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Synthesis of the C4–C17 Fragment of Saliniketals A and B

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A highly stereoselective synthesis of the C4–C17 fragment of saliniketals A and B was completed. The key steps in this synthesis included a *syn*-aldol reaction mediated by a boron enolate and a double diastereodifferentiating aldol reaction mediated by a titanium enolate. Moreover, a substrate-controlled Grignard reaction, an intramolecular Wacker-type cyclization and a Seyferth–Gilbert homologation provided the C4–C17 fragment of saliniketals A and B in 16 steps and with a 7 % overall yield.

Introduction

The marine-derived saliniketals A (**1**) and B (**2**) (Figure 1) were isolated from strains of the marine actinobacteria *Salinispora arenicola* by Fenical and co-workers in 2007.[1] These polyketides (**1** and **2**) are important targets in cancer prevention as they are inhibitors of ornithine decarboxylase (ODC), with IC_{50} values of 1.95 ± 0.37 and 7.83 ± 1.2 μg/mL, respectively.[1,2] The planar structures and relative stereochemistries of these polyketides were determined using 2D NMR spectroscopy experiments, and the absolute stereochemistries were assigned using the modified Mosher method.[1] A total synthesis of these compounds was completed by the Paterson group in 2008,[3] and this confirmed the absolute stereochemistry proposed by Fenical and co-workers.

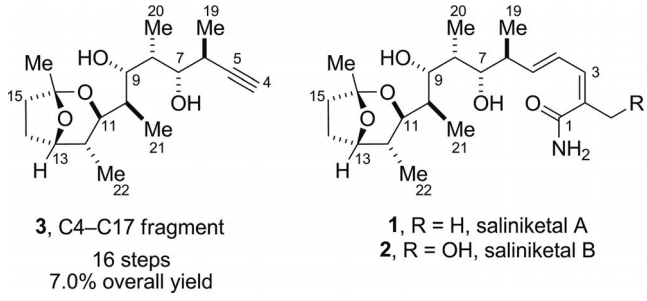

Figure 1. Saliniketals A (**1**) and B (**2**) and fragment C4–C17 (**3**).

Since the isolation of saliniketals A and B in 2007, their interesting molecular architectures and potent inhibition of ODC have attracted great interest from the scientific community. To date, two total syntheses of saliniketal B,[3,4] one total synthesis of saliniketal A,[3] and a formal synthesis of both polyketides have been completed.[5] In 2010, a study regarding their biosynthesis was reported by Moore and co-workers.[6]

We were inspired by the synthetic challenge and the structural complexity presented by these bicyclic polyketides, saliniketals A (**1**) and B (**2**). In this paper, we report the synthesis of the C4–C17 fragment of **1** and **2**, which contains the nine stereogenic centers and the 2,8-dioxabicyclo[3.2.1]octane core of these natural products. As fragment **3** was an important intermediate in the synthesis of **1** and **2** by Paterson and co-workers, this approach constitutes a formal total synthesis of saliniketals A (**1**) and B (**2**).[3]

Results and Discussion

Our proposal for the total synthesis of saliniketals A (**1**) and B (**2**) includes a Stille coupling of a common advanced intermediate **3**.[3] The retrosynthesis of C4–C17 fragment **3** began with a disconnection of the triple bond leading to aldehyde **4**; we proposed that this reaction could be achieved in the forward sense by a Seyferth–Gilbert homologation.[7] We hypothesized that aldehyde **4** could be constructed from **5** by an intramolecular Wacker-type cyclization followed by removal of the benzyl protecting group and oxidation of the primary alcohol functionality.[3,5] We recognized that intermediate **5** could be prepared from a Grignard reaction between **6** and aldehyde **7**.[5,8] Aldehyde **7** could be obtained from an aldol reaction between the titanium enolate of **8** and (*S*)-**9**.[9] We hypothesized that fragment **8** could be obtained from a *syn*-selective aldol reaction of (*S*)-**11** and (*R*)-**10** (Scheme 1).[10]

Our approach began with the preparation of fragment **8** (C8–C13). The aldol reaction of the boron enolate generated from (*S*)-**11** with aldehyde (*R*)-**10**[11] provided aldol product **12** in 75 % yield (over two steps, i.e., preparation

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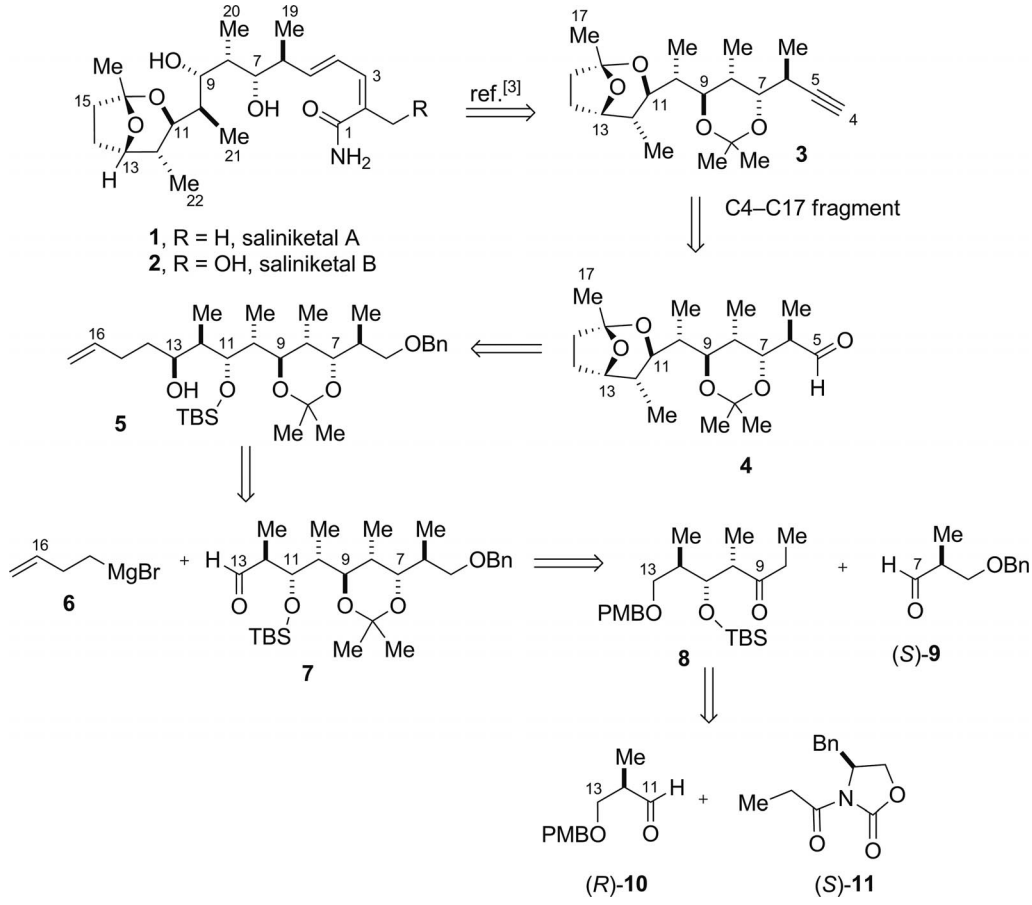
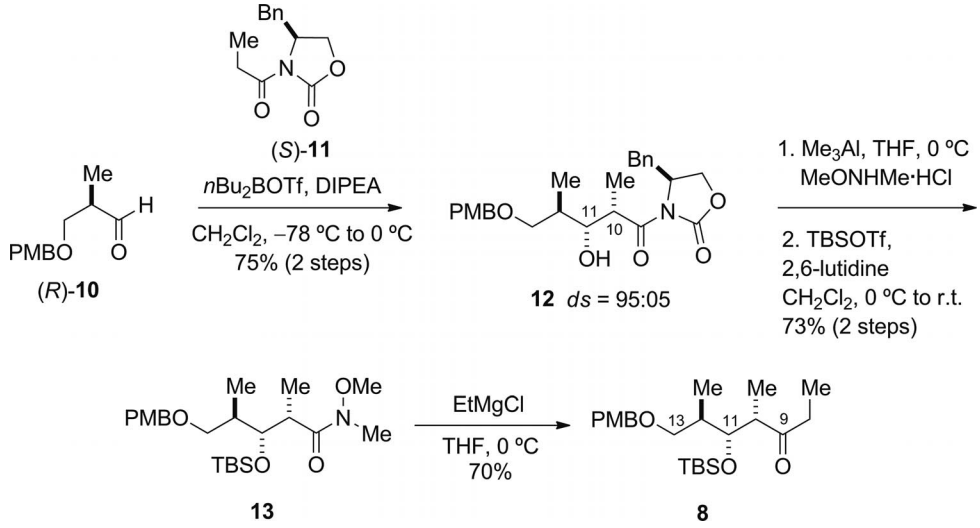


