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A nature-inspired concise synthesis of (+)-*ent*-chromazonarol

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A large number of sesquiterpene quinone/hydroquinone natural products including (+)-*ent*-chromazonarol have been isolated and received great attention from the synthetic community. Herein, we report a nature-inspired concise synthesis of (+)-*ent*-chromazonarol in 4 steps from a readily available starting material. The synthesis relied on a Lewis acid mediated cyclization which correctly installed two vicinal stereocenters in one step. This highly efficient synthetic route allows us to further prepare natural product congeners for further biological studies.

sesquiterpene, hydroquinone, total synthesis, chromazonarol

1 Introduction

A large number of sesquiterpene quinones/hydroquinones [1] with a normal drimane (**1**) skeleton (Figure 1) or a rearranged drimane skeleton have been isolated and received great attention from the synthetic community due to their abundance of structural diversities (compounds **2–10**) as well as a wide range of attractive biological activities [2], including antitumor [3], anti-HIV [4], anti-inflammation [5], and anti-microbial activities [6]. Within this family of natural products, (+)-*ent*-chromazonarol (**7**) and its natural congeners have the most challenging tetracyclic chemical structures. (+)-*ent*-Chromazonarol (**7**) was isolated from marine sponge *dysidea pallescens* [7], and its epimer, 8-*epi*-chromazonarol (**8**) was isolated from *smenospongia aurea* and *smenospongia echina* [8]. In addition, two closely related natural products (−)-chromazonarol (**9**) and isochromazonarol (**10**) were also isolated from marine sponge [9] and algae [10], respectively.

The striking chemical structure and promising antitumor activity of chromazonarol have prompted a number of remarkable synthetic studies [3a, 11]. In 2004, Yamamoto and co-workers [11b] reported an elegant synthesis of (−)-chromazonarol (**9**) through a biomimetic cyclization of polyprenoid using Lewis acid-assisted chiral Brønsted acid. Very recently, Baran and co-workers [11e] reported an efficient synthesis of (+)-*ent*-chromazonarol (**7**) through a versatile borono-sclareolide intermediate.

Biosynthetically, the generation of (+)-*ent*-chromazonarol (**7**) presumably involves a stereoselective cyclization of polyene (**12**) derived from the coupling between farnesyl pyrophosphate (**11**) and hydroquinone, to generate the tertiary carbocation (**13**). This carbocation intermediate could then undergo a cyclization to afford (+)-*ent*-chromazonarol (Scheme 1) [12]. Inspired by this biosynthetic pathway, we envisioned that alkene **14** might be a desired synthon to generate the required carbocation intermediate for the final cyclization. Herein, we report a highly concise synthesis of (+)-*ent*-chromazonarol based on this nature-inspired synthetic strategy.

2 Experimentals

2.1 General

Unless otherwise noted, all reagents were used as supplied by Sigma-Aldrich, J&K and Alfa Aesar Chemicals. CH_2Cl_2

