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

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The first total synthesis of a norsesquiterpene alkaloid (*R*)-8-hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopenta[*e*]isoindole-1,3(2*H*,6*H*)-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 the 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 the mushroom-forming fungus *Flammulina velutipes* fermented on rice by Kai-Shun Bi's group from China.[1] The structure of **(+)-1** was elucidated by spectroscopic methods and the absolute configuration was assigned using the circular dichroism data of its $[Rh_2(OCOCF_3)_4]$ complex. Compound **(+)-1** showed cytotoxicity against KB cells *in vitro*, with an IC_{50} 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[2] with an IC_{50} 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** (Fig. 1).

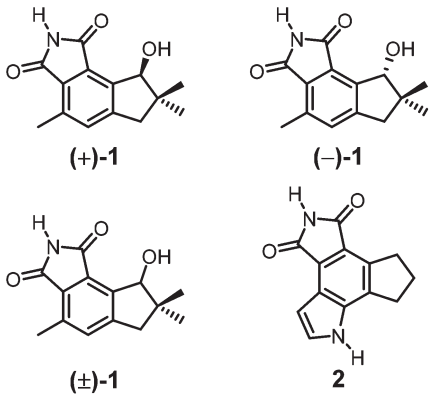

Fig. 1 Structures of natural product (racemic & enantiomeric forms) and a PARP-1 inhibitor.

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* a 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** (ref. 3) or pantolactone.

The synthesis of racemate **(±)-1** commenced with a Grignard reaction of 1-propenyl magnesium bromide on a known aldehyde **3**,[3] followed by benzyl protection/TBS protection of alcohol, which furnished the enyne intermediate **4a**/**4b**. The enyne **4a**/**4b**, on ring-closing metathesis (RCM) with Grubbs' 1st generation catalyst followed by a Diels–Alder reaction[4,5] with maleimide, provided **6a**/**6b** in good overall yields. We have not put much effort into analyzing the stereochemical

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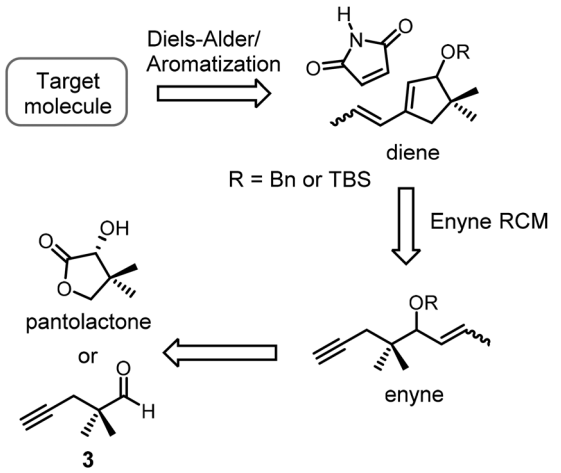
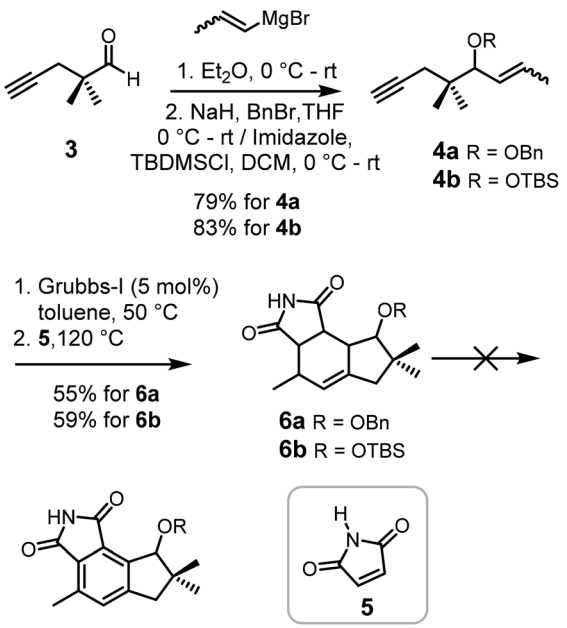


