JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

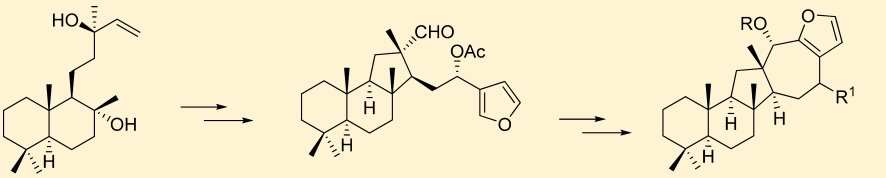
Biomimetic Synthesis of Two Salmahyrtisanes: Salmahyrtisol A and Hippospongide A

María Martín,[†] Aitor Urosa,[†] Isidro S. Marcos,[†] David Díez,[†] José M. Padrón,[‡] and Pilar Basabe*[,†]

[†]Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caidos 1-5, 37008 Salamanca, Spain

[‡]BioLab, Instituto Universitario de Bio-Orgánica "Antonio González " (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Universidad de La Laguna, C/Astrofísico Francisco Sánchez 2, 38206 La Laguna, Spain

Supporting Information



ABSTRACT: Sesterterpenes with a salmahyrtisane skeleton have been synthesized for the first time. (−)-Sclareol has been selected as a precursor for the synthesis of two novel natural products: salmahyrtisol A (**1**) and hippospongide A (**2**). Our results represent a biomimetic approach to obtaining salmahyrtisanes from hyrtiosanes. Salmahyrtisol A has shown an activity comparable to that of the standard anticancer drugs in the cell lines A549, HBL-100, HeLa, and SW1573.

INTRODUCTION

Marine organisms, mainly sponges and nudibranchs, have provided a large number of sesterterpenoids with novel carbon skeletons. Sesterterpenoids (C25) form a group of pentaprenyl terpenoids that exhibit a wide variety of biological activities.[1−7] Until now, only three tetracarbocyclic sesterterpenoids with the novel salmahyrtisane skeleton are known, namely, salmahyrtisol A (**1**), hippospongide A (**2**), and similan A (**3**) (Figure 1). These compounds could be used as tools in the treatment of cancer,[3] diabetes,[4] or infectious diseases.[5]

Salmahyrtisol A (**1**) was isolated[8] from the Red Sea sponge *Hyrtios erecta* and showed significant cytotoxicity to murine leukemia (P-388), human lung carcinoma (A549), and human colon carcinoma (HT-29). Hippospongide A (**2**) was isolated[9] from the sponge *Hippospongia* sp. and has no significant biological activity. Similan A (**3**) was isolated[10] from the Thai sponge *Hyrtios gumininae* and showed weakly cytotoxic activities against several cancer cell lines. The structures of similan A (**3**) and salmahyrtisol A (**1**) are closely related, and the authors suspect that similan A could be an artifact since the extraction of metabolites was done in methanol. The structures of all of these new pentacyclic sesterterpenoids have been determined by spectroscopic methods.

Scheuer and co-workers,[8] considering the coexistence of salmahyrtisol A (**1**) and the sesterterpene of hyrtiosane skeleton hyrtiosal (**4**), proposed a biosynthetic route that could explain the formation of salmahyrtisol A (**1**) from hyrtiosal (**4**) (Scheme 1). Earlier, Iguchi and co-workers[11] proposed the biogenetic origin of hyrtiosal (**4**) from sesterterpenes with a cheilantane skeleton (Scheme 1). With all of these considerations, a biogenetic sequence for the biosynthesis of salmahyrtisanes can be planned, as depicted in Scheme 1.

Previously, we reported the synthesis of hyrtiosal (**4**) from (−)-sclareol.[12,13] With this tool in hand, we planned a biomimetic route toward salmahyrtisanes from hyrtiosanes. For the synthesis of the tetracarbocyclic skeleton, we envisioned two different strategies (Scheme 2). In the first one, we considered the cyclization of intermediate **I** by means of a "Prins-type reaction". An alternative is the Friedel−Craft reaction of intermediate **II**.

In the present work, we report the first synthesis of compounds with a salmahyrtisane skeleton, the structure and stereochemistry of salmahyrtisol A (**1**) and hippospongide A (**2**) being confirmed. In addition, the antiproliferative activity of **1** and its synthetic precursors was evaluated in a panel of representative human solid tumor cell lines.

RESULTS AND DISCUSSION

The synthesis of the salmahyrtisanes reported in this work was started from commercially available (−)-sclareol. The synthesis of the tetracyclic framework of salmahyrtisanes is shown in Scheme 3. Hence, (−)-sclareol was transformed into the hyrtiosanes **5** and **6** (epimers in C-16), as reported earlier.[12] To test our first hypothesis, we submitted **5**−**6** to a "Prins-type

Received: February 23, 2015
Published: April 8, 2015

DOI: 10.1021/acs.joc.5b00420
J. Org. Chem. 2015, 80, 4566−4572

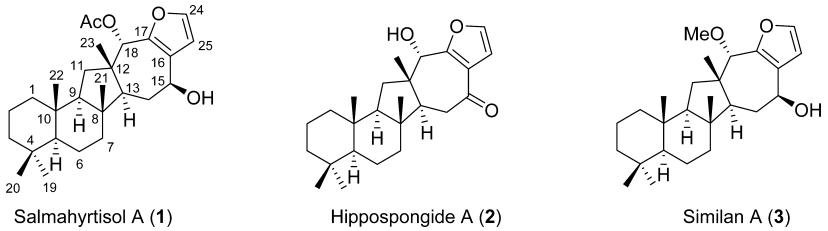
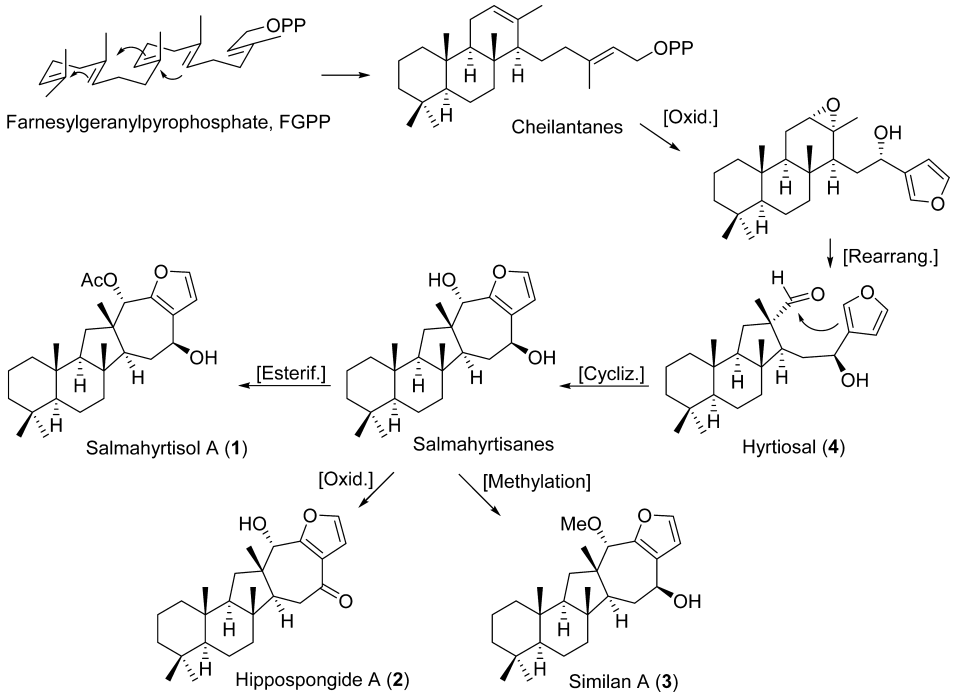
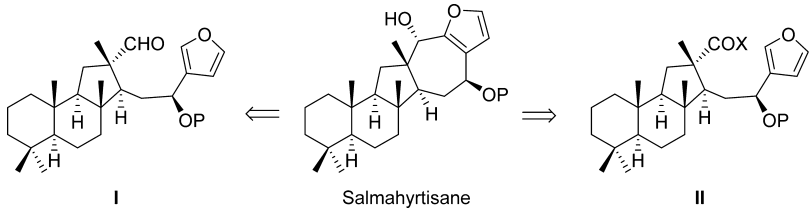


Figure 1. Natural tetracarbocyclic salmahyrtisanes sesterterpenoids.