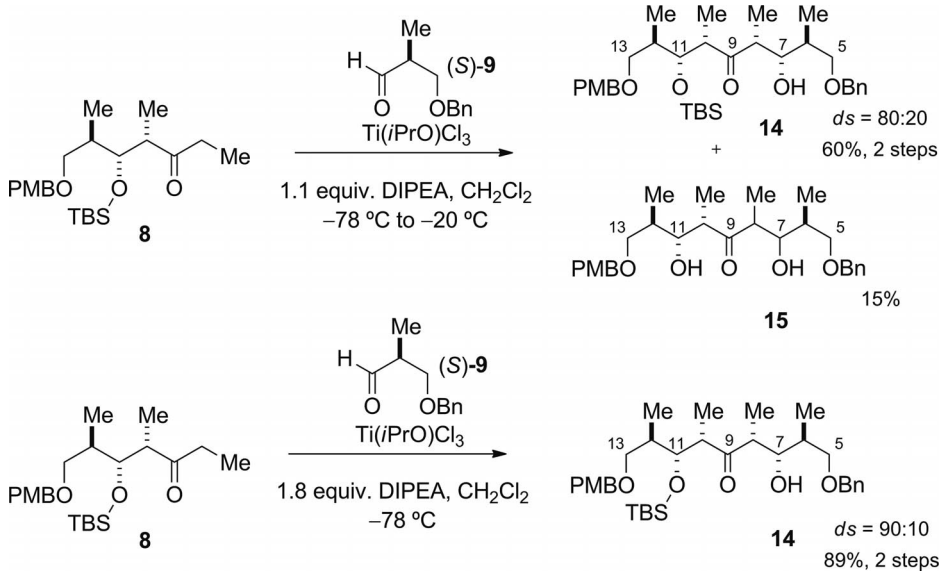
Scheme 1. Retrosynthetic analysis for the C4–C17 fragment of saliniketals A and B.



Scheme 2. Preparation of ethyl ketone **8**.

of the aldehyde and aldol coupling) and greater than 95:5 diastereoselectivity (Scheme 2).[10,12,13] Transamidation of **12** with MeOMeNH·HCl and Me_3Al in THF at 0 °C was followed by silylation with TBSOTf (TBS = *tert*-butyldimethylsilyl) and 2,6-lutidine in CH_2Cl_2 to provide amide **13** in 73% yield over two steps. Treatment of Weinreb amide **13** with the corresponding Grignard reagent led to the formation of ethyl ketone **8** in 51% yield over three steps.

Next, aldehyde (*S*)-**9**[11] and ethyl ketone **8** were subjected to a double diastereodifferentiating aldol reaction (Scheme 3) using Ti(*i*PrO)Cl_3 as a Lewis acid in the presence of DIPEA (diisopropylethylamine).[9,14] Aldol product



Scheme 3. Double diastereodifferentiating aldol reaction leading to **14**.

14 was obtained in 60% yield and 80:20 diastereoselectivity for the two-step sequence (Scheme 3). We also isolated product **15**, with a free secondary hydroxy group at C11, in 15% yield. When we tested the reaction using an excess of DIPEA (1.8 equiv.) at –78 °C, we avoided the deprotection at C11 (Scheme 3), and aldol adduct **14** was obtained in 89% yield and 90:10 diastereoselectivity.

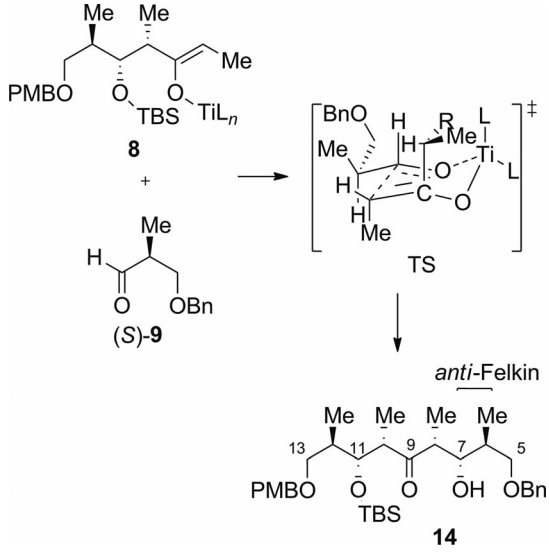
The assignment of the relative stereochemistry of the major diastereomer (i.e., **14**) was carried out based on the rules of Murata and co-workers. This method is based on the conformational analysis of acyclic systems, and relies on proton–proton ($^3J_{H,H}$) and carbon–proton $^{2,3}J_{C,H}$ coupling constants.[15,1]