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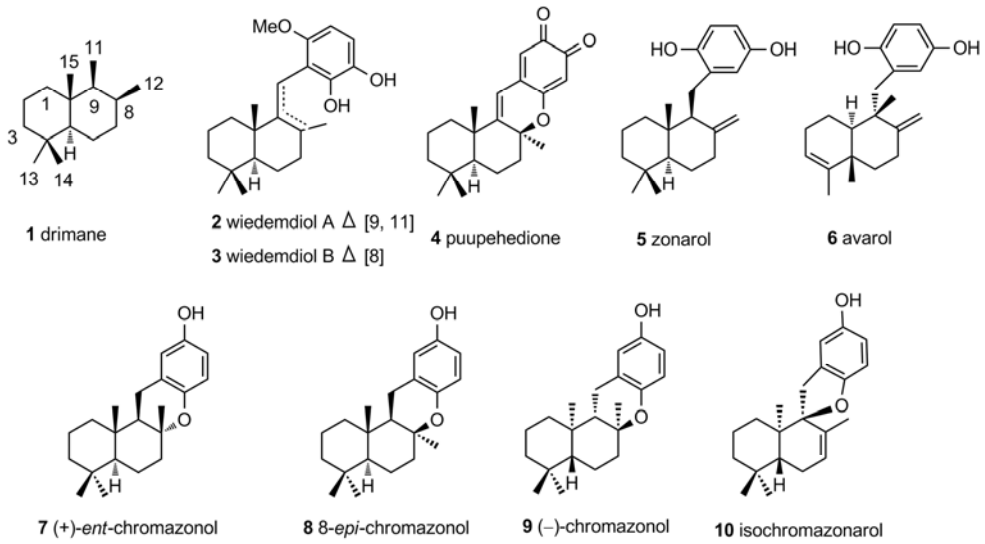
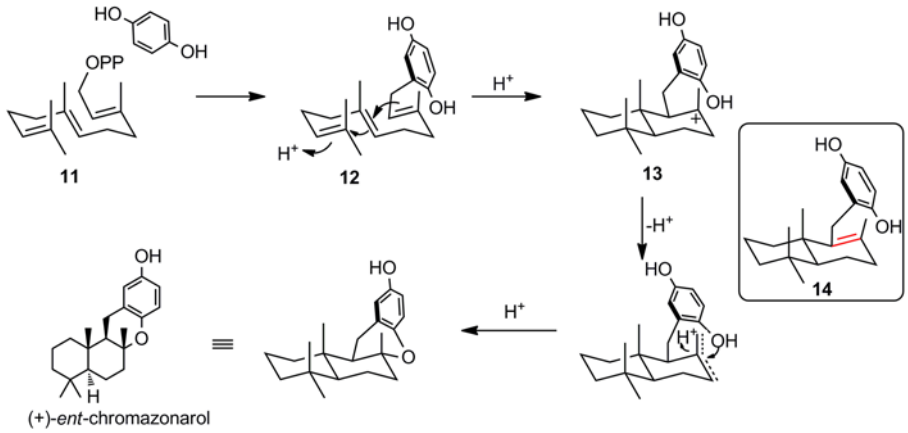


Figure 1 Drimane and the representative members of the sesquiterpene quinone/hydroquinone natural products.



Scheme 1 Proposed biosynthesis of chromazonarol.

was distilled from calcium hydride, THF and Et_2O were distilled from sodium/benzophenone ketyl prior to use. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a Varian 100 MHz spectrometer (with complete proton decoupling) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.26; ^{13}C, δ 77.00). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Infrared spectra were recorded on a Thermo Fisher FT-IR200 spectrophotometer. High-resolution mass spectra were obtained at Peking University Mass Spectrometry Laboratory using a Bruker APEX Flash chromatography.

2.2 Synthesis of compound 18

To a solution of **16** (126 mg, 0.57 mmol) in Et_2O (2 mL) at −78 °C was added *t*-BuLi (1.7 M in pentene, 0.87 mL, 1.14 mmol) dropwise. The reaction was stirred at −78 °C for 30 min and a solution of aldehyde **15** (210 mg, 0.93 mmol) in anhydrous Et_2O (2 mL) was added dropwise. The resultant mixture was stirred at −78 °C for 30 min, then allowed to warm to room temperature. The mixture was quenched with saturated NH_4Cl solution (15 mL) and extracted with Et_2O (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:PE = 1:50) to afford alcohol **17** (314mg) as a mixture of two dia-

stereomers, which was directly used for the next step.