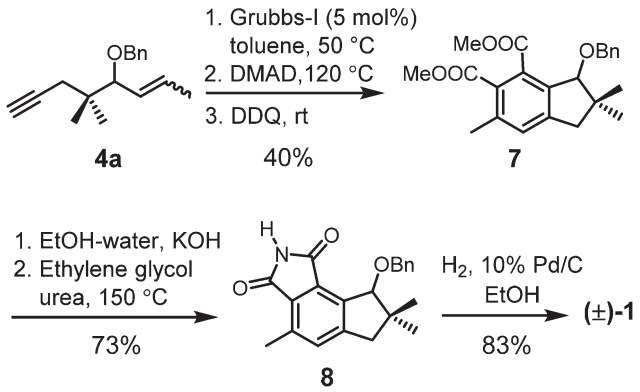
Scheme 1 Retrosynthetic analysis for the target molecule.

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 unsuccessful (Scheme 2).[6]

At this stage, we changed the strategy to use one of our previously developed[4] 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 the 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.



Scheme 2 Initial attempts towards the target molecule.



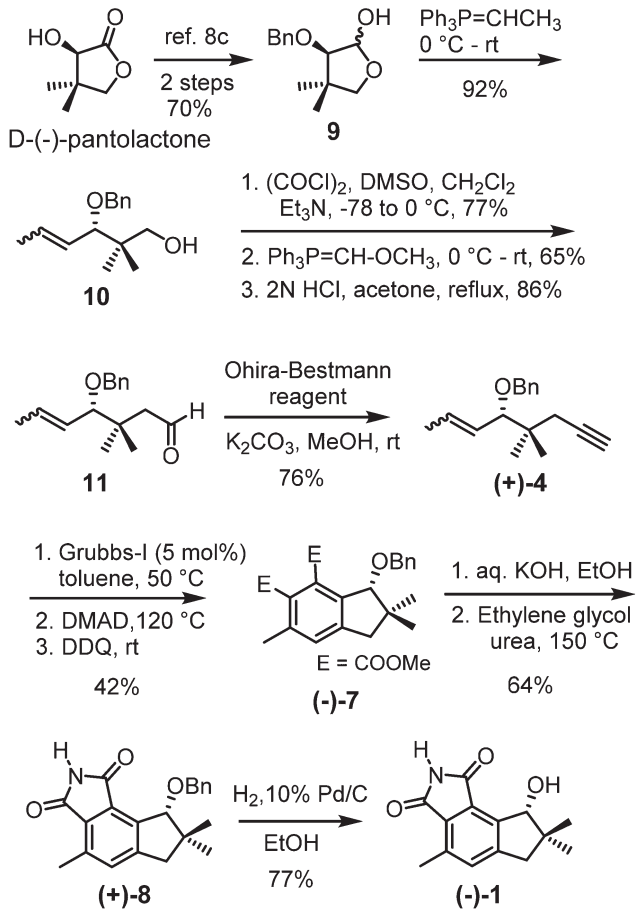
Scheme 3 Total synthesis of (±)-1.

KOH followed by heating with urea in ethylene glycol[7] furnished the desired compound **8**. The final step, deprotection of the benzyl group, was performed using 10% Pd/C under the blanket of a hydrogen atmosphere, which furnished the racemic norsesquiterpene alkaloid (±)-**1** in 83% yield (Scheme 3). The spectral data (^{1}H NMR, ^{13}C NMR and MS) were compared with the isolated natural product and were found to be identical.[1]

After the successful synthesis of racemate (±)-**1**, we turned our attention to the synthesis of the natural product in an 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 undergoing a 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 using the Ohira–Bestmann reagent[11] in which the aldehyde arm of **11** was transformed to the corresponding alkyne. The spectral data (^{1}H NMR & ^{13}C NMR) and TLC analysis of compound (+)-**4** were compared to that of 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 intermediacy of (−)-**7** and (+)-**8** (Scheme 4). The optical rotation of the 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



Scheme 4 Enantiospecific total synthesis of (−)-**1**.

