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Syntheses of (+)-Alismoxide and (+)-4-*epi*-Alismoxide

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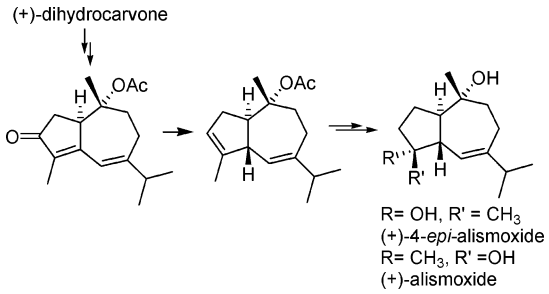

The first total syntheses of (+)-alismoxide and (+)-4-*epi*-alismoxide are reported. Formal chemo-, regio-, and stereoselective addition of water to 10α-acetoxy-1α*H*,5*β*-*H*-guaia-3,6-diene afforded the target compounds after reduction. The absolute stereochemistry of (+)-alismoxide has been established. The low $[\alpha]_D$ +8.6 value indicates that significant amounts of alismoxide result from biosynthetic processes. Furthermore, the structure of the natural guaienediol isolated from *Silphium perfoliatum* has been corrected to (−)-alismoxide.

Alismoxide (**1a**) (guaianediol, nephalbidol) is a natural guaiane derivative which has been isolated from terrestrial and marine sources,[1] especially from the rhizome of *Alisma orientale*, an important crude drug used in oriental traditional medicine.[2] Compound **1a** has been isolated as racemic[2b,4] and dextro-[2a,d−e,3b] and levorotatory samples[3a,5,6] and shows interesting biological properties. Diuretic,[2c] antiinflammatory,[7a] and vasorelaxant[7b] activities and inhibition of urinary calculi formation[7c] have been reported for (±)-**1a**. (−)-**1a** has shown cytotoxic activity against four cancer cell lines (murine leukemia P-388, human lung carcinoma A-549, human colon carcinoma HT-29, and human melanoma cells MEL-28).[6a]

Structure **1a** has been determined by spectroscopic analysis and chemical correlation with alismol (**2a**) (Figure 1).[2c,e,4b,8] From the presumed absolute stereostructure for (+)-alismol (**2a**) (which was determined by CD spectral analysis),[2c] the absolute stereochemistry as shown in **1a** has been proposed for (+)-alismoxide.[2c,e] The attempts to establish the absolute stereochemistry of **1a** by X-ray analysis failed.[9] (±)-**1a** and (±)-**2a** were first reported by Bowden and co-workers in *Lemnalia africana*[4a] and *Nephthea chabrolii*,[4b] respectively. From their $[\alpha]_D$ value the authors suggested the co-occurring unstable germacrane C (**3**) as their likely precursor (Scheme 1). This proposal was confirmed by Kitagawa and co-workers, who found that (±)-**1a** could be obtained from an aqueous acetone solution of **3**.[5] Since then, it has been assumed than **1a** and **2a** and related guaienes result from oxidation−cyclization of germacrene C (**3**) during the isolation procedure (Scheme 1), although it can be also biosynthesized by the organism.[2b−c,5]

On the other hand, in 1979, Bohlmann and Jakupovic assigned structures **1b** and **2b** (4-*epi*-derivatives of **1a** and **2a**, respectively) to two natural guaienes isolated from *Silphium perfoliatum*.[10a] Later on, **1b** was identified in *Sparattanthelium botocudorum*[10b] and *Amoora yunnanensis*.[10c] Nevertheless, the identical ^{1}H and ^{13}C NMR spectroscopic features reported for **1a** and **1b** suggest than they could be the same compound.

In this paper, we report the syntheses of **1a** and **1b** in enantiomerically pure form. Retrosynthetic analysis (Scheme 2) suggests that **1a** and **1b** could be accessible from a common intermediate, 1α*H*,5*β*-*H*-guaiadiene **6** or its parent alcohol **7**, through chemo-, regio-, and stereoselective addition of water to the C_3-C_4 double bond. The nonconjugated diene system in **6** and **7** could be available by reduction−olefin transposition[11] from guaiadienone **8**, whose synthesis from (+)-dihydrocarvone (**5**) has been recently reported by us.[12]

(1) (a) For natural sources and mp and $[\alpha]_D$ ($CHCl_3$) values for natural and synthetic alismoxide (**1a**) and 4-*epi*-alismoxide (**1b**), see Supporting Information. (b) For selected ^{1}H and ^{13}C NMR Data for compounds **1a** and **1b,** see Supporting Information.