This study was performed after all of the ^{1}H and ^{13}C NMR signals were assigned based on the DEPT-135 spectrum and the correlations observed in HSQC, HMBC, COSY, and NOESY experiments. A mixture of [D_5]pyridine and [D_4]methanol (1:1) was used as the NMR solvent to minimize intramolecular hydrogen bonding.[15]

After obtaining the $^{2,3}J_{C,H}$ coupling constants using the HSQC-TOCSY-IPAP[16] technique and the $^3J_{H,H}$ coupling constants by analyzing the ^{1}H NMR spectra (see Supporting Information for more details), it was possible to use the empirical rules of Murata and co-workers[15] for the assignment of the relative stereochemistry of the major aldol product.

For the major diastereomer (i.e., **14**), the coupling constants $^3J_{H7,H8}$ = 4.5 Hz, $^3J_{C3,H7}$ = 4.1 Hz and $^2J_{C8,H7}$ = –3.5 Hz indicated that the two rotamers, I and II, were the predominant species in solution with respect to the C7–C8 bond (Figure 2). The data suggested that H8 and 7-OH have *gauche* and *anti* interactions, similar to the pair of rotamers shown in Figure 2. These rotamers indicated a *syn*-H7,H8 relationship. The observed values of $^3J_{H6,H7}$ = 7.2 Hz (medium), $^3J_{C4,H7}$ = 2.0 Hz (small) and $^2J_{C7,H6}$ = –4.7 Hz (medium) indicated that the rotamers III and IV predominate for the C6–C7 bond, (Figure 2), suggesting an *anti*-H6,H7 relationship. Because the C6 stereocenter is known to have an *R* configuration, as in the starting material, it was concluded that the major diastereomer (i.e., **14**), was the compound with the desired stereochemistry for the synthesis of saliniketals A and B, as shown in Figure 2.

The preferential formation of diastereomer **14** can be explained by a chelated cyclic transition state leading to the *anti*-Felkin adduct as the major product (Scheme 4).[17]



Scheme 4. Proposed transition state for the formation of **14**.

The next step in the synthesis was the 1,3-*anti* stereoselective reduction of aldol product **14** using $NaBH(OAc)_3$ generated in situ by adding $NaBH_4$ to glacial acetic acid (92% yield, *ds* > 95:5).[18] Compound **16** was treated with 2,2-dimethoxypropane and a catalytic amount of CSA for 24 h to provide the corresponding acetonide (i.e., **17**) in 98% yield (Scheme 5). NMR analysis of acetonide **17** also confirmed the 1,3-*anti* stereochemical relationship between

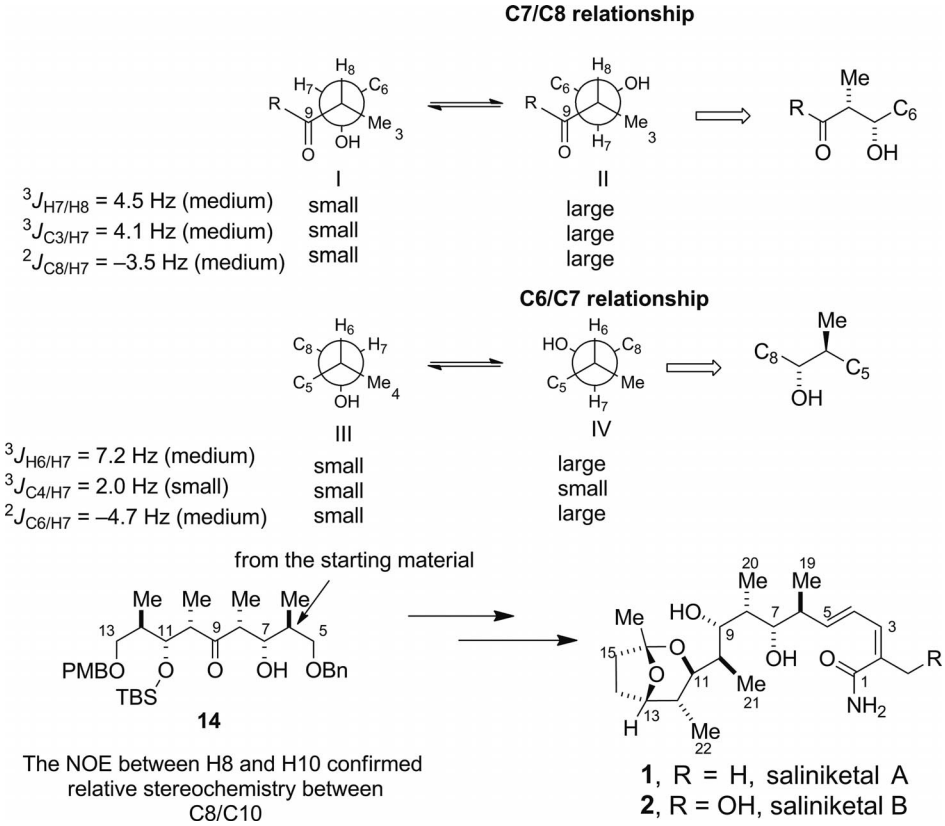
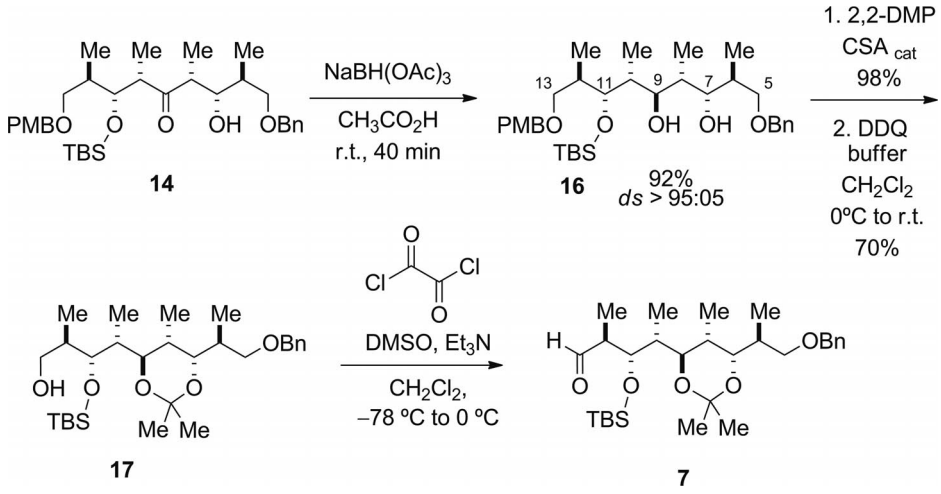
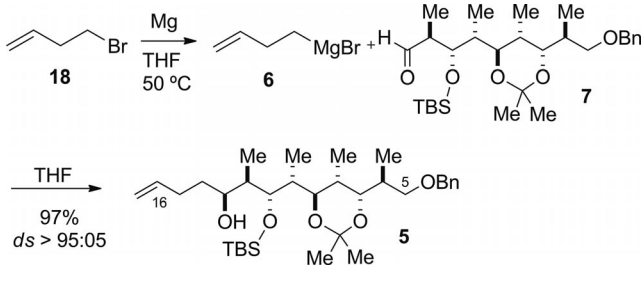


