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Natural Product Synthesis

A Total Synthesis of (–)-Nardoaristolone B

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Abstract: A stereoselective total synthesis of (–)-Nardoaristolone B, a nor-aristolane sesquiterpenoid natural product with an unusual 3/5/6 tricyclic ring system is described. The highlights of the present work includes use of (+)-(*R*)-Pulegone as a chiral-pool starting material, ring-closing metathesis, allylic oxidation and stereoselective cyclopropanation. In addition, a new analogue of Nardoaristolone B (minor product from the final step) was isolated in pure form and fully characterized with the help of single-crystal X-ray analysis.

Introduction

Sesquiterpenoids are a class of terpenoids that consist of three isoprene units followed by biochemical modifications such as oxidation or rearrangement. Isolation of such a sesquiterpenoid natural product, Nardoaristolone B (**1**), was reported in 2013 by Yao and co-workers from the underground parts of the *Nardostachys chinensis* plant.[1a] The investigation of this particular plant suggests that it is a source of a series of natural products such as aristolane,[1b] nardosinane,[1c–1e] guaiane types,[1f,1g] lignans,[1h] sesquiterpenoids, debilon,[1i] and kanshone A.[1d] The roots and rhizomes of *Nardostachys chinensis* Batalin (*Valerianaceae* family) have been used as stomachic and sedative agents[2a] in Chinese traditional medicine for centuries.[2b] In addition, it exhibits antimalarial, antinociceptive,[1g] and cytotoxic activities[1i] and also helps to enhance the nerve growth factor.[2c] The natural product Nardoaristolone B isolated from the same species exhibits a protective activity on the injury of neonatal rat cardiomyocytes in a dose-dependent manner and is believed to be biogenetically derived from Kanshone C (**4**).[1a] This compound is also expected to have many interesting biological activities such as 5′-adenosine monophosphate activated protein kinase (AMPK) activation, insect repellent, and insecticidal activities due to its structural resemblance to that of Nootkatone (**5**).[2d–2h] In fact, in our hands, compound **1** in recemic form showed excellent mosquito-repellent activity against the *Aedes* mosquito, which is the vector for Dengue fever and the Zika virus.[3] Isolation of the closely related sesquiterpene (–)-Aristolone (**6**)[4] was reported in 1955 from the roots of *Aristochia debilis*, and its several syntheses were reported in the literature.[5] There are a few more natural products reported in the literature like Lindenene (**2**)[6] and Chloranthalactone A (**3**),[7] having a similar 3/5/6 structural core as Nardoar-

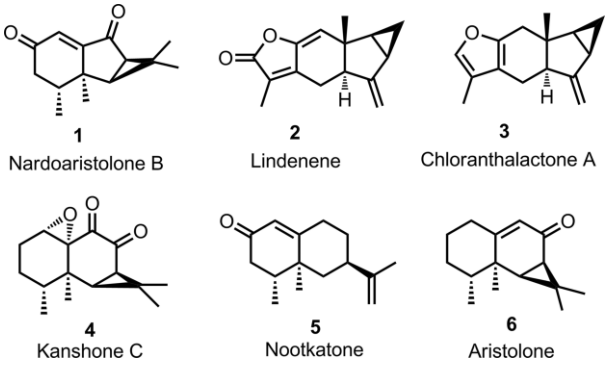

Figure 1. Structures of selected natural products.