(2) (a) Oshima Y.; Iwakawa, T. Hikino, H. *Phytochemistry* **1983**, *22*, 183−185. (b) Yoshikawa, M.; Hatakeyama, S.; Tanaka, N.; Matsuoka, T.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1993**, *41*, 2109−2112. (c) Yoshikawa, M.; Yamaguchi, S.; Matsuda, H.; Kohda, Y.; Ishikawa, H.; Tanaka, N.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 1813−1816 and references therein. (d) Nakajima, Y.; Satoh, Y.; Katsumata, M.; Tsujiyama, K.; Ida Y.; Shoji, J. *Phytochemistry* **1994,** *36*, 119−127. (e) Peng, G.-P.; Tian, G.; Huang, X.-F.; Lou, F.-C. *Phytochemistry* **2003**, *63*, 877−881.

(3) (a) Gao, K.; Yang, L.; Jian, Z.-J. *J. Chin. Chem. Soc*. **1999**, *46*, 619−622. (b) Min, Y. D.; Kwon, H. C.; Choi, S. Z.; Lee, K. R. *Yakhak Hoeji* **2004**, *48*, 65−69.

(4) (a) Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 2737−2747. (b) Bowden, B. F.; Coll, J. C.; Mitchell, S. J. *Aust. J. Chem.* **1980**, *33*, 1833−1839.

(5) Kitagawa, I.; Kobayashi, M.; Cui, Z.; Kiyota, Y.; Ohnishi, M. *Chem. Pharm. Bull*. **1986**, *34*, 4590−4596.

(6) (a) El Sayed, K.; Hamann, M. T. *J. Nat. Prod*. **1996**, *59*, 687−689. (b) Su, J.-Y.; Kuang, Y.-Y.; Zeng, L.-M. *Huaxue Xuebao* (*Acta Chim. Sin.)* **2003**, *61*, 1097−1100.

(7) (a) Kubo, M.; Matsuda, H.; Tomohiro, N.; Yoahikawa, M. *Biol. Pharm. Bull.* **1997**, *20*, 511−516. (b) Yoshikawa, M.; Murakami, T.; Morikawa, T.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1186−1188. (c) Zhou, X.; Yin, R.; Ruan, H.; Zhang, Y.; Pi, H.; Zhao, X.; Wu, J. *Bopuxue Zazhi* **2005**, *22*, 195−200.

(8) Lange, G. L.; Gottardo, C.; Merica, A. *J. Org. Chem.* **1999**, *64*, 6738−6744.

(9) Faulkner, D. J. *Nat Prod. Rep.* **1984**, *1*, 551−598. The structure was determined by X-ray analysis but apparently has not been published, because the crystal has two molecules per unit cell and only one of these was clearly observed while the second was extensively disordered.

(10) (a) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1979**, *18*. 1987−1992. (b) De Almeida, R. N.; Barbosa-Filho, J. M. *J. Braz. Chem. Soc*. **1991**, *2*, 71−73. (c) Luo, X.; Wu, S.; Ma, Y.; Wu, D. *Zhiwu Xuebao (Acta Bot. Sin.)* **2001**, *43*, 426−430.

(11) (a) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem*. **1976**, *41*, 574−575. (b) Greene, A. E.; Edgar, M. T. *J. Org. Chem*. **1989**, *54*, 1468−1470 and references therein.

(12) Blay, G.; Garcia, B.; Molina, E.; Pedro, J. R. *Org. Lett*. **2005**, *7*, 3291−3293.

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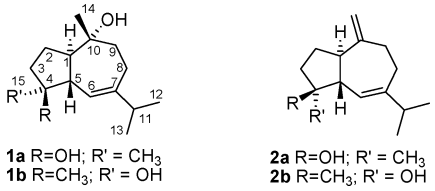
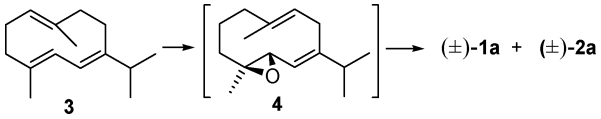
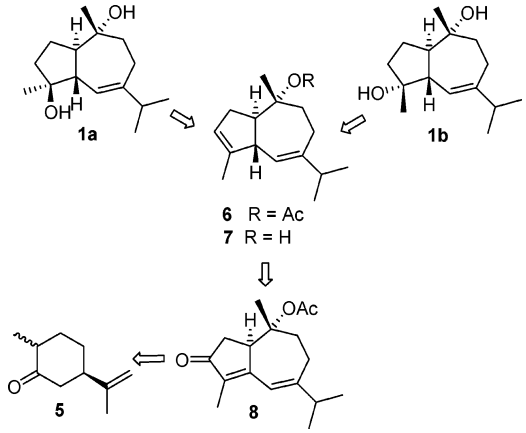


FIGURE 1. Alismoxide (**1a**), 4-*epi*-alismoxide (**1b**), alismol (**2a**), and 4-*epi*-alismol (**2b**).