Scheme 1. Biosynthesis of Hyrtiosanes and Salmahyrtisanes



Scheme 2. Retrosynthetic Relationship between Hyrtiosanes and Salmahyrtisanes



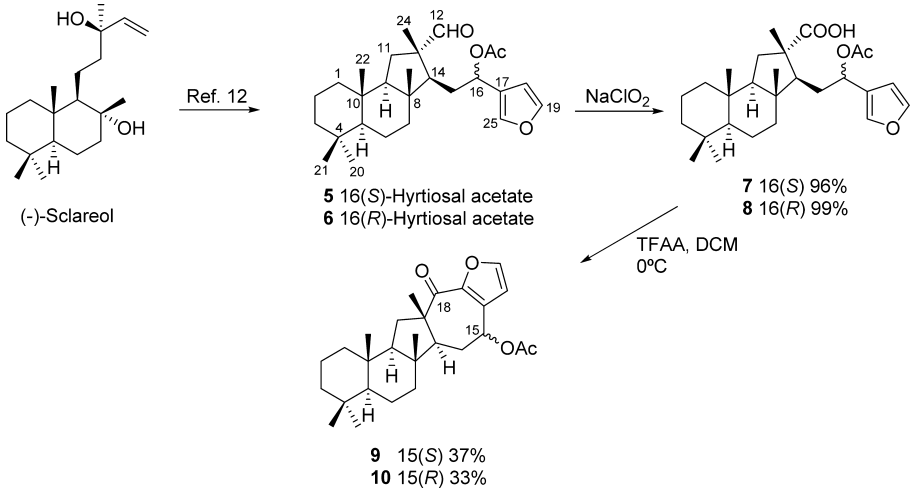
reaction" using diverse Lewis acids, such as $BF_3{\cdot}Et_2O$,[14] $TiCl_4$,[15] or $Yb(OTf)_3$,[16] or Brønsted acids, such as *p*-TsOH or PPA.[17] Unfortunately, the cyclization process did not take place. Alternatively, we tried the synthesis of the tetracyclic system of salmahyrtisanes by a Friedel–Crafts reaction. The aldehyde group of **5**–**6** was oxidized with sodium chlorite to the carboxylic acid, leading to **7**–**8** in almost quantitative yields. Compounds **7**–**8** were transformed into the corresponding acyl chlorides with oxalyl chloride. However, when these compounds were treated with $SnCl_4$,[18] the desired tetracyclic ketone was not obtained under the diverse experimental conditions attempted. In contrast, the direct cyclization of acids **7**–**8** was accomplished by treatment with TFAA,[19] affording the cycloheptanones **9**–**10** that have the salmahyrtisane skeleton.

Once the salmahyrtisane skeleton was obtained, the functional modification was carried out in order to achieve the functionality present at C-15 and C-18 of the objective molecule salmahyrtisol A (**1**). The sequence of reactions is described in Scheme 4.

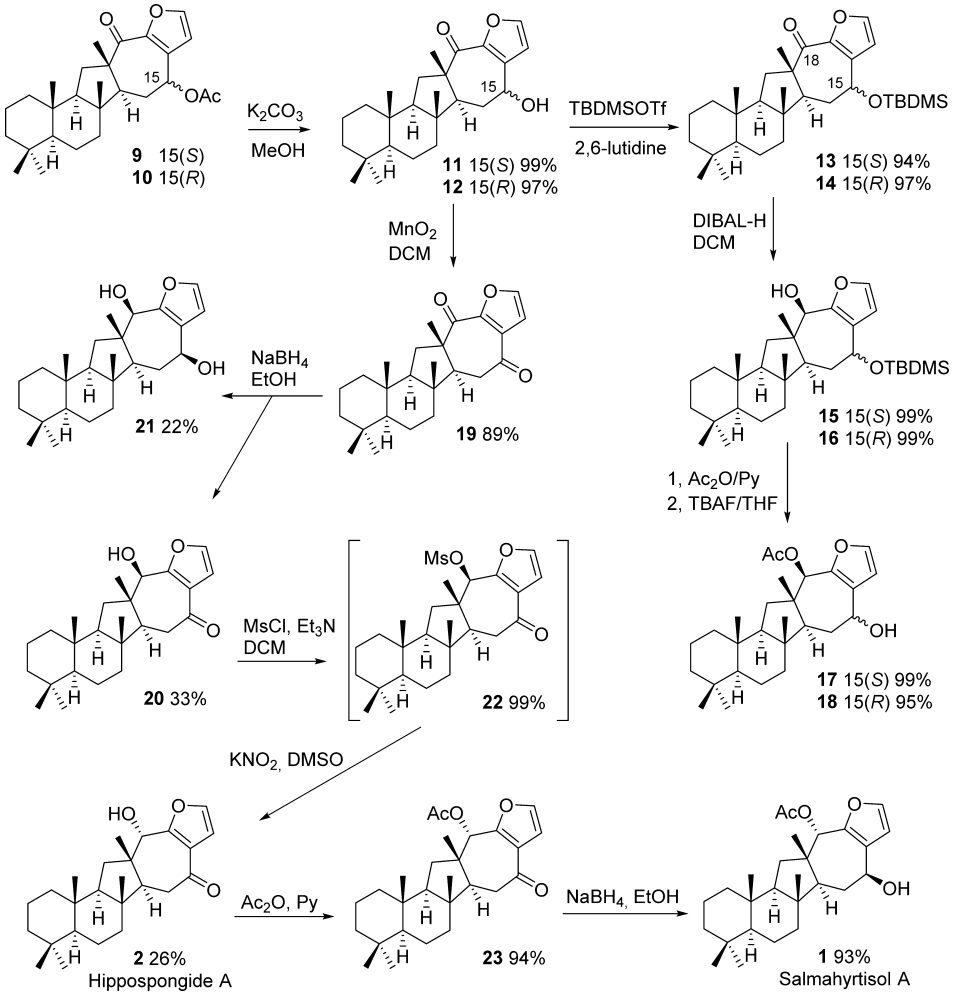
The hydrolysis of the ester group of **9**–**10** gave hydroxyketones **11**–**12**. The protection of the hydroxyl group as a TBDMS derivative under standard conditions led to compounds **13**–**14**. The reduction of the carbonyl group at C-18 of these compounds with several reducing agents always gave exclusively the hydroxyl group in a β configuration corresponding with the entry of the hydride to the less hindered face. The method of choice was DIBAL-H,[20] which led to compounds **15**–**16** in excellent yield. Due to the α configuration of the hydroxyl at C-18 in the natural products salmahyrtisol A (**1**) and hippospongide A (**2**), it was necessary