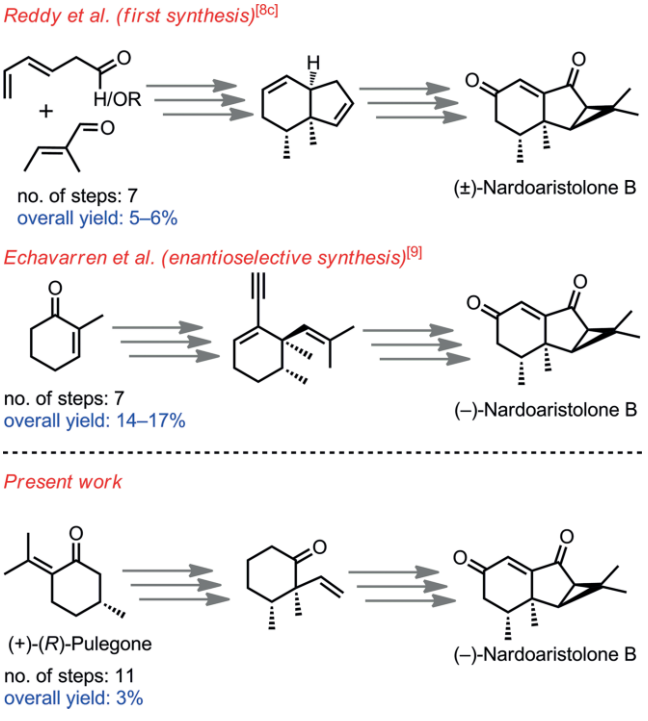

Figure 2. Previous and present synthetic approaches.

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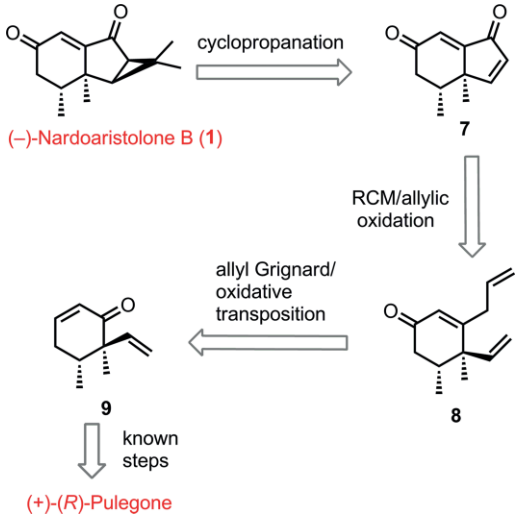
istolone B (Figure 1). Due to its potential biological activity, along with the unusual 3/5/6 tricyclic structural features, compound **1** has already attracted the attention of a few research groups including our own. The first total synthesis of Nardoaristolone B in racemic form was reported from our group in 2014.[8] The key features of this synthesis are a Diels–Alder/Wittig/ring closing metathesis (RCM) reaction sequence, double allylic oxidation, followed by stereoselective cyclopropanation.

Later, Echavarren's group documented an interesting enantioselective total synthesis of (–)-Nardoaristolone B using a highly selective copper(I)-catalyzed conjugate addition/enolate trapping sequence and a gold(I)-catalyzed oxidative cyclization[9] (Figure 2). Here we describe a stereoselective total synthesis of (–)-Nardoaristolone B using a chiral-pool approach starting from commercially available (+)-(*R*)-Pulegone.