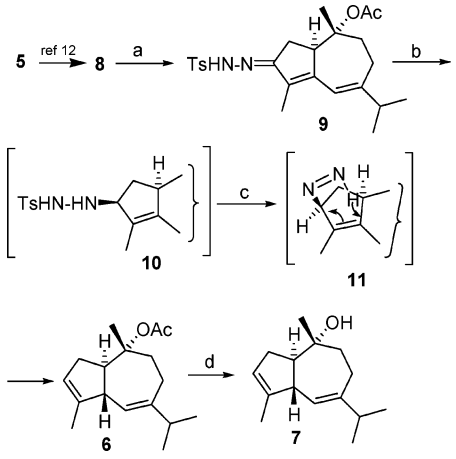
SCHEME 1. Formation of 1a and 2a from Germacrane C (3)



SCHEME 2. Retrosynthetic Analysis



SCHEME 3. Synthesis of Guaiadiene 6[a]



[a] Reagents and conditions: (a) *p*-$TsNHNH_2$, EtOH, Δ; (b) catecholborane, $CHCl_3$, −50 °C; (c) $NaOAc·3H_2O$, Δ, 71% from **8**; (d) $LiAlH_4$, THF, 97%.

The transformation of **8** into **6** was carried out following the procedure applied by Greene and co-workers in the synthesis of 1α*H*,5β*H*-guai-3-ene derivatives[11b] (Scheme 3). Sequential treatment of **8** with *p*-$TsNHNH_2$, catecholborane, and NaOAc afforded nonconjugated diene **6** in 71% yield. Treatment of **6** with $LiAlH_4$ gave the parent alcohol **7** in excellent yield (98%). The stereochemistry at C_5 was confirmed by the positive NOE between H_5 and H_{14} in **7** (Figure 2). This stereochemistry results

FIGURE 2. Conformational depiction and observed NOE for **7**.

from the approach of the borane from the less hindered α-face of hydrazone **9** to give the 3β-hydrazine **10** followed of loss of TsH to afford diazene **11**, which decomposes sigmatropically inserting H_5 on the β-face of the molecule without migration of the C_6-C_7 double bond.

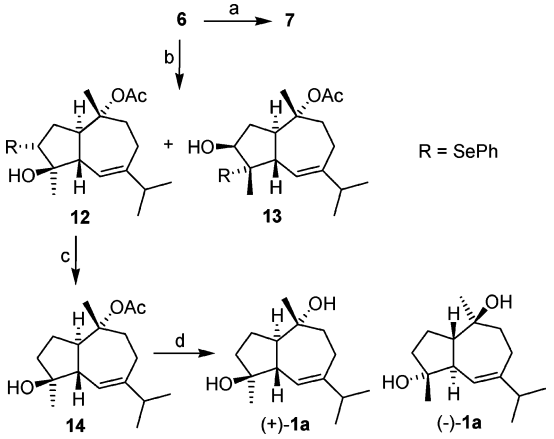
Looking at the structures of compounds **6** and **7** (Figure 2), a preferential reactivity at the C_3-C_4 versus the C_6-C_7 trisubstituted double bond was expected due to the steric hindrance of the isopropyl group on C_7. In addition, the β-disposition of H_5 and the $C_{10}-CH_3$ should favor electrophilic attack from the α-face at C_3-C_4. However, hydroxymercuration−demercuration[13] as well as several attempts of hydroxy phenylselenylation[14] failed to insert a β-hydroxyl group at C_4 as in alismoxide (**1a**). Low chemoselectivity in hydroxymercuration−demercuration was observed,[13] giving mixtures (^{1}H NMR) of starting **6**, its guaia-4,6-diene isomer, and nonolefinic polar compounds. Treatment of **6** with PhSeCl in CH_3CN-H_2O[14a] gave unexpectedly alcohol **7** (84%). β-Hydroxyselenide adducts could be obtained by treatment of **6** with PhSeOH generated in situ, with $PhSeO_2H-H_3PO_2$ as precursors.[15] With successive additions of both reagents (total amount: 6 equiv of $PhSeO_2H$, 9 equiv of H_3PO_2) starting **6** was consumed and **12** and **13** could be isolated in low yields of 21% and 10%, respectively. Compounds **12** and **13** result from the electrophilic addition of phenylselenyl ion to the α-face of **6** followed by hydroxyl attack to C_4 or C_3, respectively, from the β-face of the molecule.