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 one-pot procedure by combining three reactions to construct the appropriately substituted indane skeleton. As the structure of the target alkaloid (**1**) is close to one of the known potent PARP-1 inhibitors (**2**), the synthesized compounds and the related ones 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* a syringe or a cannula and were introduced into 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 s. Column chromatography was performed on silica gel (100–200 or 230–400 mesh size). High resolution mass spectra (HRMS, ESI) were recorded with an ORBITRAP mass analyser (Q Exactive). Mass spectra were measured by 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 P-2000 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)methyl)benzene (4a)

To a solution of 2,2-dimethylpent-4-ynal **3** (ref. 3) (2.0 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), the organic layer was separated and the aqueous layer was extracted with diethyl ether (50 mL × 2). Combined organic layers were washed with a brine solution (30 mL), dried over Na_2SO_4 and the 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 the 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) were 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 × 3). The organic layer was washed with brine solution (20 mL), dried over Na_2SO_4, and 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 a ~3 : 2 *E*, *Z* mixture. IR ν_{max} (film): 3306, 2968, 2938, 2359, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{22}ONa$ 265.1563, found 265.1561.

tert-Butyl((5,5-dimethyloct-2-en-7-yn-4-yl)oxy)dimethylsilane (4b)

To a solution of the above synthesized 5,5-dimethyloct-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 TBSCl (1.5 g, 9.9 mmol) at 0 °C. After being stirred at 0 °C for 1 h the reaction mixture was allowed to warm to rt and stirred overnight. Water (20 mL) was added and extracted with diethyl ether (50 mL × 2). The

organic layer was washed with brine solution (20 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (hexanes) to afford **4b** (720 mg, 83%, pale yellow liquid) as a ~1 : 1 *E*, *Z* mixture. IR ν_{max} (film): 3310, 2957, 2886, 2117, 1719 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (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, 1 H), 2.33–2.00 (m, 4H), 1.96 (q, J = 2.8 Hz, 2 H), 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $(M + Na)^+$.

8-(Benzyloxy)-4,7,7-trimethyl-4,6,7,8,8a,8b-hexahydrocyclopenta[*e*]isoindole-1,3 (2*H*,3*aH*)-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' 1st 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; IR ν_{max} (film): 3162, 3065, 2929, 1761, 1691, 1468, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}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 $C_{21}H_{25}O_3NNa$ 362.1727, found 362.1724.

8-((*tert*-Butyldimethylsilyl)oxy)-4,7,7-trimethyl-4,6,7,8,8a,8b-hexahydrocyclopenta[*e*]isoindole-1,3(2*H*,3a*H*)-dione (6b)

The compound **6b** was synthesized from **4b** in 59% yield by following the procedure used for the synthesis of **6a**. mp 204–206 °C; IR ν_{max} (film): 3244, 2953, 2891, 1772, 1710, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 5.37 (bs, 1H), 4.55 (d, J = 8.6 Hz, 1H), 3.23 (t, J = 7.8 Hz, 1H), 3.10–2.99 (m, 1H), 2.46–2.27 (m, 2H), 2.14–1.91 (m, 2H), 1.39 (d, J = 7.3 Hz, 3H), 1.03 (s, 3H), 0.92 (s, 9H), 0.83 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.8, 177.7, 142.7, 123.7, 78.6, 47.7, 47.2, 42.8, 42.6, 42.3, 31.8, 26.4, 26.0, 20.1, 18.1, 16.9, −3.8, −4.8; MS: 362 (M − H); HRMS calculated for $C_{20}H_{33}ONNaSi$ 386.2122, found 386.2119.