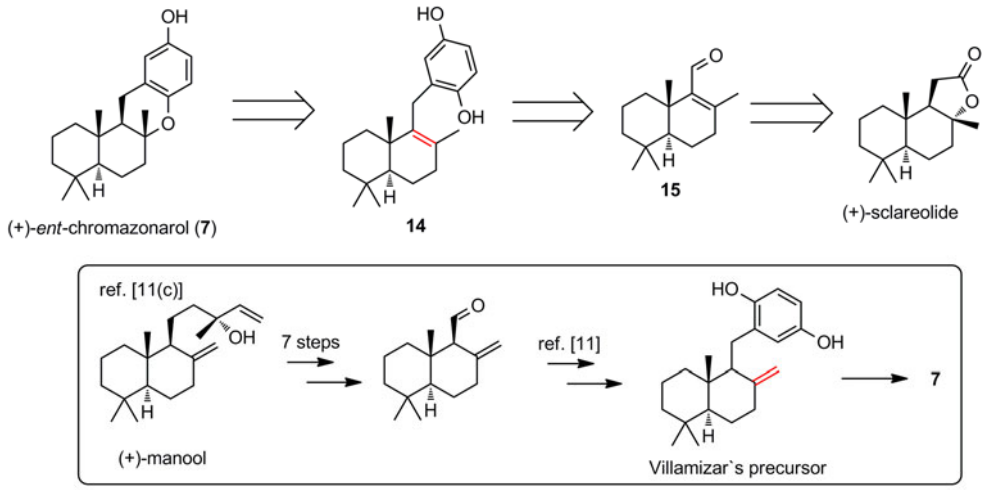
To a stirred mixture of liquid NH_3 (20 mL) and anhydrous THF (10 mL) at −78 °C was added Li (39 mg, 5.6 mmol). After stirred for 15 min, a solution of **17** (314 mg, crude from previous step) in THF (5 mL) was added. The resulting solution was stirred at −78 °C for 15 min, then quenched with solid NH_4Cl (1.00 g) and the NH_3 was allowed to evaporate by warming to room temperature. The resultant mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography using PE to afford **18** as a colorless oil (230 mg, 75% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.19 (s, 6H), 0.84 (s, 3H), 0.90 (s, 3H), 0.95 (s, 9H), 0.99 (s, 3H), 1.02 (s, 9H), 1.04–1.11 (m, 1H), 1.23–1.36 (m, 4H), 1.49 (s, 3H), 1.45–1.56 (m, 4H), 1.71–1.76 (m, 1H), 2.05–2.22 (m, 2H), 3.17 (d, J = 17.6 Hz, 1H), 3.32 (d, J = 17.6 Hz, 1H), 6.49–6.55 (m, 2H), 6.61 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.28, −4.26, −4.14, −4.11, 18.3, 18.3, 18.8, 19.2, 20.1, 20.3, 21.6, 25.8, 25.9, 27.6, 33.3, 33.5, 35.8, 38.8, 41.7, 52.0, 117.1, 118.7, 120.1, 128.6, 132.5, 137.7, 147.3, 149.4; HRMS (ESI) [M+H$^+$] calculated for $C_{33}H_{59}O_2Si_2$: 543.4048, found: 543.4051; IR (neat) ν_{max}: 2928, 1487, 1251, 1203, 837, 777 cm^{-1}; $[\alpha]_D^{21}$ +72.4 (c 0.49, $CHCl_3$).

2.3 Synthesis of compound 14

To a solution of **18** (43 mg, 0.08 mmol) in THF (1.5 mL) was added TBAF (1 M in THF, 0.17 mL, 0.17 mmol) at 0 °C. The reaction was stirred at 0 °C for 20 min, then quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:PE = 1:5) to afford **14** as a white solid (21 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.85–0.88 (m, 1H), 0.90 (s, 3H), 0.99 (s, 3H), 0.93–1.10 (m, 1H), 1.05–1.14 (m, 1H), 1.21 (d, J = 2.4 Hz, 1H), 1.25 (t, J = 3.6 Hz, 1H), 1.28–1.37 (m, 1H), 1.55 (s, 3H), 1.45–1.60 (m, 2H), 1.70–1.75 (m, 1H), 2.05–2.22 (m, 2H), 3.31 (q, J = 17.2, 7.6 Hz, 2H), 4.70 (s, 1H, OH), 5.07 (s, 1H, OH), 6.51–6.55 (m, 2H), 6.62–6.64 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 18.8, 19.0, 20.2, 20.2, 21.7, 27.8, 33.2, 33.3, 33.5, 36.1, 39.0, 41.5, 51.7, 112.8, 115.8, 116.1, 128.2, 130.0, 137.2, 147.7, 149.1; HRMS (ESI) [M$^+$] calculated for $C_{21}H_{30}O_2$: 314.2240, found: 314.2242; IR (neat) ν_{max}: 3311, 2925, 2358, 1186 cm^{-1}; $[\alpha]_D^{22}$ +103.0 (c 0.5, MeOH).