Deselenylation of **12** with Raney nickel followed by treatment with $LiAlH_4$ afforded compound (+)-**1a** {$[\alpha]^{26}_D$ +8.6} in excellent yield (95%) from **12**. The spectroscopic data of synthetic (+)-**1a** were identical with those reported for the natural products.[1b] It follows from the value of $[\alpha]_D$ +8.6 that (+)-**1a** is biosynthesized by *A. orientale* {$[\alpha]_D$ +3.1,[2a] +8.7,[2d] +5.2[2e]} and that the product isolated from corals and other sources[1a] has absolute stereochemistry opposite that of (−)-**1a** (Scheme 4).

The synthesis of 4-*epi*-derivative **1b** was straightforward by selective epoxidation at C_3-C_4 followed by reduction (Scheme 5). Low chemoselectivity was observed in the reaction of **6** with bulky reagents as *m*-chloroperbenzoic acid (*m*-CPBA)[16] or magnesium monoperphthalate (MMPP),[16] but good results were obtained with dimethyldioxirane.[17] Treatment of guaiadienes

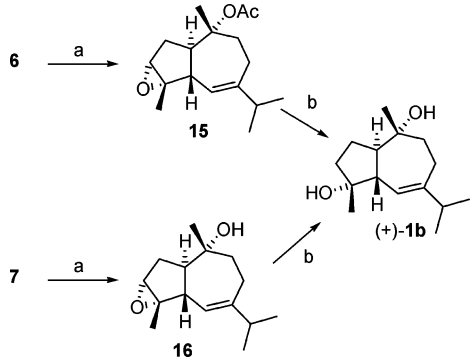
(13) Brown, H. C.; Lynch, G. J. *J Org. Chem.* **1981**, *46*, 531−538.
(14) (a) Toshimitsu, A.; Aoai, T.; Owada, H.; Uemura, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1980**, 412−413. (b) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.* **1981,** *46*, 1564−1570. (c) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689−1697.
(15) Labar, D.; Krief, A.; Hevesi, L. *Tetrahedron Lett.* **1978,** *41*, 3967−3970.
(16) (a) Blay, G.; Bargues, V.; Cardona, L.; Collado, A. M.; Garcia, B.; Pedro, J. R. *J. Org. Chem.* **2000**, *65*, 2138−2144 and references therein. (b) Mehta, G.; Ramesh, S. S.; Bera, M. K. *Chem. Eur. J.* **2003**, *9*, 2264−2272.
(17) (a) Adam, W.; Curci, R.; Edward, J. O. *Acc. Chem. Res.* **1989**, *22*, 205−211. (b) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Zhao, L. *J. Org. Chem.* **1998**, *63*, 254−263 and references therein.

SCHEME 4. Synthesis of (+)-Alismoxide (1a)[a]



[a] Reagents and conditions: (a) PhSeCl, CH_3CN-H_2O, 84%; (b) $PhSeO_2H$, 50% H_3PO_2, THF (21% **12** + 10% **13**); (c) Raney Ni, EtOH, 96%; (d) $LiAlH_4$, THF, 97%.

SCHEME 5. Synthesis of (+)-4-*epi*-Alismoxide (1b)[a]



[a] Reagents and conditions: (a) dimethyldioxirane, CH_2Cl_2, 0 °C, (60% **15**; 68% **16**); (b) $LiAlH_4$, THF (87% from **15**; 53% from **16**).

6 or **7** with dimethyldioxirane afforded as products only α-monoepoxides **15** and **16** in 60% and 68% yield, respectively. The stereochemistry of the oxirane ring was assigned by the positive NOE between H_{15} and H_3 and H_5 in **15**. These results show clearly that the steric shielding of H_5 and the $C_{10}-CH_3$ highly favored the α attack. Reduction of **15** or **16** with $LiAlH_4$ afforded guaiadienol (+)-**1b** {$[\alpha]^{26}_D$ +39.7} in 52% yield from **6** or 36% yield from **7**. The spectroscopic features of (+)-**1b** are similar to those of (+)-**1a**,[1b] but some clear differences in δ values, especially in the ^{13}C NMR spectra, can be observed: 25.8 (CH_3), 22.5 (CH_2), 120.6 (CH), 52.5 (CH), 150.9 (C), 80.9 (C) for (+)-**1b** versus 22.8 (CH_3), 21.7 (CH_2), 121.5 (CH), 50.9 (CH), 149.9 (C), 80.4 (C) for (+)-**1a**. A comparison of these spectroscopic features with those reported for the natural guaienediol.[10] show clearly than the reported data for the natural product agree with those of (+)-**1a** but not with those of (+)-**1b** and consequently this natural guaienediol is identical to alismoxide (**1a**). It follows from the $[\alpha]_D$ sign that levorotatory enantiomer (−)-**1a** (Scheme 4) is the main component in *S. perfoliatum*.[10a]

