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Synthesis of 8-Hydroxygeraniol

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Abstract

An operationally simple protocol for the conversion of geranyl acetate to 8-hydroxygeraniol is reported. The convenient two-step procedure relies on an efficient, chemo- and regioselective SeO₂-promoted oxidation, followed by straightforward deacetylation. This facile means to prepare 8-hydroxygeraniol is expected to enable biosynthetic studies pertaining to thousands of monoterpene indole alkaloids.

Graphical Abstract

Monoterpene indole alkaloids (MIAs) have provided chemists and biologists with the inspiration to pursue countless scientific endeavors.^{1–4} To date, over 3000 MIAs have been discovered, many of which possess striking biological activity. Select examples of MIAs are the notorious poison strychnine (**1**) and the life-changing anticancer drug vinblastine (**2**), both of which are shown in Figure 1. All MIAs are prepared by nature through a remarkable biosynthetic pathway, which has been under investigation for decades.^{1,5–11}

This Note focuses on 8-hydroxygeraniol (**3**, Figure 1), an early biosynthetic precursor to MIAs. 8-Hydroxygeraniol (**3**) is made biosynthetically through a controlled enzymatic oxidation of geraniol⁶ before being elaborated to nepetalactol (**4**).¹² Many further biosynthetic manipulations ultimately give rise to strictosidine (**5**), the last common biosynthetic precursor to all MIAs. Given the relative simplicity of **3** compared to its successors in the biosynthetic pathway (e.g., **5**), **3** has been used to enable several biosynthetic studies, including the biosynthesis of nepetalactol (**4**)^{13,14} and the biosynthesis of strictosidine (**5**).¹⁵

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01544.

¹H NMR and ¹³C NMR spectra for compounds **12** and **3** (PDF)

The authors declare no competing financial interest.

Several synthetic approaches to 8-hydroxygeraniol (**3**) have been reported in the literature (Figure 2). The earliest reports appeared back-to-back in 1970, where multistep synthetic routes were developed beginning from either levulinaldehyde (**6**)¹⁶ or dehydrolinalool (**7**).¹⁷ An alternative strategy was reported by Williams and Lin, which involved photocycloaddition of **8** and **9**, with subsequent elaboration using a thermolysis/Cope rearrangement strategy.¹⁸ Perhaps the most direct approach relies on the use of geranyl acetate (**10**) as the starting material. In this regard, Kobayashi has reported a procedure for the C8-oxidation of **10** using stoichiometric SeO₂, which proceeds in low yields and with extensive overoxidation to the corresponding enal.¹⁹ Around the same time, Sharpless reported a similar protocol that relies on catalytic SeO₂ and stoichiometric t-butyl hydroperoxide.²⁰ This procedure, which has subsequently been repeated with similar results,²¹ leads to a significant recovery of the starting material²⁰ with some minimization of the overoxidation byproduct (i.e., 45% yield of the desired alcohol and 19% enal²¹). A promising biocatalytic approach to 8-hydroxygeraniol using a cytochrome P450 has also been described,²¹ although it has yet to be rendered practical for material throughput.

One further point regarding 8-hydroxygeraniol (**3**) and its naming should be noted. Throughout the aforementioned literature and other sources, the compound is often referred to as “10-hydroxygeraniol” instead (Figure 3).^{6,7,12,13,16–19} We believe this is a simple nomenclature error that has propagated for many decades. Similarly, 8-oxogeraniol (**11**), the biosynthetic successor to 8-hydroxygeraniol (**3**), has been referred to as “10-oxogeraniol.”^{7,12,22} From a nomenclature standpoint, this is also incorrect. We suggest the chemical and biosynthetic community use the “8-” prefix going forward for 8-hydroxygeraniol to minimize confusion, as this is consistent with IUPAC standards where “8” should reflect the longest carbon chain in the molecule, with C8 being the *trans* substituent on the alkene.^{23,24} Additionally, the “8-” prefix is accepted according to various enzymology resources.^{25,26}