Dimethyl 3-(benzyloxy)-2,2,6-trimethyl-2,3-dihydro-1*H*-indene-4,5-dicarboxylate (7)

A solution of compound **4a** (0.5 g, 2.0 mmol) in toluene (5 mL) was degassed for 10 min in a stream of argon and then treated with Grubbs' 1st generation catalyst (85 mg, 5 mol%) in one portion. After being stirred at 50 °C for 12 h, the reaction mixture was cooled to room temperature, and freshly distilled dimethyl acetylenedicarboxylate (DMAD) (0.5 mL, 4.1 mmol) was added and heated at 120 °C for 10 h. Cooled to room temperature, DDQ (562 mg, 2.5 mmol) was added and stirred for 8 h, the reaction mixture was filtered through a Celite pad and washed with dichloromethane, the filtrate was evaporated to dryness and the crude product was purified by column chromatography (5% ethyl acetate in hexanes) to furnish **7** (0.32 g, 40% for three steps); IR ν_{max}(film): cm^{-1} 2925, 1732, 1435, 1267; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.29 (m, 5H), 7.19 (s, 1H), 4.86 (s, 1H), 4.70 (d, J = 11.3 Hz, 1H), 4.58 (d, J = 11.3 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 2.95 (d, J = 15.9 Hz, 1H), 2.60 (d, J = 15.9 Hz, 1H), 2.40 (s, 3H), 1.28 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 168.0, 146.4, 140.6, 138.8, 136.9, 131.0, 129.9, 129.1, 128.3, 128.2, 127.4, 127.3, 89.1, 73.0, 52.3, 52.2, 45.5, 44.5, 28.0, 22.7, 20.0; MS: 405 $(M + Na)^+$; HRMS calculated for $C_{23}H_{26}O_5Na$ 405.1672, found 405.1670.

8-(Benzyloxy)-4,7,7-trimethyl-7,8-dihydrocyclopenta[*e*]-isoindole-1,3(2*H*,6*H*)-dione (8)

To a solution of **7** (80 mg, 0.2 mmol) in EtOH (2 mL), KOH (35 mg, 0.62 mmol, in 0.5 mL water) was added and stirred for 3 h at room temperature. Solvent was removed under reduced pressure and the residue was acidified with 1 N HCl (pH ~3) and extracted with ethyl acetate (10 mL × 2). The combined organics were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude acid.

The above acid was taken in ethylene glycol (0.5 mL), urea (12 mg, 0.2 mmol) was added and heated at 150 °C for 2 h. The reaction mixture was cooled to rt, quenched with water (5 mL) and extracted with ethyl acetate (10 mL × 2). Combined organic layers were washed with brine solution (5 mL) and dried over Na_2SO_4. The crude material obtained after removal of solvent was purified by column chromatography (10% ethyl acetate in hexanes) to afford 8-(benzyloxy)-4,7,7-trimethyl-7,8-dihydrocyclopenta[*e*]iso-indole-1,3(2*H*,6*H*)-dione **8** (51 mg, 73%) as a colorless sticky liquid. IR ν_{max}(film): cm^{-1} 3647, 3445, 2923, 1635, 1731, 1457; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (bs, 1H), 7.41–7.18 (m, 6H), 4.84–4.75 (m, 2H), 4.75–4.58 (m, 1H), 3.08 (d, J = 16.3 Hz, 1H), 2.69 (s, 3H), 2.52 (d, J = 16.3 Hz, 1H), 1.40 (s, 3H), 0.99 (s, 3H); ^{13}C 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, 127.3, 86.0, 72.6, 44.9, 27.3, 22.4, 17.8; MS: 358 $(M + Na)^+$; HRMS calculated for $C_{21}H_{21}O_3NNa$ 358.1414, found 358.1412.

8-Hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopenta[*e*]isoindole-1,3(2*H*,6*H*)-dione (±)-1

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 a 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-dihydrocyclopenta[*e*]isoindole-1,3-(2*H*, 6*H*)-dione **(±)-1** (24 mg, 83%) as a white solid. mp 148–150 °C; IR

ν_{max}(film): cm^{-1} 3733, 1716, 1738, 1652, 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 169.1, 149.4, 143.0, 138.3, 133.1, 128.8, 127.6, 81.0, 46.0, 45.8, 26.4, 21.4, 17.8. MS: 268 $(M + Na)^+$; HRMS calculated for $C_{14}H_{15}O_3NNa$ 268.0944, found 268.0944.