Figure 2. Proof of the relative stereochemistry of major diastereomer **14**.



Scheme 5. Preparation of aldehyde **7**.



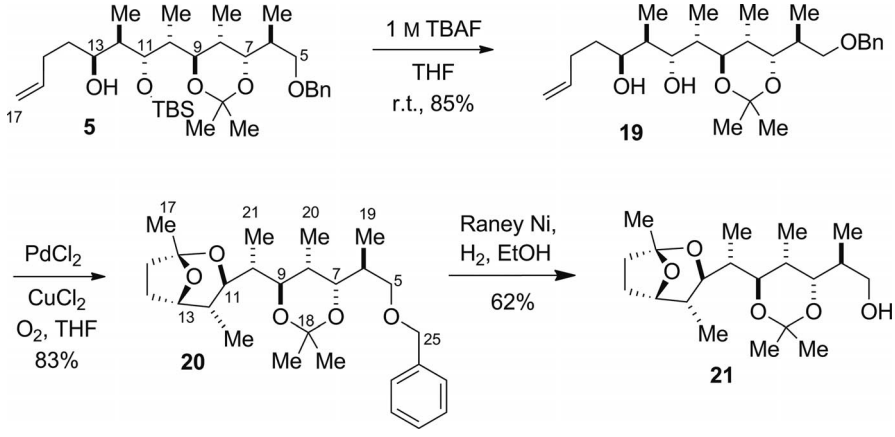
Scheme 6. Preparation of compound **5**.

C7 and C9.[19] Removal of the PMB (*para*-methoxybenzyl) group in the presence of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and a buffer (pH = 7) followed by oxidation of the primary alcohol functionality under Swern conditions provided aldehyde **7**, which was used in the next step without further purification (Scheme 5). The strategy behind using the Grignard reaction was based on the Felkin-controlled addition of **6** to aldehyde **7**.[5,20] The Grignard reagent was slowly added to a solution of **7** in THF at –78 °C. Product **5** was obtained in 97% yield and 95:5 diastereoselectivity (Scheme 6).

To confirm the relative stereochemistry of product **5** and continue the synthesis, the secondary TBS group was removed using TBAF (tetrabutylammonium fluoride) in THF, and this was followed by a Wacker-type intramolecular cyclization reaction using catalytic amounts of $PdCl_2$ together with Cu^{II} as a co-oxidant.[3] This sequence provided spiroketal **20** in 83% yield and with high regio- and stereoselectivity (Scheme 7). At this point, we confirmed that the spectral and optical rotation data of advanced intermediate **20** agreed with the data reported for this compound by Paterson and co-workers in their synthesis of saliniketals A and B.[3] The ^1H and ^{13}C NMR chemical shifts and the observed optical rotation, i.e., $[\alpha]_D^{20} = -8.3$ ($c = 0.30$, $CHCl_3$) matched the reported values for this compound, i.e., $[\alpha]_D^{20} = -8.6$ ($c = 0.33$, $CHCl_3$).[3,21]

Next, removal of the benzyl protecting group in the presence of Raney nickel provided primary alcohol **21**, which was also synthesized and characterized by Paterson and co-workers in their synthesis of saliniketals A and B. This allowed for a comparison of our data with their reported data; the ^1H and ^{13}C NMR chemical shifts of our synthetic compound perfectly matched the values reported for this compound by the Paterson group (see Table 1 and Supporting Information).[3,5] The optical rotation for compound **21** obtained in our work was +6.0 ($c = 0.78$, $CHCl_3$), whereas the optical rotation for the same compound obtained by Paterson and co-workers was +6.2 ($c = 0.81$, $CHCl_3$).

Oxidation of alcohol **21** in the presence of TPAP (tetrapropylammonium perruthenate),[22] followed by Seyferth–Gilbert homologation using freshly prepared Bestmann–

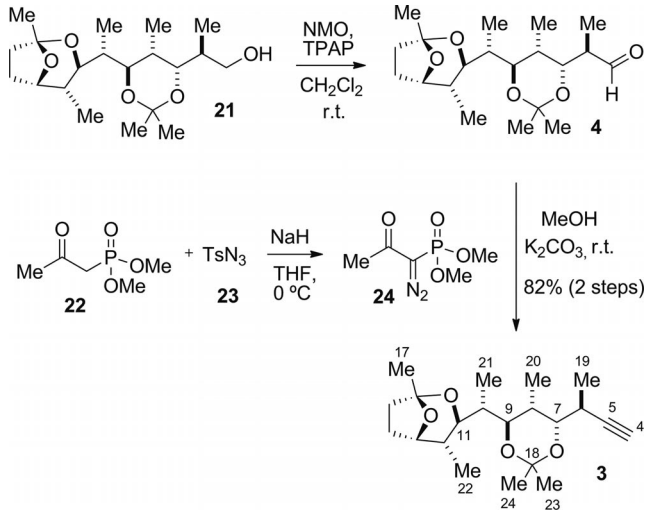


Scheme 7. Preparation of spiroketal **21**.

Table 1. Comparison between the ^1H and ^{13}C NMR spectroscopic data for compound **3** obtained in this work with the same compound described by Paterson and co-workers.[3].