2.4 Synthesis of (+)-*ent*-chromazonarol (7)

To a solution of **14** (31 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) at −20 °C was added $BF_3{\cdot}Et_2O$ (0.06 mL, 0.5 mmol). The reaction mixture was stirred at −20 °C for 2 h, and then quenched with saturated NH_4Cl solution. The mixture was then extracted with CH_2Cl_2 (15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (EtOAc:PE = 1:7) to afford (+)-*ent*-chromazonarol (**7**) as a white solid (30 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.87 (s, 3H), 0.90 (s, 3H), 0.93–0.98 (m, 1H), 1.02 (dd, J = 12.4, 2.4 Hz, 1H), 1.13–1.20 (m, 1H), 1.17 (s, 3H), 1.25–1.49 (m, 3H), 1.61–1.62 (m, 1H), 1.63–1.70 (m, 3H), 1.72–1.78 (m, 1H), 2.04 (dt, J = 12.4, 2.8 Hz, 1H), 2.56–2.58 (m, 2H), 4.55 (s, 1H, OH), 6.55–6.58 (m, 2H), 6.62 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 18.5, 19.7, 20.6, 21.6, 22.5, 33.1, 33.4, 36.7, 39.1, 41.1, 41.8, 52.0, 56.1, 76.7, 114.2, 115.8, 117.5, 123.3, 147.0, 148.5; HRMS (ESI) [M$^+$] calculated for $C_{21}H_{30}O_2$: 314.2240, found: 314.2241; IR (neat) ν_{max}: 3372, 2926, 2359, 1493 cm^{-1}; $[\alpha]_D^{23}$ +42.0 (c 1.0, $CHCl_3$).



Scheme 2 Retrosynthetic plan for (+)-*ent*-chromazonarol (**7**).

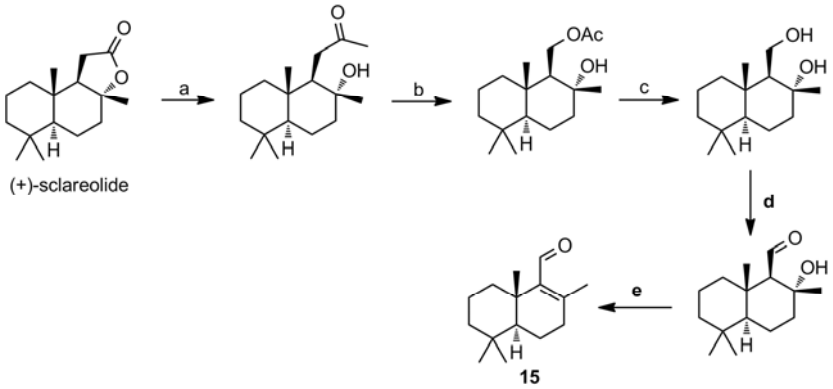
3 Results and discussion

Accordingly, our retrosynthetic analysis is shown in Scheme 2. (+)-*ent*-Chromazonarol (**7**) might be derived from the aforementioned intermediate **14**. Compound **14** should be generated from aldehyde **15** through a similar synthetic route reported previously by Villamizar and coworkers [11c]. However, we envisioned that aldehyde **15** could be prepared more efficiently from the commercially available (+)-sclareolide rather than the previously used (+)-manool.