In conclusion, the first total synthesis of (+)-alismoxide (**1a**) and (+)-4-*epi*-alismoxide (**1b**) has been accomplished starting from the readily available (+)-dihydrocarvone (**5**). The synthesis of these compounds has allowed the establishment of the absolute configuration of alismoxide. Furthermore, the low $[\alpha]_D$ value of pure (+)-**1a** (Table 1, Supporting Information) indicates that significant amounts of **1a** result from biosynthetic processes. Comparison of the spectroscopic features of (+)-**1a** and (+)-**1b** with those reported for the natural guaienediol isolated from *S. perfoliatum*,[10a] *S. botocudorum*,[10b] and *A. yunnanensis*[10c] has allowed the establishment of the identity of this guaienediol with alismoxide (**1a**).

Experimental Section[18]

(−)-10α-Acetoxy-1α*H*,5β*H*-guaia-3,6-diene (6). A solution of compound **7** (400 mg, 1.45 mmol) and *p*-$TsNHNH_2$ (349 mg, 1.90 mmol) in abs EtOH (2.4 mL) was refluxed for 90 min, and after this time the solvent was removed under vacuum to afford crude tosylhydrazone **8** as a yellow foamy solid. A solution under argon of crude **8** in $CHCl_3$ (4.3 mL, filtered through basic Al_2O_3) was cooled at −50 °C, catecholborane (1 M in THF, 6 mL, 6.0 mmol) was added via syringe, and the mixture was stirred at −50 °C for 30 min. After this time, $NaAcO\cdot 3H_2O$ (1.44 g, 10.60 mmol) was added, the bath was removed, and the mixture was refluxed for 1 h. Filtration through neutral Al_2O_3 and removal of the solvent under vacuum followed by column chromatography (hexanes/ethyl ether 100:0 to 98:2) afforded 271 mg (71%) of compound **6** as a colorless oil: $[\alpha]_D^{22}$ −15.4 (*c* 0.52); IR (NaCl) 3040, 1730, 1610 cm^{-1}; MS *m/e* 262 (M^+, 5), 202 (32), 187 (14), 159 (100), 131 (21); HRMS found 262.1939 (M^+), $C_{17}H_{26}O_2$ required 262.1933; ^1H NMR (400 MHz) δ 5.61 (1H, d, J = 3.1 Hz), 5.31 (1H, br s), 2.96 (1H, br d, J = 9.6 Hz), 2.57 (1H, q, J = 9.6 Hz), 2.30−2.06 (6H, m), 2.02−1.92 (1H, m), 1.94 (3H, s), 1.73 (3H, br s), 1.52 (3H, s), 0.98 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz) δ 170.4 (C), 148.2 (C), 140.6 (C), 124.4 (CH), 123.4 (CH), 87.4 (C), 54.1 (CH), 47.1 (CH), 36.8 (CH), 36.6 (CH_2), 32.0 (CH_2), 24.8 (CH_2), 22.7 (CH_3), 21.4 (CH_3), 21.0 (CH_3), 19.7 (CH_3), 15.0 (CH_3).

(−)-10α-Hydroxy-1α*H*,5β*H*-guaia-3,6-diene (7). To a suspension of $LiAlH_4$ (137 mg, 3.61 mmol) in THF (2.5 mL) at 0 °C was added dropwise a solution of compound **6** (108 mg, 0.41 mmol) in THF (4.5 mL). After removal of the bath, the reaction mixture was stirred at room temperature for 2 h, quenched with aqueous saturated NH_4Cl, and extracted with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4), and the solvent was removed. Column chromatography (hexanes−EtOAc, 7:3) gave compound **7** (88 mg, 97%) as a solid: colorless crystals; mp 65−67 °C (hexanes−EtOAc); $[\alpha]^{24}_D$ −6.6 (*c* 0.06); IR (KBr) 3500−3250, 1610 cm^{-1}; MS *m/e* 220 (M^+, 7), 202 (46), 177 (23), 159 (100); HRMS found 220.1834 (M^+), $C_{15}H_{24}O$ required 220.1827; ^1H NMR (400 MHz) δ 5.63 (1H, d, J = 3.9 Hz), 5.31 (1H, s), 2.89 (1H, br d, J = 9.3 Hz), 2.32−2.06 (5H, m), 2.00 (1H, dd, J = 11.2, 15.7 Hz), 1.84 (1H, dd, J = 7.2, 13.4 Hz), 1.73 (3H, s), 1.43 (1H, dd, J = 11.0, 13.2 Hz), 1.35 (1H, br s), 1.25 (3H, s), 0.99 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 148.2 (C), 141.0 (C), 124.8 (CH), 123.3 (CH), 74.9 (C), 56.6 (CH), 48.1 (CH), 42.5 (CH_2), 36.8 (CH), 31.6 (CH_2), 25.2 (CH_2), 22.2 (CH_3), 21.3 (CH_3), 21.0 (CH_3), 14.9 (CH_3).