Position	^1H, compound **3**[a]	^1H, compound **3** (ref.[3])[b]	^{13}C, compound **3**[a]	^{13}C, compound **3** (ref.[3])[b]
4	2.04 (1 H, d J = 2.3 Hz)	2.04 (d, 1 H, J = 2.3 Hz)	68.4	68.4
5	–	–	87.2	87.2
6	2.53 (1 H, ddq, J = 13.8, 6.8, 2.3 Hz)	2.53 (1 H, ddq, J = 13.7, 6.7, 2.2 Hz)	27.1	27.1
7	3.65 (dd, 1 H, J = 10.3, 3.7 Hz)	3.65 (dd, 1 H, J = 10.5, 3.7 Hz)	72.9	72.8
8	1.75–1.91 (m, 1 H)	1.75–1.91 (m, 1 H)	36.0	36.0
9	3.30 (1 H, dd, J = 9.0, 6.5 Hz)	3.30 (dd, 1 H, J = 8.9, 6.5 Hz)	80.3	80.2
10	1.64–1.71 (m, 1 H)	1.64–1.71 (m, 1 H)	38.8	38.8
11	3.73 (dd, 1 H, J = 10.8, 2.0 Hz)	3.73 (dd, 1 H, J = 10.8, 2.1 Hz)	72.8	72.7
12	1.93–2.00 (m, 1 H)	1.93–2.00 (m, 1 H)	33.8	33.8
13	4.20 (dd, 1 H, J = 6.2, 3.9 Hz)	4.20 (dd, 1 H, J = 6.0, 3.8 Hz)	74.5	74.5
14	1.75–1.91 (m, 2 H)	1.75–1.91 (m, 2 H)	24.2	24.2
15	1.75–1.91 (m, 2 H)	1.75–1.91 (m, 2 H)	34.2	34.2
16	–	–	104.9	104.8
17	1.42 (s, 3 H)	1.42 (s, 3 H)	25.6	25.6
18	–	–	100.8	100.8
19	1.13 (d, 3 H, J = 7.0 Hz)	1.13 (d, 3 H, J = 6.9 Hz)	16.6	16.6
20	0.88 (d, 6 H, J = 6.8 Hz)	0.88 (d, 6 H, J = 6.9 Hz)	12.4	12.4
21	0.88 (d, 6 H, J = 6.8 Hz)	0.88 (d, 6 H, J = 6.9 Hz)	7.8	7.8
22	0.68 (d, 3 H, J = 7.0 Hz)	0.69 (d, 3 H, J = 7.0 Hz)	12.5	12.5
23	1.34 (s, 3 H)	1.34 (s, 3 H)	23.4	23.4
24	1.36 (s, 3 H)	1.36 (s, 3 H)	24.0	24.0

[a] ^1H and proton-decoupled ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz (^1H) and 100 MHz (^{13}C). [b] In the literature report, the ^1H and proton-decoupled ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz (^1H) and 125 MHz (^{13}C).



Scheme 8. Preparation of alkyne **3**.

Ohira reagent, provided alkyne **3** in 82% yield over two steps (Scheme 8).[7]

These satisfactory results allowed us to complete the preparation of C4–C17 fragment **3**, which contains all nine stereogenic centers present in the structures of saliniketals A (**1**) and B (**2**). This fragment also contains the 2,8-dioxabicyclo[3.2.1]octane core and a triple bond, which is amenable to further functionalization.

Conclusions

In conclusion, we have achieved the formal total synthesis of the bicyclic polyketides saliniketals A (**1**) and B (**2**).[3] The synthesized C4–C17 fragment contains all of the nine contiguous stereogenic centers present in the saliniketals, a triple bond and the core 2,8-dioxabicyclo[3.2.1]octane. Our synthetic route used 16 steps and provided the desired product in 7% overall yield for the longest linear route.

Experimental Section

General Remarks: All reactions, unless otherwise specified, were performed under an atmosphere of argon. Dichloromethane, toluene, triethylamine (Et_3N), diisopropylethylamine (DIPEA), titanium tetrachloride, tin tetrachloride, acetonitrile (CH_3CN), and dimethyl sulfoxide (DMSO) were treated with calcium hydride and distilled prior to use. Tetrahydrofuran (THF) and ethyl ether (Et_2O) were treated with calcium hydride, distilled, and treated with sodium and benzophenone prior to use. Acetic acid (AcOH) was distilled in the presence of acetic anhydride and $KMnO_4$. Oxalyl chloride was distilled immediately prior to use. Titanium tetraisopropoxide Ti(*i*PrO)$_4$ was distilled under vacuum (0.8 Torr, 60 °C) and used immediately. Camphorsulfonic acid (CSA) was recrystallized from ethyl acetate and then dried under vacuum. Raney nickel (2 g) was heated at 50 °C for 4 h in aqueous NaOH (6 M, 250 mL) and then cooled to room temperature; next, the supernatant was decanted, and the solid was washed repeatedly with distilled water until the pH reached 7.0. The solid was then washed with absolute ethanol and used immediately. Molecular sieves (4 Å) were activated at 160–200 °C under vacuum (0.8 Torr) for 12 h. Other reagents were used without pretreatment. Compounds were purified by flash column chromatography using silica gel (230–400 mesh) as the stationary phase. The mobile phase used is specified for each experimental procedure. Thin-layer chromatography (TLC) on silica gel 60 and GF (5–40 μm thickness) plates was used for monitoring the progress of reactions. TLC plates were visualized using UV light and then stained with phosphomolybdic acid and heat. The maximum absorbance wavelengths (max) of infrared spectra are presented in wavenumbers (cm^{-1}). The angles of deviation of the polarized light (α) are described as follows: (c [g/100 mL], solvent). High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI). ^1H and proton-decoupled ^{13}C NMR spectra were recorded in C_6D_6, $CDCl_3$, [D_4]-methanol, or [D_5]pyridine at 250 MHz (^1H) and 62.9 MHz (^{13}C); 400 MHz (^1H) and 100 MHz (^{13}C); or 500 MHz (^1H) and 125 MHz (^{13}C). The chemical shifts (δ) are reported in ppm using the solvent peak as an internal standard ([D_4]methanol at δ = 3.30 ppm, C_6D_6 at δ = 7.16 ppm, and $CDCl_3$ at δ = 7.26 ppm for ^1H NMR spectra, and [D_4]methanol at δ = 49.0 ppm, C_6D_6 at δ = 128.0 ppm, and $CDCl_3$ at δ = 77.0 ppm for ^{13}C NMR spectra). Data are reported as follows: multiplicity (s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, td = triplet of doublets, tt = triplet of triplets, qd = quartet of doublets, or m = multiplet), coupling constant(s) in Hz, integration.