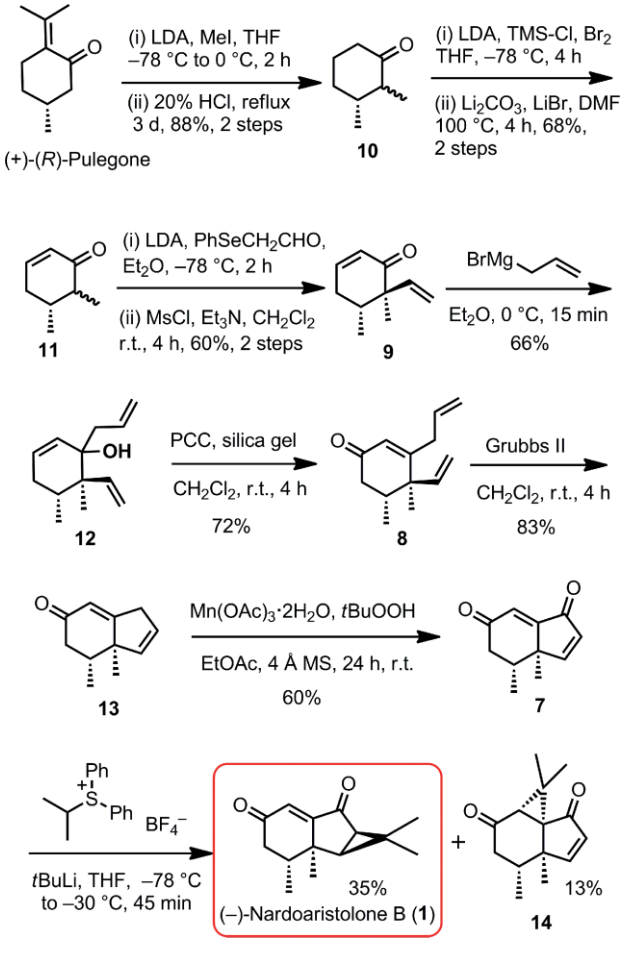
Results and Discussion

We envisioned the target molecule **1** by a stereoselective cyclopropanation of dienone **7** as planned in our racemic synthesis. The dienone **7** could be prepared from trienone **8** by RCM followed by allylic oxidation. A sequence of introducing allyl groups followed by oxidative transposition on compound **9** would afford **8**, which in turn could be constructed using known methods from a commercially available starting material (+)-(*R*)-Pulegone (Scheme 1).



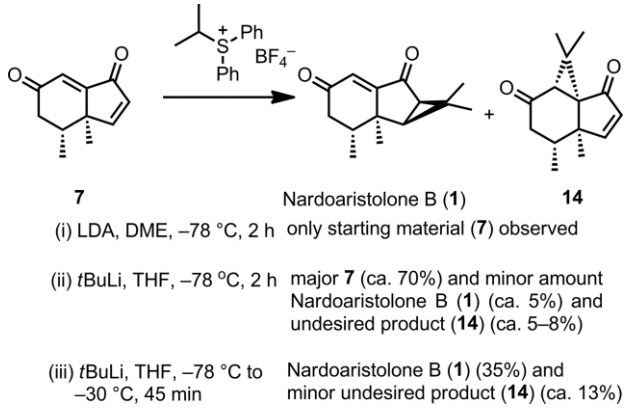
Scheme 1. Retrosynthetic analysis of (–)-Nardoaristolone B.

Our synthetic route commenced with the preparation of the known intermediate **9**[10a] by applying literature procedures starting from (+)-(*R*)-Pulegone.[10,11] The reaction of (+)-(*R*)-Pulegone with LDA and MeI at –78 °C followed by retro-aldol reaction in 20 % HCl under reflux conditions for 3 d gave 2,3-dimethylcyclohexanone (**10**) in 88 % yield as a mixture of diastereomers.[11] 2,3-Dimethylcyclohexanone (**10**) on TMS enolate formation followed by a bromination/elimination sequence gave 2,3-dimethyl-2-cyclohexenone (**11**) with 68 % yield over two steps. The quaternary stereocenter was then installed by insertion of a vinyl group at the α-position of 2,3-dimethyl-2-cyclohexenone (**11**) with phenylselenoacetaldehyde using an aldol reaction, converting the OH group into an OMs group, and elimination using MsCl/triethylamine reaction conditions to give compound **9** in 60 % yield.[10] This reaction sequence proceeded with complete diastereoselectivity, efficiently installed the vinyl group, and no olefin isomerization to the conjugated enone was observed. Grignard reaction of allyl magnesium bromide with enone **9** furnished the tertiary alcohol **12** in 66 % yield.[12] Although we observed excellent diastereoselectivity, we did not attempt to establish the stereochemistry of the new center as it would be destroyed in the next step. The tertiary alcohol **12** was then oxidized with PCC to afford compound **8** in 72 % yield with the desired transposition.[12] Compound **8** on ring closing metathesis using Grubbs' second-generation catalyst resulted in hydrindane derivative **13** in 83 % yield. The next major task was to introduce the oxygen functionality on the five-membered ring; we tested a few conditions to achieve the desired allylic oxidation product. When we tried the allylic oxidation of **13** using PDC/*t*BuOOH[8a] and $NaClO_2$/*t*BuOOH[8b] conditions, we could not isolate clean compound **7** and always obtained a mixture of compounds, which are probably resulting from the isomerization of the double bond. However, after a few attempts, the allylic oxidation of compound **13** was successful with a combination of $Mn(OAc)_3{\cdot}2H_2O$/*t*BuOOH[13] resulting in the desired dienone **7** in 60 % yield.[8c] Compound **7** was previously synthesized in racemic form in our group, and