DOI: 10.1021/acs.joc.5b00420
J. Org. Chem. 2015, 80, 4566–4572

Scheme 3. Synthesis of the Salmahyrtisane Skeleton



Scheme 4. Synthesis of Salmahyrtisanes 1 and 2



to invert that stereogenic center. First of all, a Mitsunobu-type reaction under different conditions, such as DEAD/TPP (using several conditions and nucleophiles AcOH,[21] PhCOOH[22]), DIAD/TPP and PhCOOH, and TMAD/TBP using *p*-$MeOC_6H_4COOH$, was tried.[23] In any of the conditions related before, the inversion was not achieved due to the C-18 hydroxyl situation, hindered by the Me-21 and Me-23, recovering the starting material. Then, acetylation of the hydroxyl group at C-18 and deprotection of the hydroxyl group at C-15 of compounds **15**–**16** gave alcohols **17**–**18**, whose structures correspond to 18-*epi*-salmahyrtisol A (**17**) and 15,18-di-*epi*-salmahyrtisol A (**18**). Due to the impossibility to obtain an *S*-configuration for the C-18 hydroxy group, a bioreduction of ketone **13** was planned. Several alcohol dehydrogenases

DOI: 10.1021/acs.joc.5b00420
J. Org. Chem. 2015, 80, 4566–4572

Table 1. Antiproliferative Activity (GI_{50}) against Human Solid Tumor Cells[a]

	cell line					
compound	A549	HBL-100	HeLa	SW1573	T-47D	WiDr
1	4.7 (±1.0)	0.8 (±0.2)	0.6 (±0.4)	1.7 (±0.7)	52 (±5.6)	77 (±32)
9−10	15 (±0.5)	16 (±0.9)	13 (±1.1)	15 (±2.1)	28 (±3.3)	38 (±5.0)
11−12	44 (±5.9)	57 (±9.3)	34 (±5.9)	59 (±8.9)	>100	>100
19	28 (±0.5)	>100	30 (±2.0)	48 (±7.7)	67 (±7.0)	75 (±4.9)
20	35 (±3.2)	28 (±1.6)	25 (±1.9)	52 (±6.9)	73 (±20)	>100
21	33 (±1.6)	31 (±2.4)	22 (±3.2)	31 (±7.0)	98 (±2.6)	>100
cisplatin	2.1 (±0.6)	1.9 (±0.2)	2.0 (±0.3)	3.0 (±0.4)	15 (±2.3)	26 (±5.3)
etoposide	0.7 (±0.2)	2.3 (±0.9)	3.0 (±0.9)	15 (±1.5)	22 (±5.5)	23 (±3.1)

[a]Values are given in μM and are means of two to three experiments; standard deviation is given in parentheses.

(ADHs) were tried under different conditions, but no positive result was obtained. Among the different biocatalysts tested, ADs from *Rhodococcus ruber* (ADH-A), *Ralstonia* sp. (RasADH), and *Lactobacillus brevis* (LDADH) were included.[24] All the results showed that it was necessary to change the strategy to achieve the objective molecules.

Oxidation of the mixture of **11−12** with MnO_2 in DCM[25] gave diketone **19**, which was the key compound for the synthesis of the natural products. Reduction of **19** with sodium borohydride[26] gave hydroxyketone **20** and diol **21**. Mesylation of **20** in the usual conditions[27] gave mesylate **22**, which was not isolated and submitted to further transformation. The inversion of the configuration at C-18 was finally achieved by treatment of mesylate **22** with KNO_2/DMSO[28] at 70 °C for 7 h, obtaining compound **2**. The configuration at C-18 of **2** was corroborated by ROESY data, where NOE between H-23 and H-18 can be observed, confirming the β configuration of H-18. The physical properties of the obtained compound **2** ($[\alpha]_D^{20}$ = −62.0, lit. $[\alpha]_D^{20}$ = −66.0) are in full agreement with the ones described for the natural product hippospongide A isolated from the sponge *Hippospongia* sp.[9]

From compound **2**, by acetylation of the hydroxyl group at C-18, the acetyl derivate **23** was obtained. Ulterior reduction of **23** with sodium borohydride gave compound **1** in excellent yield (Scheme 4). The physical and spectroscopical properties ($[\alpha]_D^{20}$ = −57.0, lit. $[\alpha]_D^{20}$ = −59.0) are equivalent with the ones described for the natural product salmahyrtisol A isolated from *Hyrtios erecta*.[8]

We next evaluated the in vitro antiproliferative activity of compound **1** and its synthetic intermediates **9−12** and **19−21** against the panel of human solid tumor cell lines A549 (lung), HBL-100 (lung), HeLa (cervix), SW1573 (lung), T-47D (breast), and WiDr (colon) using the National Cancer Institute protocol.[29] The set of epimers **9−10** and **11−12** were tested as a mixture. The results expressed as GI_{50} (50% growth inhibition) are shown in Table 1. The standard anticancer drugs cisplatin and etoposide were used as reference agents. We found that salmahyrtisol A (**1**) was the most potent compound of the series with GI_{50} values in the range of 0.6−77 μM. The activity was comparable to that of the standard anticancer drugs in the cell lines A549, HBL-100, HeLa, and SW1573. In A549 cells, the results on antiproliferative activity are consistent with the reported value of IC_{50} > 2.2 μM.[8]

CONCLUSIONS

In conclusion, the first synthesis of tetracarbocyclic sesterterpene salmahyrtisane natural compounds has been achieved. Two new natural compounds, salmahyrtisol A (**1**) and hippospongide A (**2**), have been synthesized, and their structure and stereochemistry were confirmed. The biological tests have been done in a representative panel of human solid tumor cell lines. All compounds, **9**, **10**, **11**, **12**, **19**, **20**, **21**, and **1**, tested present a significant activity, salmahyrtisol A (**1**) being the most active one.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on a 200, 400 MHz (^1H) and 50 and 100 MHz (^{13}C) spectrometer for all compounds. 2D HMQC and 2D HMBC experiments were carried out on compounds **9**, **18**, and **21** for full assignments of the signals of these compounds. FTIR spectra were recorded as films. HRMS spectra were recorded by Q-TOF using an electrospray ionization method.

16*S*-Acetoxy-19,25-epoxy-hyrtiosa-17(25)-18-dien-12-oic acid: 7. To a solution of **5** (25 mg, 0.06 mmol) and 2-methyl-2-butene (0.4 mL) in 0.5 mL of *t*-BuOH was added a solution of 44 mg of NaH_2PO_4 in 0.3 mL of water and 0.2 mL of $NaClO_2$ 25% $NaClO_2$ (0.5 mmol). The reaction was stirred for 2.5 h. Afterward, H_2O was added and the mixture was acidulated with 2 M HCl. The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **7** as a colorless oil (25 mg, 96%). $[\alpha]_D^{22}$ = −32.9 (*c* = 0.5, $CHCl_3$); IR (film) 3200, 2930, 1738, 1694, 1464, 1387, 1371, 1236, 1161, 1024, 874, 801, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.5 (1H, s, COO<u>H</u>), 7.44 (1H, s, H-19), 7.35 (1H, s, H-25), 6.41 (1H, s, H-18), 5.77 (1H, m, H-16), 2.14−0.82 (17H, m), 2.01 (3H, s, <u>Me</u>COO), 1.25 (3H, s, Me-24), 0.84 (9H, s, Me-20, Me-21 and Me-23), 0.82 (3H, s, Me-22); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.4, 170.8, 143.3, 141.1, 124.9, 109.2, 67.1, 60.3, 57.4, 53.1, 48.3, 44.7, 42.7, 41.1, 40.2, 37.0 (2), 33.7, 33.3, 31.1, 22.4, 21.4 (2), 19.1, 18.5, 16.1, 16.0; HRMS calcd for $C_{27}H_{41}O_5$ requires $(M + 1)^+$ 445.2954; found 445.2947.