(*S*)-4-Benzyl-3-{(2*S*,3*R*,4*R*)-3-hydroxy-5-[(4methoxybenzyl)oxy]-2,4-dimethylpentanoyl}oxazolidin-2-one (12): Freshly distilled nBu$_2$BOTf (1.9 g, 6.9 mmol, 1.74 mL, d = 1.089 g/mL) was slowly added to a solution of chiral auxiliary (*S*)-**11** (1.50 g, 6.3 mmol) in CH_2Cl_2 (4 mL) at –10 °C under an argon atmosphere. Then, DIPEA (1.4 g, 10.7 mmol, 1.8 mL) was added dropwise. The temperature was reduced to –78 °C, and a cooled solution (ice bath) of aldehyde (*R*)-**10** (1.7 g, 8.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was maintained at –78 °C for 30 min and then at –10 °C for 2 h. Then, phosphate buffer (11 mL) and methanol (31 mL) were added, followed by the slow addition of a 2:1 mixture of MeOH (28 mL) and H_2O_2 (25% aq.; 14 mL), with stirring, over 1 h at –5 °C. The solvents were removed under vacuum, and the crude mixture was extracted with ethyl ether (3 × 30 mL). The organic phase was washed with $NaHCO_3$ (saturated aq.; 90 mL) and NaCl (saturated aq.; 90 mL), and dried with anhydrous Na_2SO_4, and the solvents were evaporated under vacuum. The crude reaction product was purified by flash column chromatography (silica gel, hexane/CH_2Cl_2/EtOAc, 75:20:5) to give 2.1 g of compound **12** (75%, dr = 95:5) as a pale yellow oil. R_f = 0.21 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +21.0 (c = 1.1, $CHCl_3$).[23] ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.5 Hz, 3 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.95–2.09 (m, 1 H), 2.79 (dd, J = 10.0, 13.5 Hz, 1 H), 3.32 (dd, J = 3.0, 13.5 Hz, 1 H), 3.54 (dd, J = 7.0, 9.5 Hz, 1 H), 3.58 (dd, J = 4.5, 9.5 Hz, 1 H), 3.80 (s, 3 H), 3.88 (dd, J = 3.3, 8.3 Hz, 1 H), 3.96 (dq, J = 3.3, 7.0 Hz, 1 H), 4.17 (m, 2 H), 4.45 (s, 2 H), 4.68 (m, 1 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.26 (m, 7 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 9.6, 13.4, 35.8, 37.5, 40.5, 54.8, 55.4, 65.9, 73.0, 74.4, 75.2, 113.6, 127.1, 128.2, 128.8, 129.1, 129.7, 135.1, 153.0, 159.1, 176.0 ppm. IR (film): $\tilde{\nu}$ = 3481, 3010, 2968, 2935, 1780, 1699, 1514, 1386, 1245, 1211, 757 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{25}H_{32}NO_6$ 442.2230; found 442.2208.

(2*S*,2*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-*N*-methoxy-5-[(4-methoxybenzyl)oxy]-*N*,2,4-trimethylpentanamide (13)

Step 1: $Al(CH_3)_3$ (2.0 M in toluene; 25.5 mL, 51 mmol) was added slowly to a suspension of *N*,*O*-dimethylhydroxyamine (5.2 g,

53 mmol) in THF (38 mL). The reaction mixture was maintained at 0 °C for 30 min and then at room temperature for 90 min. Next, the reaction temperature was adjusted to –20 °C, and a solution of aldol product **12** (5.8 g, 13.2 mmol) in THF (26.4 mL) was added by cannula. The temperature was increased to 0 °C, and the reaction mixture was stirred for 90 min. Then, the reaction mixture was transferred by cannula to a flask containing HCl (0.5 M; 153 mL, 77 mmol) and CH_2Cl_2 (153 mL), and the resulting mixture was stirred at 0 °C for 90 min. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL), and the organic phase was washed with NaCl (saturated aq.; 300 mL) and dried with anhydrous Na_2SO_4. The product was obtained as a yellow oil and was used in the next step without purification.

Step 2: CH_2Cl_2 (34 mL) was added to a flask containing the Weinreb amide (8.2 g, 25 mmol), and the resulting solution was cooled to 0 °C. Then, 2,6-lutidine (19.4 mL, 166 mmol) was added, followed by TBSOTf (15.1 mL, 70 mmol). The reaction mixture was stirred at 0 °C for 10 min, and then at 25 °C for 1.5 h. After this time, ethyl ether (30 mL) and cold $NaHSO_4$ (1 N; 100 mL) were added. The reaction mixture was extracted with ethyl ether (3 × 100 mL), and the organic extracts were washed with distilled water (100 mL), $NaHCO_3$ (saturated aq.; 100 mL), and NaCl (saturated aq.; 100 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash column chromatography (silica gel, hexane/EtOAc at a gradient concentration of 20–40% EtOAc), providing 8.2 g of product **13** as a pale yellow oil in 73% yield over two steps. R_f = 0.36 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +8.0 (*c* = 1.02, $CHCl_3$).[24] ^{1}H NMR (250 MHz, C_6D_6): δ = 0.10 (s, 3 H), 0.14 (s, 3 H), 1.02 (s, 9 H), 1.18 (d, *J* = 7.0 Hz, 3 H), 1.34 (d, *J* = 7.0 Hz, 3 H), 2.27–2.18 (m, 1 H), 2.86 (s, 3 H), 3.08 (br. s, 3 H), 3.30 (dd, *J* = 5.3, 9.0 Hz, 2 H), 3.31 (s, 3 H), 3.68 (dd, *J* = 8.3, 2.8 Hz, 1 H), 4.31 (dd, *J* = 7.5, 12.0 Hz, 1 H), 4.38 (s, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = –3.9, 15.0, 15.4, 18.3, 26.1, 32.1, 38.8, 39.2, 55.2, 61.2, 71.8, 72.6, 76.0, 113.6, 129.2, 130.8, 159.0, 176.7 ppm. IR (film): $\tilde{\nu}$ = 3018, 2958, 2935, 2858, 1649, 1512, 1249, 1215, 757 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{23}H_{42}NO_5Si$ 440.2832; found 440.2805.

