); HRMS calculated for $C_{39}H_{38}ONaNa$: 358.2984, found 358.2982.

8-Hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopent[a] [e]isoindole-1,3(2H,6f)-dione (-4): To a solution of 8 (40 mg, 0.1 mmol) in EtOH (2 mL), 10% Pd/C (10 mg) was added and stirred for 10 h under H$_2$ atmosphere. The reaction mixture was filtered, concentrated under reduced pressure and purified by column chromatography (12% ethyl acetate in hexanes) to afford 8-hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopent[a] [e]isoindole-1,3(2H,6f)-dione (-4) (73 mg, 83%) as a white solid. mp 148 - 150 °C; IR $\nu_{\text{max}}$(film): cm$^{-1}$ 3733, 1716, 1382, 1252, 1156, 1456; 1H NMR (400 MHz, CDCl$_3$): δ 7.86 (bs, 1H, NH proton), 7.25 (s, 1H), 5.08 (s, 1H), 4.52 (s, 1H, OH proton), 2.81-2.73 (m, 2H), 2.63 (s, 3H), 1.33 (s, 3H), 0.98 (s, 3H); 13C NMR (100 MHz, CDCl$_3$): δ 170.1, 169.1, 149.4, 143.0, 138.3, 133.1, 128.7, 127.6, 81.0, 46.0, 45.8, 26.4, 21.4, 17.8. MS: 268 (M+Na$^+$); HRMS calculated for $C_{14}H_{13}O$_7Na: 268.0944, found 268.0942.

($S$)-3-(Benzyloxy)-2,2-dimethylhex-4-en-1-ol (10): To a solution of ethyl triphenylphosphonium iodide (31.0 g, 74.3 mmol) in dry THF (150 mL) was added $n$-BuLi (1.6 M in hexanes, 46.4 mL, 74.3 mmol) at 0 °C. After stirring for 30 min, a solution of (S)-3-(benzyloxy)-4,4-dimethyltetrahydrofuran-2-ol (9$^k$ (3.3 g, 14.8 mmol) in dry THF (30 mL) was added. After completion of addition, the reaction mixture was warmed to room temperature and stirred for overnight. The reaction mixture was cooled to 0 °C, quenched by the addition of saturated ammonium chloride solution (30 mL) and extracted with ethyl acetate (50 mL). Combined organic layer was washed with water (20 mL), brine (20 mL) and dried over Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography (5% ethyl acetate in hexanes) to furnish 7 (0.32 g, 40% for three steps); IR $\nu_{\text{max}}$(film): cm$^{-1}$ 3446, 2961, 1668, 1496; 1H NMR (200 MHz, CDCl$_3$): δ 7.38 - 7.28 (m, 5H), 5.70 - 5.61 (dq, $J$ = 15.2, 6.7 Hz, 1H), 5.54 - 5.37 (m, 1H), 4.60 (d, $J$ = 11.9 Hz, 1H), 4.28 (d, $J$ = 11.9 Hz, 1H), 3.95 (s, 3H), 2.97 (t, $J$ = 6.4 Hz, 2H), 2.86 - 2.73 (m, 2H), 2.63 (s, 3H), 1.75 (d, $J$ = 6.7 Hz, 1H), 1.54 - 1.37 (m, 10H), 0.99 (s, 3H); 13C NMR (100 MHz, CDCl$_3$): δ 163.8, 163.8, 138.8, 133.4, 128.7, 127.7, 126.8, 81.1, 71.6, 70.0, 38.7, 22.7, 19.9, 17.8; MS: 257 (M+Na$^+$); HRMS calculated for $C_{25}H_{25}O$_7Na: 257.1512, found 257.1508.

(S)-4-(Benzyloxy)-3,3-dimethylhept-5-enal (11): To a cooled solution of oxalyl chloride (1.8 mL, 21.2 mmol) in DCM (30 mL) was added DMSO (3.0 mL, 42.7 mmol) at -78 °C. After 20 min, a solution of (S)-3-(benzyloxy)-4,4-dimethyltetrahydrofuran-2-ol (9$^k$ (3.3 g, 14.8 mmol) in dry THF (30 mL) was added. After completion of reaction, the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C, quenched with water (30 mL) and extracted with DCM (30 mL x 3). Combined organic layer was washed with water (30 mL), brine (30 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford (S)-4-(benzyloxy)-3,3-dimethylhept-5-enal (11) (70 mg, 57%). Combined organic layer was washed with water (30 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford (S)-4-(benzyloxy)-3,3-dimethylhept-5-enal (11) (70 mg, 57%).
To a stirred solution of (Methoxymethyl) triphenylphosphonium chloride (8.0 g, 23.2 mmol) in dry THF (120 mL) was added n-BuLi (1.6 M in hexanes, 14.5 mL, 23.2 mmol) at 0 °C. After stirring for 30 min, a solution of (5)-((5,5-dimethyloct-2-en-7-yn-4-yl)oxy)methyl)benzene (1.3 g, 5.0 mmol) in acetone (30 mL), 2N HCl (6.2 mL, 12.5 mmol) was added and then refluxed for 40 min. The reaction mixture was cooled to 0 °C, quenched by the addition of saturated ammonium chloride solution (25 mL) and extracted with ethyl acetate (20 mL), brine (20 mL) and dried over Na2SO4. The solvent was concentrated under reduced pressure and purified by column chromatography (5% ethyl acetate in hexanes) to give 1.3 g (65%) of (5)-((5,5-dimethyloct-2-en-7-yn-4-yl)oxy)methyl)benzene as a colorless oil.

A solution of ((5)-4-(benzyloxy)-3,3-dimethylhept-5-enal as a colorless oil. [α]D 25 +59.3 (c 1.7, CHCl3).

(R)-8-(benzoxyl)-4,7,7-trimethyl-7,8-dihydrocyclopenta[e]isoino-dole-1,3(2H,6H)-dione (+) 8: The compound (+)-8 (56 mg, 64%) was prepared from (+)-7 by following the similar procedure mentioned for the synthesis of 8. The Nmr data was found to be identical with 8; [α]D 25 +7.8 (c 0.2, CHCl3).

(R)-8-Hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopenta[e]isoino-dole-1,3(2H,6H)-dione(-)-1: The compound (-)-1 (28 mg, 77%) was synthesized from (+)-8 by following the similar procedure mentioned for the synthesis of (+)-1. The optical rotation of synthesized (-)-1 found to be comparable but with opposite sign, [α]D 25 -21.4 (c 0.4, MeOH) vs [α]D 25 +22.3 (c 0.4, MeOH).

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Notes and references


(6) We have tried several reagents such as DDQ, MnO2, TFA and Br2 by varying reaction parameters, but we were not successful in obtaining the desired aromatized product.