16*R*-Acetoxy-19,25-epoxy-hyrtiosa-17(25),18-dien-12-oic acid: 8. To a solution of **6** (12 mg, 0.03 mmol) and 2-methyl-2-butene (0.3 mL) in 1 mL of *t*-BuOH was added a solution of 21 mg of NaH_2PO_4 in 0.2 mL of water and 0.1 mL of $NaClO_2$ 25% $NaClO_2$ (0.3 mmol). The reaction was stirred for 4 h. Afterward, H_2O was added and the mixture was acidulated with 2 M HCl. The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **8** as a colorless oil (13 mg, 99%). $[\alpha]_D^{22}$ = −2.8 (*c* = 0.9, $CHCl_3$); IR (film) 3397, 1732, 1717, 1456, 1373, 1260, 1086, 1024, 957, 874, 801, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.50 (1H, s, COO<u>H</u>), 7.40 (1H, s, H-19), 7.36 (1H, s, H-25), 6.40 (1H, s, H-18), 5.79 (1H, dd, *J* = 8.8, 6.2 Hz, H-16), 2.15−0.85 (17H, m), 2.00 (3H, s, <u>Me</u>COO), 1.27 (3H, s, Me-24), 0.83 (6H, s, Me-20 and Me-21), 0.81 (6H, s, Me-22 and Me-23); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.6, 170.1, 143.1, 141.4, 124.1, 108.6, 67.6, 60.0, 57.1, 53.4, 48.1, 44.6, 42.4, 40.4, 40.0, 36.9, 36.6, 33.4, 33.0, 31.0, 22.4, 21.4, 21.2, 18.8, 18.2, 15.8 (2); HRMS calcd for $C_{27}H_{41}O_5$ requires $(M + 1)^+$ 445.2954; found 445.2948.

15*S*-Acetoxy-17,24-epoxy-salmahyrtisa-16,24-dien-18-one: 9. To a solution of **7** (8 mg, 0.02 mmol) in dry DCM (0.2 mL) at 0 °C was added TFAA (0.02 mL, 0.16 mmol). The reaction was stirred for 3.5 h at 0 °C, and then 10% $NaHCO_3$ (aq) was added. After that, the

DOI: 10.1021/acs.joc.5b00420
J. Org. Chem. 2015, 80, 4566−4572

mixture was stirred for 30 min and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with 10% $NaHCO_3$ (aq) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt 9/1) to obtain **9** as a colorless oil (3 mg, 37%). $[\alpha]_D^{22} = -25.7$ (c = 0.3, $CHCl_3$); IR (film) 2929, 1742, 1677, 1462, 1371, 1232, 1033, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, d, J = 1.8 Hz, H-25), 6.34 (1H, d, J = 1.8 Hz, H-24), 6.00 (1H, dd, J = 9.6, 8.0 Hz, H-15), 2.80 (1H, dd, J = 12.8, 6.8 Hz, H_A-11), 2.16 (1H, dd, J = 13.4, 8.0 Hz, H_A-14), 2.14 (3H, s, MeCOO), 1.97 (1H, dd, J = 13.4, 9.6 Hz, H_B-14), 1.73−0.75 (14H, m), 1.31 (3H, s, Me-23), 0.86 (3H, s, Me-22), 0.83 (3H, s, Me-21), 0.81 (6H, s, Me-19 and Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 170.2, 145.8, 145.2, 129.9, 112.9, 69.8, 60.4, 57.6, 53.3, 53.1, 44.9, 42.4, 39.9 (2), 36.7, 33.4, 33.0, 30.7, 27.4, 25.7, 21.2, 21.1, 18.5, 18.2, 16.0, 15.3; HRMS(E.I.) calcd for $C_{27}H_{38}O_4$ requires $(M)^+$ 426.2770; found 426.2768.

15*R*-Acetoxy-17,24-epoxy-salmahyrtisa-16,24-dien-18-one: 10. To a solution of **8** (12 mg, 0.03 mmol) in dry DCM (0.2 mL) at 0 °C was added TFAA (0.03 mL, 0.24 mmol). The reaction was stirred for 12 h at 0 °C, and then 10% $NaHCO_3$ was added (aq). After that, the mixture was stirred for 30 min and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt 9/1) to obtain **10** as a colorless oil (5 mg, 33%). $[\alpha]_D^{22} = +9.7$ (c = 0.4, $CHCl_3$); IR (fim) 2927, 1739, 1678, 1463, 1371, 1233, 1018, 891, 787 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54 (1H, d, J = 1.8 Hz, H-25), 6.45 (1H, d, J = 1.8 Hz, H-24), 6.12 (1H, dd, J = 5.2, 3.0 Hz, H-15), 2.80 (1H, dd, J = 12.4, 6.2 Hz, H_A-11), 2.20 (1H, dd, J = 13.2, 5.2 Hz, H_A-14), 2.06 (3H, s, MeCOO), 1.98 (1H, d, J = 13.2 Hz, H_B-14), 1.90−0.80 (14H, m), 1.24 (3H, s, Me-23), 0.87 (3H, s, Me-22), 0.85 (3H, s, Me-21), 0.83 (6H, s, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.8, 170.3, 147.0, 146.0, 128.6, 114.0, 67.5, 60.9, 57.9, 53.4, 51.0, 44.6, 42.7, 40.2, 39.8, 37.0, 33.8, 33.3, 31.0, 27.6, 24.7, 21.5 (2), 18.8, 18.5, 16.4, 15.6; HRMS(E.I.) calcd para $C_{27}H_{38}O_4$ requires $(M)^+$ 426.2770; found 426.2766.

15*S*-Hydroxy-17,24-epoxy-salmahyrtisa-16,24-dien-18-one: 11. To a stirred solution of **9** (18 mg, 0.04 mmol) in MeOH (1 mL) was added anhydrous K_2CO_3 (30 mg, 0.22 mmol). The mixture was stirred at r.t., following the evolution of reaction by TLC. When the reaction was finished, water was added and MeOH was removed under reduced pressure. It was extracted with AcOEt, and the combined organic layer was washed with water until neutral pH was reached, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **11** as a colorless oil (16 mg, 99%). $[\alpha]_D^{22} = -19.4$ (c = 0.6, $CHCl_3$); IR (film) 3446, 2926, 1653, 1457, 1387, 1264, 1061, 970, 892, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55 (1H, d, J = 1.8 Hz, H-25), 6.66 (1H, d, J = 1.8 Hz, H-24), 4.81 (1H, dd, J = 10.6, 7.0 Hz, H-15), 2.81 (1H, dd, J = 12.6, 6.6 Hz, H_A-11), 2.40−0.80 (16H, m), 1.31 (3H, s, Me-23), 0.87 (3H, s, Me-22), 0.86 (3H, s, Me-21), 0.83 (6H, s, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.8, 146.1, 144.6, 133.8, 113.3, 69.6, 60.7, 58.0, 53.6, 53.3, 45.2, 42.7, 40.2, 40.1, 37.0, 33.7, 33.3, 31.8, 30.9, 26.4, 21.5, 18.8, 18.5, 16.4, 15.5; HRMS(E.I.) calcd for $C_{25}H_{36}O_3$ requires $(M)^+$ 384.2664; found 384.2669.