Scheme 2. Total synthesis of (–)-Nardoaristolone B.

the spectral data was matching. Finally, the *gem*-dimethylcyclopropyl group was installed[14] on compound **7** by treatment of isopropyldiphenylsulfonium tetrafluoroborate[15] with *t*BuLi in THF at –78 °C to –30 °C to furnish the target compound (–)-Nardoaristolone B (**1**) in 35 % yield and compound **14** with an *exo*-cyclopropyl ring in 13 % yield (Scheme 2).[8c] To improve the yield in the final steps, we attempted a few other conditions, but the results were inferior. The three different conditions tried for the cyclopropanation are captured in Scheme 3.



Scheme 3. Optimization conditions for the cyclopropanation.

All the spectral data (IR, ^{1}H NMR, ^{13}C NMR and HRMS) were found to be identical to those of the earlier reports, and the optical rotation of synthetic Nardoaristolone B was measured at $[\alpha]_D^{26}$ = –7.8 (*c* = 0.5, CH_3OH) with the reported value being at $[\alpha]_D^{26}$ = –7.4 (*c* = 0.5, CH_3OH).[1,8c,9] Since we had racemic Nardoaristolone B in hand from a previous synthesis, we were also able to determine the enantiomeric purity of synthesized (–)-Nardoaristolone B using chiral HPLC,[16] and it was found to be > 99 %. Thus, we have accomplished the stereoselective and protecting-group-free total synthesis of (–)-Nardoaristolone B (**1**) in eleven steps and 3 % overall yield. We have also isolated a minor product (**14**) from the same reaction and characterized it as a novel analogue of the natural product Nardoaristolone B. The assigned *exo* stereochemistry of the cyclopropane ring in compound **14** was confirmed unambiguously by its single-crystal X-ray analysis (Figure 3). Although our synthesis is not the best one and inferior to Echavarren's synthesis, our route can be an alternative to prepare the target and related compounds using chiral-pool starting materials.

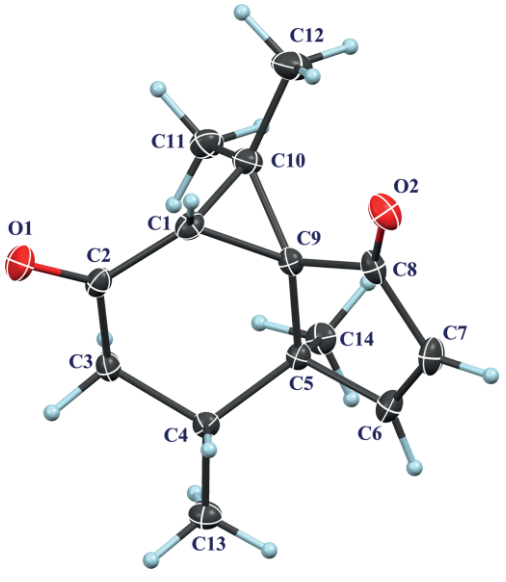


Figure 3. Crystal structure of compound **14**.