10α-Acetoxy-3α-phenylselenyl-4β-hydroxy-1α*H*,5β*H*-guaia-6-ene (12) and 10α-Acetoxy-4α-phenylselenyl-3β-hydroxy-1α*H*,5β*H*-guaia-6-ene (13). To a suspension of compound **6** (34 mg, 0.13 mmol) and $PhSeO_2H$ (37 mg, 0.19 mmol) in THF (2 mL) at rt under argon was added 32 μL (0.30 mmol) of 50% aq H_3PO_2, and the mixture was stirred at rt. After 90 min, additional portions of $PhSeO_2H$ (37 mg, 0.19 mmol) and 50% aq H_3PO_2 (32 μL, 0.30 mmol) were added, and stirring was resumed for 3 h. New additions of $PhSeO_2H$ (37 mg, 0.19 mmol) and 50% aq H_3PO_2 (32 μL, 0.30 mmol) and 30 min additional reaction time consumed starting **6**, and the reaction was quenched with aq saturated $NaHCO_3$. Extraction

(18) For a description of the general experimental methods, see the Supporting Information.

with EtOAc as usual and removal of the solvent under vacuum followed by column chromatography (hexanes−EtOAc, 9:1 to 7:3) separated compound **12** (12 mg, 21%) and **13** (5.5 mg, 10%).

Compound 12: colorless crystals; mp 110−113 °C (hexanes−EtOAc); IR (KBr) 3550−3400, 3057, 1702, 1578 cm^{-1}; MS *m*/*e* 436 (M^+, 1), 434 (0.5), 376 (25), 374 (13), 219 (15), 157 (35), 77 (100); HRMS found 436.1530 (M^+), $C_{23}H_{32}O_3Se$ required 436.1517; ^1H NMR (300 MHz) δ 7.65−7.55 (2H, m), 7.30−7.20 (3H, m), 5.49 (1H, br s), 3.33 (1H, dd, J = 9.2, 12.3 Hz), 1.95 (3H, s), 1.54 (3H, s), 1.22 (3H, s), 0.97 (3H, d, J = 6.9 Hz), 0.96 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz) δ 170.4 (C), 149.9 (C), 133.5 (CH, 2C), 129.8 (C), 128.9 (2C, CH), 127.2 (CH), 120.8 (CH), 87.4 (C), 81.0 (C), 55.4 (CH), 47.4 (CH), 46.8 (CH), 37.1 (CH), 36.2 (CH_2), 31.1 (CH_2), 24.7 (CH_2), 22.7 (CH_3), 21.4 (CH_3), 21.1 (CH_3), 19.6 (CH_3), 18.9 (CH_3).

Compound 13: colorless oil; IR (NaCl) 3500−3400, 3060, 1710, 1560 cm^{-1}; MS *m*/*e* 436 (M^+, 0.6), 434 (0.3), 376 (20), 374 (10), 219 (30), 157 (60), 77 (100); HRMS found 436.1533 (M^+), $C_{23}H_{32}O_3Se$ required 436.1517; 1H NMR (300 MHz) δ 7.58−7.54 (2H, m), 7.34−7.16 (3H, m), 5.54 (1H, d, J = 2.4 Hz), 3.91 (1H, d, J = 5.4 Hz), 2.71 (1H, td, J = 5.3, 10.9 Hz), 2.61−2.46 (2H, m), 2.27−2.11 (3H, m), 2.03 (1H, dd, J = 9.6, 13.0 Hz), 1.95−1.82 (1H, m), 1.90 (3H, s), 1.66 (1H, dd, J = 5.3, 14.9 Hz), 1.50 (3H, s), 1.47 (3H, s), 0.96 (3H, d, J = 6.8 Hz), 0.95 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 170.5 (C), 150.7 (C), 138.6 (CH), 128.8 (CH), 128.7 (CH), 126.7 (C), 121.4 (CH), 87.6 (C), 78.0 (CH), 63.3 (C), 50.4 (CH), 47.4 (CH), 37.3 (CH), 36.6 (CH_2), 34.1 (CH_2), 24.7 (CH_2), 22.9 (CH_3), 21.9 (CH_3), 21.5 (CH_3), 21.2 (CH_3), 20.0 (CH_3).