(4*S*,5*R*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-7-(4-methoxybenzyl)-oxy-4,6-dimethylheptan-3-one (8): EtMgBr (2.0 M in THF; 12 mL, 24 mmol) was added dropwise to a solution of **13** (3.3 g, 8.0 mmol) in dry THF (130 mL) at 0 °C. The reaction was complete after 1.5 h, and it was quenched by the careful addition of NH_4Cl (saturated aq.; 100 mL). The phases were separated, and the aqueous phase was extracted with ethyl ether (3 × 200 mL). The combined organic phases were dried with Na_2SO_4 (500 mL) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel and hexane/EtOAc, 80:20) gave product **8** (2.1 g, 70%) as a pale yellow oil. R_f = 0.8 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +11.0 (*c* = 2.2, $CHCl_3$). ^{1}H NMR (250 MHz, C_6D_6): δ = 0.07 (s, 3 H), 0.05 (s, 3 H), 0.95–1.01 (m, 6 H), 0.97 (s, 9 H), 1.07 (d, *J* = 7.5 Hz, 3 H), 1.96–2.29 (m, 3 H), 2.60–2.71 (m, 1 H), 3.23 (dd, *J* = 7.5, 10.0 Hz, 1 H), 3.31 (s, 3 H), 3.47 (dd, *J* = 5.0, 7.5 Hz, 1 H), 4.19–4.23 (m, 1 H), 4.28 (d, *J* = 12.5 Hz, 1 H), 4.34 (d, *J* = 12.5 Hz, 1 H), 6.80 (d, *J* = 8.9 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, C_6D_6): δ = –4.1, –4.9, 7.8, 14.7, 18.6, 26.3, 34.8, 39.5, 49.4, 54.7, 72.1, 73.0, 74.7, 114.0, 129.4, 129.8, 159.7, 212.1 ppm. IR (film): $\tilde{\nu}$ = 3016, 2958, 2935, 2856, 1708, 1612, 1514, 1461, 1361, 1249, 1095, 1039, 837, 757 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{23}H_{40}O_4SiNa$ 431.2594; found 431.2614.

(2*S*,3*S*,4*R*,6*S*,7*R*,8*R*)-1-(Benzyloxy)-7-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-9-[(4-methoxybenzyloxyl)oxy]-2,4,6,8-tetramethylnona-5-one (14): Freshly distilled Ti(*i*PrO)$_4$ (83 μL, 0.3 mmol) was added to a solution of $TiCl_4$ (92 μL, 0.8 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C under an argon atmosphere. The yellow mixture was stirred for 10 min at 0 °C, and for 10 min at room temperature. Further CH_2Cl_2 (1.0 mL) was added, and the resulting colorless solution was added over 10–15 min to a solution of ethyl ketone **8** (1 mmol) in CH_2Cl_2 (2 mL) at –78 °C under an argon atmosphere, and this was followed by the addition of DIPEA (0.2 mL, 1.1 mmol). The resulting dark red solution was stirred for 1.5 h at –78 °C. After this time, aldehyde **9** (1.5 equiv.) was added, and the mixture was stirred for 30 min at –20 °C. After the addition of NH_4Cl (saturated aq.; 5 mL) under vigorous stirring at room temperature, the mixture was diluted with ethyl ether (10 mL) and washed with H_2O (10 mL), $NaHCO_3$ (saturated aq.; 10 mL), and NaCl (saturated aq.; 10 mL). The aqueous phases were extracted with ethyl ether (60 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The crude mixture was subjected to flash column chromatography (silica gel and hexane/EtOAc/CH_2Cl_2, 75:5:20) to give **14** [35.2 mg (60%) over two steps, i.e., preparation of the aldehyde and the aldol reaction; diastereoselectivity (**14**/**15**) = 80:20] as a colorless oil, together with a by-product (15%) resulting from deprotection of the secondary alcohol. If all other parameters were kept constant but 1.8 equiv. DIPEA was used and the reaction temperature was lowered to –78 °C, the yield improved to 89% (52.2 mg) and a 90:10 diastereoselectivity in favor of the desired product (i.e., **14**). R_f = 0.5 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +13.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_4$]methanol:[D$_5$]pyridine 1:1): δ = –0.04 (s, 3 H), –0.01 (s, 3 H), 0.79 (s, 9 H), 0.81 (d, *J* = 7.1 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 1.04 (d, *J* = 7.1 Hz, 3 H), 1.11 (d, *J* = 7.1 Hz, 3 H), 1.79 (m, 1 H), 1.90 (m, 1 H), 3.04 (dd, *J* = 4.5, 7.1 Hz, 1 H), 3.14 (dd, *J* = 5.4, 7.1 Hz, 1 H), 3.20 (dd, *J* = 6.6, 9.1 Hz, 1 H), 3.42 (dd, *J* = 6.4, 9.2 Hz, 1 H), 3.50 (dd, *J* = 6.3, 9.1 Hz, 1 H), 3.60 (s, 3 H), 3.70 (dd, *J* = 5.4, 9.2 Hz, 1 H), 4.00 (dd, *J* = 4.5, 7.2 Hz, 1 H), 4.20 (t, *J* = 4.5 Hz, 1 H), 4.33 (br. s, 2 H), 4.38 (d, *J* = 4.0 Hz, 2 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 7.20–7.28 (m, 7 H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol:[D$_5$]pyridine 1:1): δ = –3.8, –3.3, 11.1, 14.1, 15.6, 15.8, 19.2, 26.8, 38.1, 39.9, 48.3, 48.9, 55.6, 72.9, 73.6, 73.8, 74.0, 74.1, 74.7, 114.7, 124.8, 128.7, 129.2, 130.3, 131.9, 137.3, 139.9, 160.4, 217.4 ppm. IR (film): $\tilde{\nu}$ = 3475, 2956, 2931, 2881, 2856, 1697, 1614, 1514, 1461, 1454, 1362, 1301, 1250, 1092, 1039, 999, 833 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{34}H_{54}O_6SiNa$ 609.3588; found 609.3587.

(2*S*,3*S*,4*R*,5*R*,6*R*,7*R*,8*R*)-1-(Benzyloxy)-7-[(*tert*-butyldimethylsilyl)-oxy]-9-[(4-methoxybenzyl)oxy]-2,4,6,8-tetramethylnonane-3,5-diol (16): $NaBH_4$ (32.3 mg, 0.89 mmol) was added to acetic acid (0.6 mL) at 0 °C. After the evolution of gas ceased (approximately 10 min), the reaction was stirred at room temperature for 1 h, followed by the addition of a solution of aldol product **14** (54 mg, 0.09 mmol) in acetic acid (0.3 mL). After 40 min, the solvent was removed under reduced pressure, and $NaHCO_3$ (saturated aq.; 2.5 mL) was added with caution to the residue. The aqueous phase was extracted with dichloromethane (3 × 3 mL), and the combined organic extracts were washed with NaCl (saturated aq.; 12 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel and hexanes/EtOAc, 90:10) to give the desired product (49.9 mg, 92%, >95:5 diasteroselectivity) as a colorless oil. R_f = 0.4 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +3.0 (*c* = 0.41, $CHCl_3$). ^{1}H NMR (250 MHz, C_6D_6): δ = 0.17 (s, 3 H), 0.30 (s, 3 H), 0.56 (d, *J* = 7.1 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 1.03 (s, 9 H), 1.13 (d, *J* = 7.3 Hz, 3 H), 1.24 (d, *J* = 7.3 Hz, 3 H), 1.73–1.81 (m, 1 H), 1.86–1.97 (m, 1 H), 2.12–2.18 (m, 2 H), 3.27–3.31 (m, 2 H), 3.31 (s, 3 H), 3.39 (dd, *J* = 7.3, 8.7 Hz, 1 H), 3.61–3.71 (m, 2 H), 3.94 (d, *J* = 9.6 Hz, 1 H), 4.04