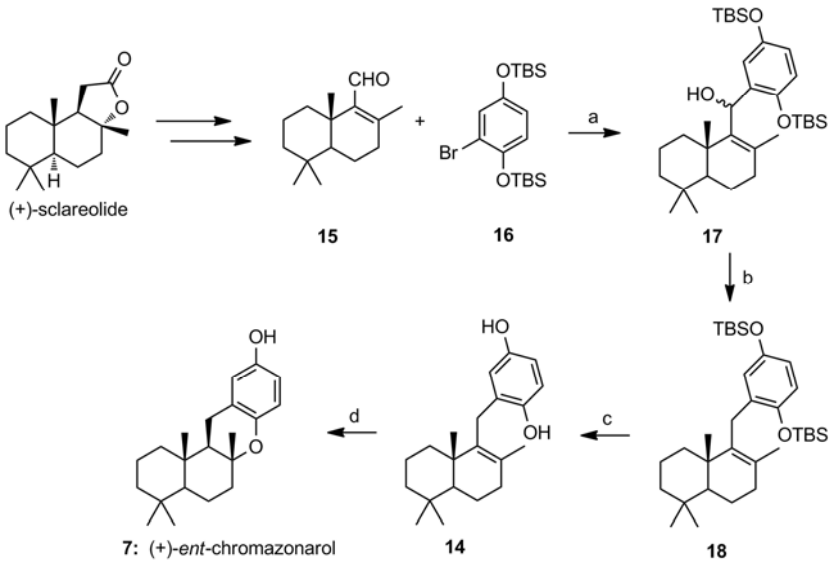
Our synthesis commenced with the readily available α,β-unsaturated aldehyde **15** which were efficiently prepared from the commercially available (+)-sclareolide [13]. A brief summary of this synthetic route is shown in Scheme 3.

1, 2-Addition of aldehyde **15** with an aryllithium species derived from aryl bromide **16** [14] afforded the secondary alcohol **17** as a mixture of two diastereomers (Scheme 4). Deoxygenation of **17** under a reductive condition (Li/NH_3) provided **18** in 75% yield over two steps. Deprotection of TBS group with TBAF afforded compound **14** in good yield. Finally, the cyclization of compound **14** was smoothly promoted upon the treatment of $BF_3 \cdot Et_2O$ at −20 °C to furnish the desired natural product (+)-*ent*-chromazonarol (**7**) in 95% yield as a single diastereomer. Comparing to the previous work reported by Villamizar *et al*. using an *exo*-methylene precursor for the final cyclization (Scheme 2) [11c], our synthesis using the *tetra*-substituted alkene **14** proved to be more efficient to install the two vicinal stereogenic centers with desired stereochemistry.

The physical and spectroscopic data of synthetic (+)-*ent*-chromazonarol (**7**) were identical with those previously reported [3a, 8, 11c, 11e], and the relative stereochemistry of **7** was further confirmed by NOESY experiment (Figure 2) [15].



Scheme 3 Efficient synthesis of aldehyde **15** from (+)-sclareolide. Reagents and conditions: a) CH_3Li, Et_2O, r.t., 15 min, 63%; b) maleic anhydride, $(CH_3CO)_2O$, 50% H_2O_2, CH_2Cl_2, H_2O, 26 h, 72%; c) KOH, MeOH, 10 min, quant; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78–0 °C, 1.5 h, 90%; e) *p*-toluenesulfonic acid cat., toluene, reflux, 2 h, 75%.



Scheme 4 Synthesis of (+)-*ent*-chromazonarol. Reagents and conditions: a) *t*-BuLi, Et_2O, −78 °C to r.t., 1 h; b) Li, liq. NH_3, THF, −78 °C, 10 min; 75% two steps; c) TBAF, THF, 0 °C, 20 min, 87%; d) $BF_3 \cdot Et_2O$, CH_2Cl_2, −20 °C, 2 h, 95%.

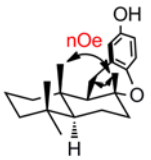


Figure 2 Relative stereochemistry of (+)-*ent*-chromazonarol (**7**) determined by NOESY experiment.

4 Conclusion

In summary, a highly concise synthesis of (+)-*ent*-chromazonarol has been accomplished from a readily available starting material in 4 steps with 62% yield. The synthesis relies on a nature-inspired strategy to construct the tetracyclic skeleton. Further biological evaluations of chromazonarol and its congeners are in progress and will be reported in due course.

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15 For details, see Supporting Information