(−)-10α-Acetoxy-4*β*-hydroxy-1α*H*,5*β*H-guaia-6-ene (14). To a solution of compound **12** (26 mg, 0.06 mmol) in 1:1 absolute EtOH−benzene (0.3 mL) was added Raney nickel (1.73 g) in portions at 30 min intervals. After 2 h, the mixture was filtered through silica gel eluting with EtOAc. Removal of the solvent afforded compound **14** (16 mg, 96%) as a colorless oil: $[\alpha]^{26}_D$ −40.6 (*c* 0.64); IR (NaCl) 3500−3350, 1720 cm^{-1}; MS (CI) *m*/*e* 221 (32), 203 (100), 159 (11); HRMS found 221.1905 (M^+ − AcO), $C_{15}H_{25}O$ required 221.1905; ^1H NMR (400 MHz) δ 5.47 (1H, d, J = 2.7 Hz), 2.40−2.30 (1H, m), 2.28−2.14 (4H, m), 2.08−1.99 (1H, m), 1.95 (3H, s), 1.97−1.86 (1H, m), 1.78−1.50 (5H, m), 1.54 (3H, s), 1.21 (3H, s), 0.98 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 170.5 (C), 149.6 (C), 121.0 (CH), 87.9 (C), 80.2 (C), 49.4 (CH), 48.5 (CH), 40.3 (CH_2), 37.2 (CH), 36.6 (CH_2), 24.8 (CH_2), 22.7 (CH_3, 2C), 21.7 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 18.9 (CH_3).

(+)-4*β*,10α-Dihydroxy-1α*H*,5*β*H-guaia-6-ene [(+)-Alismoxide] (+)-(1a). Following the procedure for the synthesis of **6a**, treatment of compound **14** (11.2 mg, 0.04 mmol) in THF (0.5 mL) with $LiAlH_4$ (6.7 mg, 0.17 mmol) in THF (2.5 mL) for 20 min afforded after chromatography (hexanes/EtOAc, 4:6) compound (+)-**1a** (9.4 mg, 99%) with the following features: colorless crystals; mp 138−141 °C (hexanes−EtOAc); $[\alpha]^{26}_D$ +8.6 (*c* 1.16); IR (KBr) 3500−3350, 1100 cm^{-1}; MS (CI) *m*/*e* 221 (M^+ − OH, 22), 219 (13), 203 (100), 202 (41), 187 (10), 159 (13); HRMS found 221.1896 (M^+ − OH), $C_{15}H_{25}O$ required 221.1905; ^1H NMR (400 MHz) δ 5.49 (1H, br d, J = 3.0 Hz, H_6), 2.21 (1H, sept, J = 6.8 Hz, H_{11}), 2.20−2.14 (2H, m, H_5, H_8), 1.92 (1H, ddd, J = 1.2, 10.6, 16.4 Hz, H_8'), 1.89−1.58 (6H, m, H_1, $2H_2$, $2H_3$, H_9), 1.52 (2H, br s), 1.46 (1H, br dd, J = 10.4, 13.2 Hz, H_9'), 1.26 (3H, s, $3H_{14}$), 1.20 (3H, s, $3H_{15}$), 0.98 (3H, d, J = 6.8 Hz, $3H_{12}$), 0.97 (3H, d, J = 6.8 Hz, $3H_{13}$); ^{13}C NMR (75 MHz) δ 149.7 (C), 121.3 (CH), 80.2 (C), 75.2 (C), 50.9 (CH), 50.5 (CH), 42.6 (CH_2), 40.4 (CH_2), 37.3 (CH), 25.1 (CH_2), 22.5 (CH_3), 21.5 (CH_2), 21.4 (CH_3), 21.3 (CH_3), 21.2 (CH_3).

(−)-10α-Acetoxy-3α,4α-epoxy-1α*H*,5*β*H-guaia-6-ene (15). To a solution of compound **6** (50 mg, 0.19 mmol) in 1 mL of dry CH_2Cl_2 at 0 °C under argon was added 0.062 M in acetone dimethyldioxirane (3.1 mL, 0.19 mmol), and the mixture was stirred at 0 °C for 2 h. Removal of the solvent followed by column chromatography (hexanes−EtOAc, 7:3) afforded 32 mg (60%) of compound **15**: mp 76−79 °C (acetone); $[\alpha]^{26}_D$ −11.2 (*c* 1.07); IR (KBr) 3032, 1726, 1261, 1240 cm^{-1}; MS *m*/*e* 278 (M^+, 0.1), 218 (79), 203 (44), 185 (31), 175 (100); HRMS found 278.1884 (M^+), $C_{17}H_{26}O_3$ required 278.1882; ^1H NMR (400 MHz) δ 5.63 (1H, d, J = 2.8 Hz), 3.27 (1H, s), 2.30−2.18 (3H, m), 2.15−2.00 (3H, m), 1.97−1.86 (2H, m), 1.92 (3H, s), 1.72−1.63 (1H, m), 1.51 (3H, s), 1.46 (3H, s), 0.98 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 170.2 (C), 150.6 (C), 120.8 (CH), 86.5 (C), 66.1 (C), 62.1 (CH), 47.9 (CH), 42.8 (CH), 36.8 (CH), 36.8 (CH_2), 28.7 (CH_2), 24.6 (CH_2), 22.6 (CH_3), 21.3 (CH_3), 20.9 (CH_3), 19.4 (CH_3), 16.5 (CH_3).