(*S*)-3-(Benzyloxy)-2,2-dimethylhex-4-en-1-ol (10)

To a stirred 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 (3*R*)-3-(benzyloxy)-4,4-dimethyltetrahydrofuran-2-ol **9** (ref. 8*c*) (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 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 × 3). Combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (5% ethyl acetate in hexanes) to afford (*S*)-3-(benzyloxy)-2,2-dimethylhex-4-en-1-ol **10** (3.2 g, 92%) as a colorless oil. $[\alpha]_D^{24}$ +28.9 (*c* 2.2, $CHCl_3$); IR ν_{max}(film): cm^{-1} 3446, 2961, 1668, 1496; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 5.75–5.61 (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), 3.58 (d, J = 9.2 Hz, 1H), 3.54 (dd, J = 10.8, 5.7 Hz, 1H), 3.37 (dd, J = 11.0, 5.0 Hz, 1H), 2.97 (t, J = 5.7 Hz, 1H), 1.80 (dd, J = 6.4, 1.4 Hz, 3H), 0.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 131.4, 128.4, 127.8, 127.7, 127.6, 88.1, 71.6, 70.0, 38.7, 22.7, 19.9, 17.8; MS: 257 $(M + Na)^+$; HRMS calculated for $C_{15}H_{22}O_2Na$ 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 **10** (2.5 g, 10.6 mmol) in DCM (12 mL) was added and stirred for 1 h. Triethylamine (8.9 mL, 64.1 mmol) was added and stirring was continued for 30 min. The reaction was quenched with water (30 mL) and extracted with DCM (50 mL × 3). Combined organic layers were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give (*S*)-3-(benzyloxy)-2,2-dimethylhex-4-enal (1.90 g, 77%) as a colorless oil. $[\alpha]_D^{24}$ +26.8 (*c* 1.1, $CHCl_3$); IR ν_{max}(film): cm^{-1} 2975, 1731, 1496, 1205; ^1H NMR (200 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.39–7.13 (m, 5H), 5.82–5.61 (m, 1H), 5.47–5.30 (m, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.27 (d, J = 12.1 Hz, 1H), 3.77 (d, J = 8.7 Hz, 1H), 1.79 (dd, J = 6.4, 1.5 Hz, 3H), 1.10 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 206.0, 138.4, 132.4, 128.3, 127.6, 127.5, 126.6, 83.8, 69.8, 49.9, 19.6, 17.9, 16.7. MS: 255 $(M + Na)^+$; HRMS calculated for $C_{15}H_{20}O_2Na$ 255.1356, found 255.1353.

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 (*S*)-3-(benzyloxy)-2,2-dimethylhex-4-enal (1.8 g, 7.7 mmol) in dry THF (30 mL) was added. After completion of addition, the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C, quenched by the addition of saturated ammonium chloride solution (25 mL) and extracted with ethyl acetate (50 mL × 3). Combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (5% ethyl acetate in hexanes) to give 1.3 g (65%) of ((((*S*)-1-methoxy-3,3-dimethylhepta-1,5-dien-4-yl)oxy)-methyl)benzene as a colorless oil.

To a solution of ((((*S*)-1-methoxy-3,3-dimethylhepta-1,5-dien-4-yl)oxy)methyl)benzene (1.3 g, 5.0 mmol) in acetone (30 mL), 2 N HCl (6.2 mL, 12.5 mmol) was added and then refluxed for 40 min. The reaction mixture was cooled to rt, water (20 mL) was added and extracted with ethyl acetate (50 mL × 2). The combined organics were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (5% ethyl acetate in hexanes) to afford 1.1 g (86%) of (*S*)-4-(benzyloxy)-3,3-dimethylhept-5-enal as a colorless oil. $[\alpha]_D^{24}$ +10.1 (*c* 0.7, $CHCl_3$); IR ν_{max}(film): cm^{-1} 2965, 1705, 1496, 1268; ^1H NMR (200 MHz, $CDCl_3$): δ 9.79 (t, J = 3.2 Hz, 1H), 7.44–7.19 (m, 5H), 5.75–5.55 (m, 1H), 5.49–5.26 (m, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.23 (dd, J = 11.8, 2.1 Hz, 1H), 3.41 (d, J = 8.5 Hz, 1H), 2.49–2.14 (m, 2H), 1.77 (dd, J = 6.3, 1.4 Hz, 3H), 1.14–0.96 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 138.7, 131.7, 128.3, 127.9, 127.8, 127.7, 127.4, 86.9, 70.0, 53.3, 38.4, 25.5, 23.5, 18.0; MS: 269 $(M + Na)^+$; HRMS calculated for $C_{16}H_{22}O_2Na$ 269.1512, found 269.1508.