With the aim of developing a practical procedure for the preparation of 8-hydroxygeraniol (**3**) to enable our biosynthetic studies,¹⁴ we opted to pursue the chemo- and regioselective allylic oxidation of geranyl acetate (**10**), shown in Figure 2, as a starting point. Select results from our efforts to reproduce and optimize the catalytic SeO₂ oxidation procedure are provided in Table 1. As shown in entries 1 and 2, the oxidation could be performed at 0 °C. After 5 h, significant amounts of unreacted geranyl acetate (**10**) remained (entry 1). However, longer reaction times at 0 °C showed promise for increasing the conversion (entry 2). For the sake of developing a more convenient protocol that would not require cooling for extended periods of time, we attempted the oxidation at 23 °C. After 30 min or 1 h, significant recovery of unreacted substrate **10** was observed (entries 3 and 4, respectively). When the reaction was performed for 1.5 h, a more desirable ratio was obtained (entry 5), with the desired product **12** being formed in 61% yield. At longer reaction times of 5 h, substrate **10** could be fully consumed, however, competitive overoxidation to enal **13** was observed (entry 6). Overall, entry 5 conditions were deemed ideal because of the convenience of the experimental protocol (23 °C, 1.5 h) and the optimal yield of **12** obtained.

With practical reaction conditions in hand for the efficient oxidation of geranyl acetate (**10**), we performed the preparation of 8-hydroxygeraniol (**3**) on a 3 mmol scale, as shown in Figure 4. SeO₂-promoted oxidation of **10** proceeded smoothly under our optimized conditions in just 1.5 h at 23 °C. This gave the desired C8-hydroxylated product **12** in 64% isolated yield. Subsequent treatment of **12** with K₂CO₃ in methanol at 23 °C smoothly delivered 8-hydroxygeraniol (**3**) in 83% yield after flash column chromatography. This exceedingly simple protocol can be used to synthesize multimol quantities of **3**.

In summary, we have developed a simple and convenient procedure to synthesize 8-hydroxygeraniol (**3**). The procedure involves a regio- and chemoselective oxidation, followed by methanolysis. Both transformations are performed at ambient temperature and can be used to easily access multimol quantities of **3**. We expect this protocol will enable biosynthetic investigations pertaining to thousands of monoterpene indole alkaloids.

EXPERIMENTAL SECTION

Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Geranyl acetate (**10**) and potassium carbonate were purchased from Alfa Aesar. Selenium dioxide and *tert*-butyl hydroperoxide solution (~5.5 M in decane, over 4 Å molecular sieves) were obtained from Sigma-Aldrich. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at 23°C. Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 precoated plates (0.25 mm) and visualized using anisaldehyde staining. Silicycle Siliacflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ¹H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to the residual solvent signal. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ¹³C NMR spectra were recorded on Bruker spectrometers (at 125 MHz) and are reported relative to the residual solvent signal. Data for ¹³C NMR spectra are reported in terms of chemical shift. IR spectra were obtained on a PerkinElmer UATR Two FT-IR spectrometer and are reported in terms of frequency of absorption (cm⁻¹). DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source, a Vapor Interface (IonSense Inc.), and an Orbitrap mass analyzer. Both the source and MSD were controlled by Excalibur software v. 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense Inc.) using CH₂Cl₂ as the solvent. Ionization was accomplished using UHP He (Airgas Inc.) plasma with no additional ionization agents. The mass calibration was carried out using Pierce LTQ Velos ESI (+) and (–) ion calibration solutions (Thermo Fisher Scientific).

Representative Procedure for Optimization of Oxidation (Table 1, Entry 3 as an Example).

To a flame-dried 10 mL round-bottom flask equipped with a magnetic stir bar and selenium dioxide (23.4 mg, 0.20 mmol, 0.4 equiv) under N₂ were added CH₂Cl₂ (2.5 mL, 0.20 M),

tert-butyl hydroperoxide (5.5 M in decane, 0.29 mL, 1.58 mmol, 3.1 equiv), and geranyl acetate (**10**, 109 μ L, 0.509 mmol, 1.0 equiv). After the mixture was stirred for 30 min at 23 °C, water (2 mL) and EtOAc (10 mL) were added, and the reaction was transferred to a separatory funnel. The layers were separated, and the organic layer was washed successively with deionized water (2 $\times$ 5 mL), saturated aqueous NaHCO₃ (1 $\times$ 5 mL), deionized water (1 $\times$ 5 mL), and brine (1 $\times$ 5 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. To the resulting crude product was added 1,3,5-trimethoxybenzene (28.3 mg, 0.33 equiv) as an external standard. The ratio and yields were determined by ¹H NMR analysis.

8-Hydroxygeranyl Acetate (**12**).