15*R*-Hydroxy-17,24-epoxy-salmahyrtisa-16,24-dien-18-one: 12. To a stirred solution of **10** (15 mg, 0.04 mmol) in MeOH (1 mL) was added anhydrous K_2CO_3 (30 mg, 0.22 mmol). The mixture was stirred at r.t., following the evolution of reaction by TLC. When the reaction was finished, water was added and MeOH was removed under reduced pressure. It was extracted with AcOEt, and the combined organic layer was washed with water until neutral pH was reached, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **12** as a colorless oil (13 mg, 97%). $[\alpha]_D^{22} = -15.2$ (c = 0.3, $CHCl_3$); IR (film) 3419, 2924, 1653, 1464, 1387, 1284, 983, 908, 793, 732, 647 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 1.8 Hz, H-25), 6.56 (1H, d, J = 1.8 Hz, H-24), 5.04 (1H, dd, J = 5.6, 3.4 Hz, H-15), 2.80 (1H, dd, J = 12.4, 6.2 Hz, H_A-11), 2.40−0.84 (16H, m), 1.22 (3H, s, Me-23), 0.88 (6H, s, Me-21 and Me-22), 0.82 (6H, s, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.2, 146.2, 145.4, 132.6, 113.8, 65.8, 61.0, 57.9, 53.4, 50.7, 44.6, 42.7, 40.2, 40.1, 37.0, 33.7, 33.3, 31.1, 30.4, 24.6, 21.5, 18.8, 18.5, 16.5, 15.7; HRMS(E.I.) calcd for $C_{25}H_{36}O_3$ requires $(M)^+$ 384.2664; found 384.2670.

15*S*-*t*-Butyldimethylsilyloxy-17,24-epoxy-salmahyrtisa-16,24-dien-18-one: 13. To a solution of **11** (14 mg, 0.036 mmol) in dry DCM (0.5 mL) at 0 °C under an argon atmosphere were added 2,6-lutidine (10 μL, 0.1 mmol) and TBDMSOTf (20 μL, 0.06 mmol). The reaction was stirred at r.t. for 2 h and then diluted with Et_2O. The organic layer was washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **13** as a colorless oil (17 mg, 94%). $[\alpha]_D^{22} = -22.6$ (c = 0.4, $CHCl_3$); IR (film) 2928, 1675, 1463, 1387, 1256, 1071, 970, 837, 778 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51 (1H, d, J = 1.8 Hz, H-25), 6.52 (1H, d, J = 1.8 Hz, H-24), 4.75 (1H, dd, J = 9.6, 6.6 Hz, H-15), 2.79 (1H, dd, J = 12.3, 6.6 Hz, H_A-11), 2.09−0.80 (16H, m), 1.30 (3H, s, Me-23), 0.97 (9H, s, SiC$(CH_3)_3$), 0.88 (3H, s, Me-22), 0.85 (3H, s, Me-21), 0.83 (6H, s, Me-19 and Me-20), 0.17 and 0.16 (6H, s, $(CH_3)_2$Si); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.6, 145.4, 144.4, 134.6, 113.2, 70.5, 60.6, 57.8, 53.2, 53.1, 44.8, 42.5, 40.0, 39.9, 36.7, 33.5, 33.0, 31.6, 30.6, 26.2, 26.0−25.8, 21.2, 18.5, 18.1, 16.2, 15.3, 1.0, −4.2, −4.8; HRMS(E.I.) calcd for $C_{31}H_{50}O_3Si$ requires $(M)^+$ 498.3529; found 498.3522.

15*R*-*t*-Butyldimethylsilyloxy-17,24-epoxy-salmahyrtisa-16,24-dien-18-one: 14. To a solution of **12** (11 mg, 0.029 mmol) in dry DCM (0.5 mL) at 0 °C under an argon atmosphere were added 2,6-lutidine (10 μL, 0.1 mmol) and TBDMSOTf (20 μL, 0.06 mmol). The reaction was stirred at r.t. for 2 h and then diluted with Et_2O. The organic layer was washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **14** as a colorless oil (14 mg, 97%). $[\alpha]_D^{22} = -11.4$ (c = 0.3, $CHCl_3$); IR (film) 2930, 1678, 1464, 1387, 1254, 1067, 986, 934, 837, 775 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.52 (1H, d, J = 1.8 Hz, H-25), 6.45 (1H, d, J = 1.8 Hz, H-24), 5.05 (1H, dd, J = 6.3, 4.2 Hz, H-15), 2.80 (1H, dd, J = 12.8, 6.4 Hz, H_A-11), 2.35−0.80 (16H, m), 1.22 (3H, s, Me-23), 0.91 (9H, s, SiC$(CH_3)_3$), 0.88 (6H, s, Me-21 and Me-22), 0.82 (6H, s, Me-19 and Me-20), 0.15 and 0.13 (6H, s, Si$(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.2, 145.4, 145.0, 133.7, 113.4, 66.2, 60.7, 57.5, 52.9, 51.0, 44.3, 42.5, 40.1, 40.0, 36.7, 33.5, 33.0, 31.9, 30.9, 25.8, 23.8, 21.2, 18.7, 18.5, 16.2, 15.5, 1.0, −4.3, −4.8; HRMS(E.I.) calcd for $C_{31}H_{50}O_3Si$ requires $(M)^+$ 498.3529; found 498.3536.

15*S*-*t*-Butyldimethylsilyloxy-17,24-epoxy-salmahyrtisa-16,24-dien-18*R*-ol: 15. To a solution of **13** (16 mg, 0.032 mmol) in dry DCM (0.4 mL) at −78 °C under an argon atmosphere was added a 1.5 M toluene solution of DIBAL-H (50 μL, 0.06 mmol), and the reaction was stirred for 30 min. Afterward, it was quenched with MeOH (0.5 mL), water (0.5 mL), and a saturated solution of sodium potassium tartrate. The mixture was stirred for 1 h and extracted with Et_2O. The combined organic layer was washed with 10% $NaHCO_3$ and water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **15** as a colorless oil (16 mg, 99%). $[\alpha]_D^{22} = -8.0$ (c = 0.5, $CHCl_3$); IR (film) 3392, 2924, 1463, 1387, 1257, 1151, 1049, 836, 775, 738 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (1H, d, J = 1.8 Hz, H-25), 6.46 (1H, d, J = 1.8 Hz, H-24), 4.51 (1H, d, J = 8.2 Hz, H-15), 4.39 (1H, s, H-18), 2.05 (1H, dd, J = 12.0, 6.2 Hz, H_A-11), 1.74−0.80 (16H, m), 1.26 (3H, s, Me-23), 0.96 (9H, s, SiC$(CH_3)_3$), 0.87 (3H, s, Me-22), 0.85 (6H, s, Me-19 and Me-20), 0.81 (3H, s, Me-21), 0.14 and 0.13 (6H, s, Si$(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.0, 139.8, 122.7, 112.5, 78.0, 71.0, 60.2, 58.3, 55.2, 45.1, 44.6, 42.8, 40.3, 40.2, 36.9, 33.9, 33.8, 33.4, 31.3, 26.2, 21.5, 21.2, 18.9, 18.6, 16.8, 15.6, 1.2, −4.2, −4.6; HRMS(E.I.) calcd for $C_{31}H_{52}O_3Si$ requires $(M)^+$ 500.3686; found 500.3680.