Conclusions

We have achieved a stereoselective total synthesis of natural product (–)-Nardoaristolone B from the commercially available monoterpene (+)-(*R*)-Pulegone. Having access to enantiopure natural product (–)-Nardoaristolone B and its analogue compound **14**, it is now possible to evaluate their biological activities.

Experimental Section

General: All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen, unless otherwise mentioned, with magnetic stirring. Air-sensitive reagents and solutions were transferred by syringe or cannula and were introduced to the apparatus through rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-dinitrophenylhydrazine (2,4-DNP), and $KMnO_4$ solution followed by heating with a heat gun for ca. 15 s. Column chromatography was performed on silica gel (100–200 or 230–400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, or 500 MHz spectrometer. Coupling constants are given in Hertz. All chemical shifts are quoted in ppm, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, td = triplet of doublets, dq = doublet of quartets, ddt = doublet of doublets of triplets, m = multiplet. HRMS (ESI) data were recordedwith an ORBITRAP mass analyser (Q Exactive). Mass spectra were measured with ESI ionization using an MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded with an FT-IR spectrometer as a thin film. Chemical nomenclature was generated using ChemBioDraw-Ultra 13.0. HPLC analysis was performed with a Shimadzu Class-VP SP5 instrument with Shimadzu SPD-10-AVP UV detector. Melting points of solids were measured with a Büchi B-545 melting-point apparatus.

(1*R*,5*R*,6*S*)-1-Allyl-5,6-dimethyl-6-vinylcyclohex-2-en-1-ol (12): To a solution of compound **9** (1.6 g, 10.65 mmol) in dry diethyl ether (60 mL) was added allyl magnesium bromide (1 M solution in diethyl ether, 21.3 mL, 21.31 mmol) dropwise at 0 °C, and the mixture was stirred for 15 min. The reaction was then quenched with saturated aqueous NH_4Cl (15 mL) and the mixture extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on silica gel (diethyl ether/petroleum ether, 1:9) afforded enol **12** (1.35 g, 66 %) as light yellow oil. $[\alpha]_D^{29}$ = –18.05 (*c* = 1.8, $CHCl_3$).

IR (film): $\tilde{\nu}_{max}$ = 3074, 1636, 1217 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.04–5.76 (m, 2 H), 5.70–5.61 (m, 1 H), 5.52–5.45 (m, 1 H), 5.23 (dd, *J* = 10.8, 1.64 Hz, 1 H), 5.19–5.10 (m, 2 H), 5.07–5.00 (m, 1 H), 2.37 (ddd, *J* = 13.6, 9.6, 7.6 Hz, 2 H), 2.18–1.98 (m, 2 H), 1.80–1.69 (m, 1 H), 0.97 (s, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 134.9, 132.3, 126.5, 117.9, 115.4, 76.1, 46.7, 44.9, 33.5, 31.7, 16.7, 10.6 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}O$ $[M - H]^-$ 191.1430, found 191.1428.

(4*S*,5*R*)-3-Allyl-4,5-dimethyl-4-vinylcyclohex-2-en-1-one (8): To a magnetically stirred solution of enol **12** (1.35 g, 7.02 mmol) in anhydrous CH_2Cl_2 (80 mL) was added a homogenous mixture of PCC (7.57 g, 35.12 mmol) and silica gel (7.57 g), and reaction mixture was stirred at room temperature for 8 h. The reaction mixture was then filtered through a small pad of silica gel using ethyl acetate (50 mL) as eluent. Evaporation of the solvent and purification of the residue on a 100–200 silica gel column (ethyl acetate/petroleum ether, 1.5:8.5 as eluent) furnished the enone **8** (962 mg, 72 %) as colorless oil. $[\alpha]_D^{29}$ = –7.23 (*c* = 0.65, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2970, 1671, 1416, 1352, 1281 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.91 (s, 1 H), 5.73 (ddt, *J* = 16.8, 9.9, 6.8 Hz, 1 H), 5.65 (dd, *J* = 17.5, 10.7 Hz, 1 H), 5.28 (d, *J* = 10.7 Hz, 1 H), 5.14–5.10 (m, 2 H), 5.06 (dq, *J* = 17.2, 1.5 Hz, 1 H), 2.85 (td, *J* = 6.9, 1.1 Hz, 2 H), 2.43 (dd, *J* = 17.2, 4.6 Hz, 1 H), 2.24 (dd, *J* = 17.2, 11.8 Hz,1 H), 2.12–2.08 (m, 1 H), 1.15 (s, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.2, 168.6, 143.1, 134.5, 126.6, 118.3, 115.8, 46.4, 41.8, 38.0, 37.7, 16.0, 15.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}ONa$ $[M + Na]^+$ 213.1250, found 213.1248.