(*S*)-(((5,5-Dimethyloct-2-en-7-yn-4-yl)oxy)methyl)benzene (+)-4

A solution of (*S*)-4-(benzyloxy)-3,3-dimethylhept-5-enal **11** (4 g, 16.2 mmol) and dimethyl-1-diazo-2-oxopropylphosphonate (6.24 g, 32.4 mmol) in MeOH (40 mL) was treated with anhydrous K_2CO_3 (4.5 g, 32.4 mmol) at rt and stirring was continued for 16 h. The mixture was diluted with diethyl ether (100 mL) and washed successively with saturated $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (2% ethyl acetate in hexanes) to furnish (*S*)-(((5,5-dimethyloct-2-en-7-yn-4-yl)oxy)methyl)-benzene **(+)-4** (3.0 g, 76%) as a colorless oil. $[\alpha]_D^{26}$ +6.2 (*c* 1.0, $CHCl_3$); IR ν_{max}(film): cm^{-1} 3307, 2961, 2359, 2130, 1590, 1473, 1065; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.28 (m, 4H), 7.26–7.24 (m, 1H), 5.72–5.60 (m, 1H), 5.44–5.33 (m, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.32–4.25 (m, 1H), 3.53 (d, J = 8.5 Hz, 1H), 2.34–2.24 (m, 1H), 2.21–2.11 (m, 1H), 1.97–1.89 (m, 1H), 1.76 (d, J = 6.4 Hz, 3H), 1.01(s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 130.7, 128.1, 127.6, 127.5, 127.2, 127.1, 85.7, 82.7, 70.1, 69.8, 37.6, 29.0, 23.5, 22.4, 17.9; MS: 265 $(M + Na)^+$; HRMS calculated for $C_{17}H_{22}ONa$ 265.1563, found 265.1561.

Dimethyl (*R*)-3-(benzyloxy)-2,2,6-trimethyl-2,3-dihydro-1*H*-indene-4,5-dicarboxylate (−)-7

The compound **(−)-7** (0.33 g, 42%) was synthesized from **(+)-4** by following a similar procedure mentioned for the synthesis of **7**. The NMR data were found to be identical with **7**; $[\alpha]_D^{25}$ −59.3 (*c* 1.7, $CHCl_3$).

(*R*)-8-(Benzyloxy)-4,7,7-trimethyl-7,8-dihydrocyclopenta-[*e*]isoindole-1,3(2*H*,6*H*)-dione (+)-8

The compound **(+)-8** (56 mg, 64%) was prepared from **(−)-7** by following a similar procedure mentioned for the synthesis of **8**. The NMR data were found to be identical with **8**; $[\alpha]_D^{25}$ +7.8 (*c* 0.2, $CHCl_3$).

(*R*)-8-Hydroxy-4,7,7-trimethyl-7,8-dihydrocyclopenta[*e*]-isoindole-1,3(2*H*, 6*H*)-dione (−)-1

The compound **(−)-1** (28 mg, 77%) was synthesized from **(+)-8** by following a similar procedure mentioned for the synthesis of **(±)-1**. The optical rotation of the synthesized **(−)-1** was found to be comparable but with opposite sign ($[\alpha]_D^{26}$ −21.4 (*c* 0.4, MeOH) *vs.* $[\alpha]_D^{25}$ +22.3 (*c* 0.4, MeOH)).

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