15*R*-*t*-Butyldimethylsilyloxy-17,24-epoxy-salmahyrtisa-16,24-dien-18*R*-ol: 16. To a solution of **14** (5 mg, 0.01 mmol) in dry DCM (0.4 mL) at −78 °C under an argon atmosphere was added a 1.5 M toluene solution of DIBAL-H (17 μL, 0.02 mmol), and the reaction was stirred for 30 min. Afterward, it was quenched with MeOH (0.2 mL), water (0.2 mL), and a saturated solution of sodium potassium tartrate. The mixture was stirred for 1 h and extracted with Et_2O. The combined organic layer was washed with 10% $NaHCO_3$ (aq) and water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to

DOI: 10.1021/acs.joc.5b00420
J. Org. Chem. 2015, 80, 4566−4572

obtain **16** as a colorless oil (5 mg, 99%). $[\alpha]_D^{22}$ = +1.6 (*c* = 0.3, $CHCl_3$); IR (film) 3402, 2926, 1463, 1386, 1255, 1046, 834, 774, 731 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (1H, d, *J* = 1.8 Hz, H-25), 6.26 (1H, d, *J* = 1.8 Hz, H-24), 4.80 (1H, d, *J* = 3.4 Hz, H-15), 4.51 (1H, s, H-18), 2.04 (1H, dd, *J* = 12.8, 6.4 Hz, H_A-11), 1.88−0.80 (16H, m), 1.26 (3H, s, Me-23), 0.90 (3H, s, Me-22), 0.87 (9H, s, SiC(CH$_3$)$_3$), 0.84 (6H, s, Me-19 and Me-20), 0.79 (3H, s, Me-21) 0.10 and 0.07 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.8, 139.9, 120.8, 109.5, 77.4, 66.3, 60.2, 58.1, 51.7, 44.6, 44.4, 42.9, 40.4 (2), 37.0, 34.2, 33.8, 33.4, 30.9, 26.1, 21.6, 19.4, 19.0, 18.6, 16.7, 15.7, 1.2, −4.2; HRMS(E.I.) calcd for $C_{31}H_{52}O_3Si$ requires $(M)^+$ 500.3686; found 500.3690.

18*R*-Acetoxy-17,24-epoxy-salmahyrtisa-16,24-dien-15*S*-ol: 17. To a solution of **15** (7 mg, 0.014 mmol) in pyridine (0.5 mL) under an argon atmosphere was added Ac_2O (1 mL). The reaction was stirred for 12 h and then was quenched with ice. The mixture was extracted with Et_2O, and the combined organic layer was washed with 2 M HCl, 10% $NaHCO_3$, and water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain 7 mg of acetate. To a solution of acetate of the last reaction in THF (0.5 mL) under an argon atmosphere was added TBAF (30 μL, 0.13 mmol). The reaction was stirred for 2 h and then was quenched with water. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **17** as a colorless oil (6 mg, 99%). $[\alpha]_D^{22}$ = +23.0 (*c* = 0.1, $CHCl_3$); IR (film) 3408, 2926, 2853, 1743, 1462, 1371, 1237, 1153, 1030, 895, 739, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (1H, d, *J* = 1.8 Hz, H-25), 6.50 (1H, d, *J* = 1.8 Hz, H-24), 5.67 (1H, s, H-18), 4.59 (1H, dd, *J* = 8.8, 6.5 Hz, H-15), 2.22 (3H, s, MeCOO), 1.94 (1H, dd, *J* = 12.8, 6.8 Hz, H_A-11), 1.76−0.80 (16H, m), 1.08 (3H, s, Me-23), 0.85 (6H, s, Me-21 and Me-22), 0.83 (3H, s, Me-19), 0.82 (3H, s, Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 144.8, 140.8, 122.2, 111.3, 77.0, 69.2, 59.5, 57.8, 54.6, 44.6, 44.0, 42.4, 40.1, 39.9, 36.5, 34.0, 33.5, 33.0, 31.9, 22.6, 21.2, 21.0, 18.6, 18.2, 16.2, 15.4; HRMS(E.I.) calcd for $C_{27}H_{40}O_4$ requires $(M)^+$ 428.2927; found 428.2921.

18*R*-Acetoxy-17,24-epoxy-salmahyrtisa-16,24-dien-15*R*-ol: 18. To a solution of **16** (16 mg, 0.032 mmol) in pyridine (0.5 mL) under an argon atmosphere was added Ac_2O (1 mL). The reaction was stirred for 12 h and then was quenched with ice. The mixture was extracted with Et_2O, and the combined organic layer was washed with 2 M HCl, 10% $NaHCO_3$, and water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain 17 mg of acetate. To a solution of acetate in THF (0.5 mL) under an argon atmosphere was added TBAF (40 μL, 0.18 mmol). The reaction was stirred for 2 h and then was quenched with water. The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **18** as a colorless oil (13 mg, 95%). $[\alpha]_D^{22}$ = +35.0 (*c* = 0.2, $CHCl_3$); IR (film) 3350, 2924, 1736, 1461, 1370, 1237, 1030, 894, 739, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 1.8 Hz, H-25), 6.33 (1H, d, *J* = 1.8 Hz, H-24), 5.79 (1H, s, H-18), 4.83 (1H, t, *J* = 3.3 Hz, H-15), 2.21 (3H, s, MeCOO), 2.00−1.70 (4H, m, H-14, H_A-11, H-13), 1.70−0.80 (13H, m, H-1, H-2, H-3, H-5, H-6, H-7, H-9, H_B-11), 1.00 (3H, s, Me-23), 0.86 (3H, s, Me-22), 0.84 (3H, s, Me-21), 0.83 (3H, s, Me-19), 0.82 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 147.4, 141.1, 121.0, 112.9, 76.9, 65.5, 59.7, 57.8, 51.8, 44.4, 43.3, 42.5, 40.0 (2), 36.6, 34.0, 33.5, 33.0, 29.3, 21.2, 21.0, 19.9, 18.4, 18.2, 16.2, 15.4; HRMS(E.I.) calcd for $C_{27}H_{40}O_4$ requires $(M)^+$ 428.2927; found 428.2936.

17,24-Epoxy-salmahyrtisa-16,24-dien-15,18-dione: 19. To a solution of **11**/**12** (39 mg, 0.1 mmol) in DCM (9 mL) under an argon atmosphere was added MnO_2 (293 mg, 3.4 mmol). The suspension was stirred for 45 min. After that time, the mixture was filtered through a short pad of Celite and concentrated *in vacuo* to obtain **19** as a colorless oil (34 mg, 89%). $[\alpha]_D^{22}$ = −35.0 (*c* = 0.1, $CHCl_3$); IR (film) 2924, 2850, 1670, 1489, 1398, 1265, 1014, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 1.8 Hz, H-24), 6.89 (1H, d, *J* = 1.8 Hz, H-25), 2.86 (1H, dd, *J* = 19.0, 12.4 Hz, H_A-14), 2.67 (1H, dd, *J* = 19.0, 2.5 Hz, H_B-14), 2.12 (1H, dd, *J* = 12.4, 2.5 Hz, H-13), 1.80−0.80 (14H, m), 1.32 (3H, s, Me-23), 0.91 (3H, s, Me-21), 0.90 (3H, s, Me-22), 0.83 (6H, s, Me-19 and Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 192.1, 148.5, 146.0, 128.4, 111.9, 60.6, 57.6, 53.6, 52.2, 44.7, 42.4, 40.1, 40.0, 38.0, 36.7, 33.4, 33.0, 30.8, 23.5, 21.2, 18.6, 18.2, 16.1, 15.6; HRMS(E.I.) calcd for $C_{25}H_{34}O_3Na$ requires $(M + Na)^+$ 405.2400; found 405.2397.