(7*R*,7a*R*)-7,7a-Dimethyl-3,6,7,7a-tetrahydro-5*H*-inden-5-one (13): Grubbs' second-generation catalyst (215 mg, 5 mol-%) was added to a magnetically stirred solution of **8** (962 mg, 5.06 mmol) in anhydrous CH_2Cl_2 (80 mL), and the mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel 100–200; ethyl acetate/petroleum ether, 1.2:8.8) to afford **13** (680 mg, 83 %) as colorless oil. $[\alpha]_D^{29}$ = +10.7 (*c* = 0.25, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2929, 2358, 1654, 1454, 1262 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.90 (d, *J* = 5.9 Hz, 1 H), 5.83 (s, 1 H), 5.80–5.79 (m, 1 H), 3.43–3.37 (m, 1 H), 3.09–3.04 (m, 1 H), 2.31–2.27 (m, 2 H), 2.12–2.06 (m, 1 H), 1.05 (s, 3 H), 1.04 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 176.6, 137.8, 126.5, 121.6, 50.9, 42.2, 38.0, 37.8, 17.2, 16.2 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}O$ $[M + H]^+$ 163.1117, found 163.1116.

(3a*R*,4*R*)-3a,4-Dimethyl-4,5-diydro-1*H*-indene-1,6(3a*H*)-dione (7): To a solution of compound **13** (680 mg, 4.19 mmol) in EtOAc (60 mL) were added 4 Å molecular sieves (1.36 g) and *t*BuOOH (5.0 M in decane, 4.2 mL, 20.9 mmol) at room temperature. The reaction mixture was stirred for 30 min before $Mn(OAc)_3 \cdot 2H_2O$ (561 mg, 2.09 mmol) was added at room temperature. The resulting mixture was stirred under nitrogen for 24 h before it was filtered through Celite, eluted with EtOAc (20 mL), and concentrated in vacuo. The crude material obtained after removal of the solvent was purified by column chromatography (silica gel 100–200, ethyl acetate/petroleum ether, 2:8) to afford **7** (443 mg, 60 %) as yellow solid. $[\alpha]_D^{29}$ = –22.7 (*c* = 2.25, $CHCl_3$). M.p. 74–76 °C. IR (film): $\tilde{\nu}_{max}$ = 2926, 2361, 1703, 1650, 1456, 1375, 1217 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 6.1 Hz, 1 H), 6.37 (d, *J* = 6.1 Hz, 1 H), 6.29 (s, 1 H), 2.56–2.48 (m, 2 H), 2.29–2.23 (m, 1 H), 1.24 (s, 3 H), 1.14 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 195.8, 165.0, 160.4, 133.7, 121.9, 46.6, 42.9, 36.3, 18.5, 15.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}O_2$ $[M + H]^+$ 177.0910, found 177.0909.