(+)-3α,4α-Epoxy-10α-hydroxy-1α*H*,5*β*H-guaia-6-ene (16). Following the procedure for the synthesis of compound **15**, from compound **7** (51 mg, 0.23 mmol) was obtained compound **16** (37 mg, 68%) of as a colorless oil: $[\alpha]^{24}_D$ +52.7 (*c* 0.91); IR (NaCl) 3500−3250, 1610, 1121 cm^{-1}; MS *m*/*e* 236 (M^+, 5), 218 (32), 203 (14), 200 (23), 175 (41), 58 (100); HRMS found 236.1786 (M^+), $C_{15}H_{24}O_2$ required 236.1776; ^1H NMR (400 MHz) δ 5.66 (1H, d, J = 3.8 Hz), 3.27 (1H, s), 2.26 (1H, sept, J = 6.8 Hz), 2.18−2.04 (4H, m), 1.93 (1H, dd, J = 11.4, 15.7 Hz), 1.79 (1H, br dd, J = 8.0, 13.0 Hz), 1.76−1.60 (2H, m), 1.45 (3H, s), 1.33 (1H, t, J = 12.2 Hz), 1.20 (3H, s), 0.99 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 150.4 (C), 121.3 (CH), 74.2 (C), 65.3 (C), 62.2 (CH), 50.0 (CH), 43.7 (CH), 42.7 (CH_2), 36.8 (CH), 28.4 (CH_2), 25.1 (CH_2), 21.5 (CH_3), 21.2 (CH_3), 20.9 (CH_3), 16.5 (CH_3).

(+)-4α,10α-Dihydroxy-1α*H*,5*β*H-guaia-6-ene [(+)-4-*epi*-Alismoxide)] (+)−(1b). From Compound 15. Following the procedure for the synthesis of compound **7**, from compound **15** (27 mg, 0.10 mmol) was obtained compound (+)-**1b** (20 mg, 87%): colorless crystals; mp 59−62 °C (hexanes−EtOAc); $[\alpha]^{26}_D$ +39.7 (*c* 0.80); IR (KBr) 3600−3400, 1104, 1087 cm^{-1}; MS *m*/*e* 238 (M^+, 0.1), 220 (27), 205 (20), 162 (100); HRMS found 238.1929 (M^+), $C_{15}H_{26}O_2$ required 238.1933; ^1H NMR (400 MHz) δ 5.50 (1H, d, J = 3.4 Hz, H_6), 2.26 (1H, sept, J = 6.8 Hz, H_{11}), 2.20−2.08 (2H, m, H_1, H_8), 1.98−1.88 (2H, m, H_5, H_8'), 1.88−1.68 (4H, m, H_2, $2H_3$, H_9), 1.55 (1H, dt, J = 10.4, 13.2 Hz, H_2'), 1.48−1.38 (1H, m), 1.30 (3H, s, $3H_{15}$), 1.21 (3H, s, $3H_{14}$), 0.98 (3H, d, J = 6.8 Hz, $3H_{12}$), 0.97 (3H, d, J = 6.8 Hz, $3H_{13}$); ^{13}C NMR (75 MHz) δ 150.9 (C), 120.6 (CH), 80.8 (C), 75.2 (C), 52.5(CH), 50.1 (CH), 42.5-(CH_2), 39.8 (CH_2), 37.3 (CH), 25.8 (CH_3), 25.1 (CH_2), 22.5 (CH_2), 21.4 (CH_3), 21.0 (CH_3), 20.8 (CH_3).

From Compound 16. Following the procedure for the synthesis of compound **7**, from compound **16** (32 mg, 0.13 mmol) was obtained compound (+)-**1b** (17 mg, 53%) with the same spectral features as compound (+)-**1b** obtained from **14**.

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Supporting Information Available: General experimental procedures; natural sources, mp and $[\alpha]_D$ ($CHCl_3$) values and selected ^1H and ^{13}C NMR data for **1a** and **1b**; ^1H NMR and ^{13}C NMR spectra of compounds **6**, **12**−**17**, (+)-**1a**, and (+)-**1b**; and NOE experiments for **7**, **15**, and (+)-**1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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