18*R*-Hydroxy-17,24-epoxy-salmahyrtisa-16,24-dien-15-one: 20, and 17,24-Epoxy-salmahyrtisa-16,24-dien-15*S*,18*R*-diol: 21. To a solution of **19** (18 mg, 0.047 mmol) in EtOH (0.5 mL) at 0 °C under an argon atmosphere was added $NaBH_4$ (1 mg, 0.02 mmol). The reaction was stirred for 1.5 h and then quenched with 2 M HCl (0.1 mL) and water (2 mL). The mixture was extracted with Et_2O; the combined organic layer was washed with water, dried (Na_2SO_4), and filtered; and the solvent was evaporated under pressure. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt 95/5 and 9/1) to obtain **19** (6 mg, 34%), **20** (6 mg, 33%), and **21** (4 mg, 22%), all as colorless oils.

20: $[\alpha]_D^{22}$ = −36.7 (*c* = 0.6, $CHCl_3$); IR (film) 3390, 2937, 1635, 1560, 1458, 1400, 1132, 1039, 748 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (1H, d, *J* = 1.8 Hz, H-24), 6.77 (1H, d, *J* = 1.8 Hz, H-25), 4.59 (1H, s, H-18), 2.64 (1H, dd, *J* = 18.9, 12.9 Hz, H_A-14), 2.47 (1H, dd, *J* = 18.9, 2.5 Hz, H_B-14), 2.08 (1H, dd, *J* = 12.9, 6.3 Hz, H_A-11), 1.43−1.35 (1H, m, H_B-11), 1.75−0.80 (13H, m), 1.10 (3H, s, Me-23), 0.90 (3H, s, Me-21), 0.87 (3H, s, Me-22), 0.85 (3H, s, Me-19), 0.84 (3H, s, Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.7, 158.5, 141.8, 121.8, 110.7, 76.9, 59.6, 57.8, 52.6, 44.2, 44.1, 42.5, 40.3, 40.2, 37.8, 36.6, 34.5, 33.5, 33.1, 21.2, 18.7, 18.3, 18.1, 15.9, 15.8; HRMS(E.I.) calcd for $C_{25}H_{36}O_3Na$ requires $(M + Na)^+$ 407.2556; found 407.2534.

21: $[\alpha]_D^{22}$ = −3.0 (*c* = 0.7, $CHCl_3$); IR (film) 3392, 2920, 1637, 1458, 1382, 1147, 1029, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* = 1.8 Hz, H-24), 6.54 (1H, d, *J* = 1.8 Hz, H-25), 4.55 (1H, ddd, *J* = 10.4, 6.6, 1.8 Hz, H-15), 4.39 (1H, s, H-18), 2.04 (1H, dd, *J* = 12.9, 6.8 Hz, H-14), 1.91 (1H, dd, *J* = 12.7, 6.5 Hz, H-11), 1.78−0.80 (15H, m), 0.99 (3H, s, Me-23), 0.86 (3H, s, Me-22), 0.84 (3H, s, Me-19), 0.83 (3H, s, Me-20), 0.81 (3H, s, Me-21); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.1, 140.3, 121.5, 111.7, 77.3, 69.4, 59.7, 57.9, 54.3, 44.9, 44.3, 42.5, 40.1, 40.0, 36.6, 33.8, 33.5, 33.1, 31.3, 21.2, 19.8, 18.6, 18.3, 16.3, 15.4; HRMS(E.I.) calcd for $C_{25}H_{38}O_3Na$ requires $(M + Na)^+$ 409.2713; found 409.2707.

18*S*-Hydroxy-17.24-epoxy-salmahyrtisa-16,24-dien-15-one: 2 (Hippospongide A). To a solution of **20** (10 mg, 0.026 mmol) in DCM (0.26 mL) at 0 °C under an argon atmosphere were added Et_3N (4.2 μL, 0.03 mmol) and MsCl (4.6 μL, 0.06 mmol). The reaction was stirred at r.t. for 1 h and then quenched with drops of 0.5 M HCl. The mixture was extracted with DCM, and the combined organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **22** as a colorless oil (12 mg, 99%). To mesylate **22** (12 mg, 0.03 mmol) in DMSO (0.1 mL) was added KNO_2 (57 mg, 0.63 mmol). The reaction was heated at 90 °C for 7 h under an argon atmosphere. After that time, the solution was quenched with brine and extracted with Et_2O. The combined organic layer was washed with brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated under pressure. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt 95/5) to obtain **2** as a colorless oil (3 mg, 26%). $[\alpha]_D^{22}$ = −62.0 (*c* = 0.3, $CHCl_3$); IR (film) 3383, 2956, 2918, 2859, 1718, 1637, 1465, 1386, 1271, 1041, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 1.6 Hz, H-24), 6.76 (1H, d, *J* = 1.6 Hz, H-25), 4.58 (1H, s, H-18), 2.64 (1H, dd, *J* = 18.4, 12.7 Hz, H_A-14), 2.55 (1H, dd, *J* = 18.4, 2.9 Hz, H_B-14), 2.20 (1H, dd, *J* = 12.7, 2.9 Hz, H-13), 1.99 (1H, d, *J* = 6.0 Hz, H_A-11), 1.70−0.90 (13H, m), 1.14 (3H, s, Me-23), 0.87 (3H, s, Me-22), 0.85 (6H, s, Me-19 and Me-21), 0.84 (3H, s, Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.7, 159.0, 142.3, 123.0, 110.8, 75.9, 61.0, 57.6, 47.6, 44.8, 43.0, 42.5, 40.2, 40.1, 39,6, 36.8, 34.9, 33.5, 33.1, 23.4, 21.3, 18.8, 18.3, 16.2, 15.6; HRMS(E.I.) calcd for $C_{25}H_{36}O_3Na$ requires $(M + Na)^+$ 407.2556; found 407.2534.

18*S*-Acetoxy-17,24-epoxy-salmahyrtisa-16,24-dien-15-one: 23. To a solution of **2** (4 mg, 0.01 mmol) in pyridine (0.5 mL) was added Ac_2O (1 mL). The reaction was stirred for 12 h and then quenched with ice. The mixture was extracted with Et_2O; the

DOI: 10.1021/acs.joc.5b00420
J. Org. Chem. 2015, 80, 4566−4572

combined organic layer was washed with 2 M HCl, 10% $NaHCO_3$, and water, dried (Na_2SO_4), and filtered; and the solvent was evaporated under pressure. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt 99/1) to obtain **23** as a colorless oil (4 mg, 94%). $[\alpha]_D^{22}$ = −64.4 (*c* = 0.2, $CHCl_3$); IR (film) 2924, 2852, 1735, 1662, 1458, 1369, 1224, 1053, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 1.8 Hz, H-24), 6.76 (1H, d, *J* = 1.8 Hz, H-25), 6.04 (1H, s, H-18), 2.65 (1H, dd, *J* = 18.4, 12.6 Hz, H_A-14), 2.57 (1H, dd, *J* = 18.4, 3.0 Hz, H_B-14), 2.24 (1H, dd, *J* = 12.6, 3.0 Hz, H-13), 2.16 (3H, s, MeCOO), 2.10−0.80 (14H, m), 1.22 (3H, s, Me-23), 0.86 (3H, s, Me-22), 0.85 (3H, s, Me-21), 0.84 (6H, s, Me-19 and Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.2, 170.2, 155.0, 142.4, 124.8, 110.7, 75.4, 61.2, 58.1, 48.9, 44.5, 42.6, 42.4, 40.0, 39.8, 39.5, 37.9, 34.7, 33.5, 33.1, 23.1, 21.3, 21.1, 18.7, 18.3, 16.1, 15.4; HRMS(E.I.) calcd for $C_{27}H_{38}O_4$ requires $(M)^+$ 426.2770; found 426.2761.