To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar and selenium dioxide (226 mg, 2.04 mmol, 0.4 equiv) under N₂ were added CH₂Cl₂ (25 mL, 0.20 M), *tert*-butyl hydroperoxide (5.5 M in decane, 2.9 mL, 15.8 mmol, 3.1 equiv), and geranyl acetate (**10**, 1.09 mL, 5.09 mmol, 1.0 equiv). After the mixture was stirred for 1.5 h at 23 °C, the reaction mixture was concentrated under reduced pressure. The crude oil was transferred to a separatory funnel with EtOAc (50 mL). The organic layer was washed successively with deionized water (2 $\times$ 20 mL), saturated aqueous NaHCO₃ (1 $\times$ 20 mL), deionized water (1 $\times$ 10 mL), and brine (1 $\times$ 10 mL). The combined aqueous layers were back-extracted with EtOAc (1 $\times$ 80 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified via flash chromatography (6:1 $\rightarrow$ 2:1 hexanes/EtOAc) to afford 8-hydroxygeranyl acetate (**12**, 688 mg, 64% yield) as a colorless oil. 8-Hydroxygeranyl acetate (**12**): *R*_f 0.43 (2:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 5.39–5.31 (m, 2H), 4.58 (d, *J* = 7.1, 2H), 3.99 (s, 2H), 2.17 (dt, *J* = 7.4, 7.4, 2H), 2.11–2.07 (m, 2H), 2.05 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.4, 141.9, 135.4, 125.4, 118.8, 69.0, 61.6, 39.2, 25.8, 21.2, 16.5, 13.8; IR (film) 3424, 2919, 2860, 1736, 1671, 1229 cm⁻¹; HRMS-APCI (*m/z*) [*M* + *H*]⁺ calcd for C₁₂H₂₁O₃⁺ 213.1485, found 213.1478. Spectral data match those previously reported.¹⁴

8-Hydroxygeraniol (**3**).

A flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was charged with 8-hydroxygeranyl acetate (**12**, 633 mg, 2.98 mmol, 1 equiv) and methanol (19 mL, 0.16 M). Potassium carbonate (495 mg, 3.58 mmol, 1.2 equiv) was added in one portion. After the mixture was stirred at 23 °C for 2.5 h, the solvent was removed under reduced pressure, and the reaction mixture was transferred to a separatory funnel with deionized water (10 mL). The aqueous layer was extracted with diethyl ether (3 $\times$ 20 mL). The combined organic layers were washed successively with 0.5 M aqueous HCl (1 $\times$ 10 mL), saturated aqueous NaHCO₃ (1 $\times$ 10 mL), brine (1 $\times$ 10 mL), and deionized water (1 $\times$ 10 mL). Next, the organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified via flash chromatography (1:1 hexanes/EtOAc) to afford 8-hydroxygeraniol (**3**, 490 mg, 83% yield) as a light yellow oil. 8-Hydroxygeraniol (**3**): *R*_f 0.18 (1:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 5.41–5.34 (m, 2H), 4.14 (d, *J* = 6.9, 2H), 3.98 (s, 2H), 2.17 (dt, *J* = 7.5, 7.1, 2H), 2.09–2.04 (m, 2H), 1.67 (s, 3H), 1.65 (s, 3H), 1.44 (br s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 139.1, 135.3, 125.6, 123.9, 68.9, 59.4,

39.1, 25.8, 16.3, 13.8; IR (film) 3307, 2916, 2859, 1669, 999 cm^{-1} ; HRMS-APCI (m/z) [$M + H$]⁺ calcd for $\text{C}_{10}\text{H}_{19}\text{O}_2^+$ 171.1380, found 171.1375. Spectral data match those previously reported.¹⁴

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Role of 8-hydroxygeraniol (3) in the biosynthesis of all monoterpene indole alkaloids, including strychnine (1) and vinblastine (2).

Figure 2.
Various approaches to 8-hydroxygeraniol (3).

Figure 3. Confusion surrounding the naming of 8-hydroxygeraniol (3) and its biosynthetic successor 8-oxogeraniol (11).

Figure 4.

Preparation of 8-hydroxygeraniol (3) on a 3 mmol scale.

Table 1.

Optimization of SeO₂-Promoted Oxidation of 10^a

Entry	Temperature	Time	Ratio of 10 : 12 : 13 ^a	Yield of 12 ^a
1	0 °C	5 h	27 : 68 : 4	43%
2	0 °C	7 h	11 : 82 : 7	57%
3	23 °C	0.5 h	42 : 55 : 2	43%
4	23 °C	1 h	28 : 67 : 5	57%
5	23 °C	1.5 h	19 : 73 : 8	61%
6	23 °C	5 h	0 : 52 : 48	24%

^aRatios and yields were determined by ¹H NMR analysis of the crude reaction mixtures (1,3,5-Trimethoxybenzene was used as an external standard).