(1a*S*,1b*R*,2*R*,6a*R*)-1,1,1b,2-Tetramethyl-1,1a,1b,2,3,6a-hexahydrocyclopropa[*a*]indene-4,6-dione, (–)-Nardoaristolone B (1): A 1.9 M solution of *t*BuLi in pentane (0.45 mL, 0.852 mmol) was added dropwise to a suspension of isopropyldiphenylsulfonium tetrafluoroborate (296 mg, 0.937 mmol) in THF (4 mL) at –78 °C. After 30 min, **7** (50 mg, 0.284 mmol) was added as a solution in THF (2 mL) at –78 °C. The resulting mixture was maintained at –30 °C for 15 min, quenched with saturated aqueous NH_4Cl (2 mL), and warmed to room temperature. The reaction mixture was then extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (silica gel 100–200, ethyl acetate/petroleum ether, 1.5:8.5) afforded (–)-Nardoaristolone B (**1**) (21 mg, 35 %) and **14** (12 mg, 13 %) as yellow solid. The *ee* of (–)-Nardoaristolone B (**1**) was determined by chiral HPLC as 99.52 %. $[\alpha]_D^{26}$ = –7.8 (*c* = 0.5, CH_3OH). M.p. 95–96 °C; IR (film): $\tilde{\nu}_{max}$ = 2923, 2852, 2360, 1713, 1460, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.18 (s, 1 H), 2.41–2.22 (m, 3 H), 1.94 (d, *J* = 5.5 Hz, 1 H), 1.77 (d, *J* = 5.5 Hz, 1 H), 1.17 (s, 3 H), 1.12 (s, 3 H), 1.08 (s, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 200.0, 165.1, 123.5, 44.3, 42.3, 42.2, 40.3, 35.5, 32.1, 28.8, 20.8, 17.8, 15.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}O_2$ $[M + H]^+$ 219.1380, found 219.1379.

(1a*S*,4*R*,4a*R*,7a*R*)-1,1,4,4a-Tetramethyl-1,1a,4,4a-tetrahydro-2*H*-cyclopropa[*d*]indene-2,7(3,H)-dione (14): M.p. 105–107 °C. $[\alpha]_D^{26}$ = –1.11 (*c* = 0.125, CH_3OH). IR (film): $\tilde{\nu}_{max}$ = 2964, 2879, 1692, 1455, 1374, 1236, 1181 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 6.1 Hz, 1 H), 6.23 (d, *J* = 6.1 Hz, 1 H), 2.22–2.16 (m, 3 H), 1.93–1.87 (m, 1 H), 1.50 (s, 3 H), 1.41 (s, 3 H), 1.29 (s, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 205.5, 169.2, 131.6, 51.9, 48.3, 46.4, 45.3, 40.1, 36.6, 21.7, 21.3, 17.6, 15.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}O_2$ $[M + H]^+$ 219.1380, found 219.1379.

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Keywords: Natural products · Total synthesis · Chiral pool · Nardoaristolone B · Cyclopropanation

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[16] HPLC column: Chiralpack-AD-H (250 × 4.6 cm), mobile phase: isopropyl alcohol/*n*-hexane (10:90), flow rate: 1.0 mL/min, 490 psi, wavelength: 254 nm, inject vol.: 5 µL, t_R(major) = 8.5–8.6 min, t_R(minor) = 12.5–12.6 min, 99.52 % *ee*.

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Natural Product Synthesis

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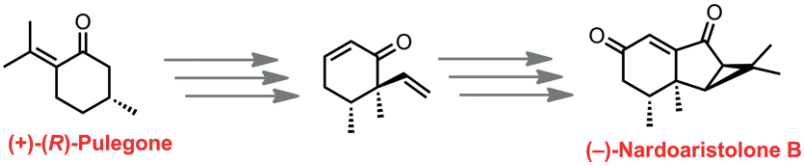
A Total Synthesis of (–)-Nardoaristolone B



A stereoselective total synthesis of (–)-Nardoaristolone B, a nor-aristolane sesquiterpenoid natural product with an unusual 3/5/6 tricyclic ring system is described. Use of (+)-(*R*)-Pulegone as a chiral-pool starting material, ring closing metathesis and stereoselective cyclopropanation are the highlights.

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