18*S*-Acetoxy-17,24-epoxy-salmahyrtisa-16,24-dien-15*S*-ol: 1 (Salmahyrtisol A). To a solution of **23** (4 mg, 0.009 mmol) in EtOH (0.5 mL) at 0 °C under an argon atmosphere was added $NaBH_4$ (4 mg, 0.1 mmol). The reaction was stirred for 1.5 h and quenched with drops of 2 M HCl and water. The mixture was extracted with Et_2O; the combined organic layer was washed with water, dried (Na_2SO_4), and filtered; and the solvent was evaporated under pressure. The resulting crude residue was purified by column chromatography (silica gel, hexane/AcOEt 9/1) to obtain **1** as colorless needles (3.6 mg, 93%). $[\alpha]_D^{22}$= −53.0 (*c* = 0.8, CH_3Cl); IR (film) 3400, 2924, 2852, 1740, 1689, 1458, 1201, 1139 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, d, *J* = 1.8 Hz, H-24), 6.50 (1H, d, *J* = 1.8 Hz, H-25), 5.87 (1H, s, H-18), 4.69 (1H, dd, *J* = 10.8, 6.1 Hz, H-15), 2.09 (3H, s, MeCOO), 1.92 (1H, dd, *J* = 12.7, 6.1 Hz, H_A-14), 1.82 (1H, d, *J* = 11.3 Hz, H-13), 1.75−0.74 (15H, m), 1.07 (3H, s, Me-23), 0.86 (3H, s, Me-19), 0.83 (3H, s, Me-20), 0.82 (3H, s, Me-22), 0.79 (3H, s, Me-21); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.3, 146.4, 141.6, 126.3, 111.2, 75.9, 70.0, 61.3, 58.2, 50.7, 44.4, 43.0, 42.6, 40.7, 40.1, 36.7, 34.5, 33.4, 33.1, 32.7, 24.9, 21.3, 21.2, 18.6, 18.2, 16.4, 15.2; HRMS(E.I.) calcd for $C_{27}H_{40}O_4$ requires $(M)^+$ 428.2927; found 428.2921.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of IR and NMR spectra and comparative tables of physical data of **1**, **2**, and natural compounds salmahyrtisol A and hippospongide A are included. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +34 923294574. Tel: +34 923294474. E-mail: pbb@usal.es (P.B.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank FSE and Junta de Castilla y León (GR178) for financial support. A.U. is grateful to the JCyL-FSE for his fellowship. We are grateful to Dr. Vicente Gotor Fernández (Univ. Oviedo, Inst. Univ. Biotecnol. Asturias, Dept. Organ. & Inorgan. Chem., Ave. Julian Claveria S-N, E-33006, Oviedo, Spain). J.M.P. thanks the EU Research Potential (FP7-REGPOT-2012-CT2012-31637-IMBRAIN), the European Regional Development Fund (FEDER), and the Spanish Instituto de Salud Carlos III (PI11/00840) for financial support.

■ REFERENCES

(1) Hanson, J. R. *Nat. Prod. Rep.* **1986**, *3*, 123−132.
(2) Hanson, J. R. *Nat. Prod. Rep.* **1992**, *9*, 481−489.
(3) Hanson, J. R. *Nat. Prod. Rep.* **1996**, *13*, 529−535.
(4) Liu, Y.; Wang, L.; Jung, J. H.; Zhang, S. *Nat. Prod. Rep.* **2007**, *24*, 1401−1429.
(5) Wang, L.; Yang, B.; Lin, X.-P.; Zhou, X.-F.; Liu, Y. *Nat. Prod. Rep.* **2013**, *30*, 455−473.
(6) González, M. A. *Curr. Bioact. Compd.* **2010**, *6*, 178−206.
(7) Ungur, N.; Kulcitki, V. *Tetrahedron* **2009**, *65*, 3815−3828.
(8) Youssef, D. T. A.; Yamaki, R. K.; Scheuer, P. J. *J. Nat. Prod.* **2002**, *65*, 2−6.
(9) Chang, Y.-C.; Tseng, S.-W.; Liu, L.-L.; Chou, Y.; Ho, Y.-S.; Lu, M.-C.; Su, J.-H. *Mar. Drugs* **2012**, *10*, 987−997.
(10) Mahidol, C.; Prawat, H.; Sangpetsiripan, S.; Ruchirawat, S. *J. Nat. Prod.* **2009**, *72*, 1870−1874.
(11) Iguchi, K.; Shimada, Y.; Yamada, Y. *J. Org. Chem.* **1992**, *57*, 522−524.
(12) Basabe, P.; Diego, A.; Díez, D.; Marcos, I. S.; Urones, J. G. *Synlett* **2000**, 1807−1809.
(13) Basabe, P.; Diego, A.; Díez, D.; Marcos, I. S.; Mollinedo, F.; Urones, J. G. *Synthesis* **2002**, 1523−1529.
(14) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988−3996.
(15) For a review, see: Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Friedel-Crafts Alkylations; Pergamon Press: Oxford, U.K., 1991; Vol. 3, p 293.
(16) Zhang, W.; Wang, P. G. *J. Org. Chem.* **2000**, *65*, 4732−4735.
(17) Krishnegowda, G.; Thimmaiah, P.; Hegde, R.; Dass, C.; Houghton, P. J.; Thimmaiah, K. N. *Bioorg. Med. Chem.* **2002**, *10*, 2367−2380.
(18) Buckley, T. F., III; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 4222−4232.
(19) Yim, H.-K.; Liao, Y.; Wong, H. N. C. *Tetrahedron* **2003**, *59*, 1877−1884.
(20) Wilson, K. E.; Seidner, R. T.; Masamune, S. *Chem. Commun.* **1970**, 213−214.
(21) Kobayashi, Y.; Ito, M.; Igarashi, J. *Tetrahedron Lett.* **2002**, *43*, 4829−4832.
(22) Knapp, S.; Morriello, G. J.; Doss, G. A. *Tetrahedron Lett.* **2003**, *44*, 2645.
(23) Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.* **1995**, *36*, 2529−2530.
(24) (a) Kedziora, K.; Bisogno, F. R.; Lavandera, I.; Gotor-Fernández, V.; Montejo-Bernardo, J.; García-Granda, S.; Kroutil, W.; Gotor, V. *ChemCatChem* **2014**, *6*, 1066−1072. (b) Lavandera, I.; Kern, A.; Ferreira-Silva, B.; Glieder, A.; de Wildeman, S.; Kroutil, W. *J. Org. Chem.* **2008**, *73*, 6003−6005.
(25) Cresp, T. M.; Sondheimer, F. *J. Am. Chem. Soc.* **1975**, *97*, 4412−4413.
(26) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567−607.
(27) Cainelli, G.; Panunzio, M.; Basile, T.; Bongini, A.; Giacomini, D.; Martelli, G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2637−2642.
(28) Raduechel, B. *Synthesis* **1980**, 292−295.
(29) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757−766.

DOI: 10.1021/acs.joc.5b00420
J. Org. Chem. 2015, 80, 4566−4572