(d, J = 7.6 Hz, 1 H), 4.16 (br. s, 2 H), 4.38 (s, 1 H), 4.41 (s, 1 H), 4.45 (m, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 7.04–7.23 (m, 5 H), 7.27 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, C_6D_6): δ = –4.2, –3.8, 11.1, 11.5, 13.0, 15.2, 18.7, 26.5, 34.2, 36.4, 39.1, 39.9, 54.8, 72.0, 73.3, 74.3, 76.1, 76.2, 78.0, 114.1, 127.8, 127.9, 128.3, 128.7, 129.4, 138.3, 159.6 ppm. IR (film): $\tilde{\nu}$ = 3460, 2930, 2856, 1651, 1643, 1633, 1614, 1506, 1464, 1265, 1094, 1036, 739 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{34}H_{57}O_6Si$ 589.3925; found 589.3918.

(2*R*,3*R*,4*R*)-4-{(4*R*,5*R*,6*S*)-6-[(*S*)-1-(Benzyloxy)propan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpentan-1-ol (17)

Step 1: A solution of CSA (5 mg) in 2,2-dimethoxypropane (6.3 mL) was added to a flask containing diol **16** (96 mg, 0.16 mmol) at 25 °C under an argon atmosphere with magnetic stirring. Magnetic stirring was maintained for 18 h at room temperature, and then $NaHCO_3$ (saturated aq.; 10 mL) and ethyl ether (10 mL) were added. The organic phase was separated and dried with anhydrous Na_2SO_4. The product was obtained as a colorless oil, which was used in the next step without purification.

Step 2: This compound (83.6 mg, 0.13 mmol) was dissolved in a mixture of CH_2Cl_2 and pH 7.0 buffer (18:1; 2.1 mL) at 0 °C, and DDQ (45.2 mg, 0.20 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Distilled H_2O (3 mL) was added, the mixture was filtered, and the supernatant was collected. The aqueous phase was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude mixture was purified by flash column chromatography (silica gel and hexanes/EtOAc, 80:20) to give the product (48.6 mg, 70%) as a pale yellow oil. R_f = 0.6 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +8.0 (c = 0.8, CH_2Cl_2). ^{1}H NMR (250 MHz, C_6D_6): δ = 0.15 (s, 6 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 1.02 (s, 9 H), 1.32 (s, 3 H), 1.37 (s, 3 H), 1.72–2.05 (m, 4 H), 2.64 (br. s, 1 H), 3.23 (dd, J = 6.6, 9.8 Hz, 1 H), 3.48–3.61 (m, 4 H), 3.78 (dd, J = 3.9, 10.8 Hz, 1 H), 4.26 (d, J = 4.4 Hz, 1 H), 4.35 (s, 2 H), 7.09–7.21 (m, 3 H), 7.30 (d, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, C_6D_6): δ = –4.3, –4.1, 11.3, 12.8, 13.4, 14.3, 18.6, 24.2, 25.4, 26.2, 34.1, 36.6, 39.1, 43.2, 65.3, 70.1, 72.3, 72.5, 73.4, 79.0, 100.9, 127.3, 127.9, 138.4 ppm. IR (film): $\tilde{\nu}$ = 3487, 2960, 2934, 2855, 1698, 1684, 1601, 1579, 1511, 1262, 1161, 1028 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{28}H_{49}O_5Si$ 493.3349; found 493.3396.

(2*S*,3*S*,4*R*)-4-{(4*R*,5*R*,6*S*)-6-[(*S*)-1-(Benzyloxy)propan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpentanal (7): DMSO (0.02 mL, 0.29 mmol) was added to a solution of oxalyl chloride (0.02 mL, 0.21 mmol) in CH_2Cl_2 (1.0 mL) at –78 °C. After 30 min, alcohol **17** (39 mg, 0.08 mmol) dissolved in CH_2Cl_2 (0.3 mL) was added. After stirring for 30 min at –78 °C, triethylamine (0.07 mL, 0.48 mmol) was added, and the resulting mixture was stirred for 1.5 h at –78 °C. After this time, the reaction was quenched by adding NH_4Cl (saturated aq.; 2 mL). The phases were separated, and the aqueous phase was extracted with ethyl ether (3× 2 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude reaction product was used in the following step without further purification. R_f = 0.7 (20% EtOAc in hexane). +23.0 (c = 1.5, CH_2Cl_2). ^{1}H NMR (250 MHz, C_6D_6): δ = 0.08 (s, 3 H), 0.13 (s, 3 H), 0.85 (d, J = 7.1 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.93–0.96 (m, 6 H), 0.97 (s, 9 H), 1.30 (s, 3 H), 1.38 (s, 3 H), 1.64–1.73 (m, 2 H), 1.81–1.91 (m, 1 H), 2.43–2.45 (m, 1 H), 3.24 (dd, J = 6.2, 9.0 Hz, 1 H), 3.55 (m, 2 H), 3.76 (dd, J = 3.6, 10.7 Hz, 1 H), 4.40 (br. s, 2 H), 7.10–7.22 (m, 3 H), 7.32 (d, J = 7.3 Hz, 2 H), 9.70 (d, J = 2.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = –4.2, –3.7, 10.4, 11.0, 12.9, 13.4, 18.7, 24.8, 25.7, 26.2, 34.3, 36.2, 42.3, 53.1, 69.8, 72.4, 72.8, 73.4, 77.3, 100.6, 127.3, 127.9, 138.5, 202.8 ppm. IR (film): $\tilde{\nu}$ = 2983, 2932, 2857, 1724, 1379, 1265, 1223, 740 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{28}H_{47}O_5Si$ 491.3193; found 491.3232.

(5*S*,6*R*,7*R*,8*R*)-8-{(4*R*,5*R*,6*S*)-6-[(*S*)-1-(Benzyloxy)propan-2-yl]-2,2,5-triemethyl-1,3-dioxan-4-yl}-7-[(*tert*-butyldimethylsilyl)oxy]-6-methylnon-1-en-5-ol (5)

Preparation of the Grignard Reagent: A solution of 4-bromo-1-butene (**18**; 7.2 g, 53.0 mmol) in THF (25 mL) was added dropwise to a suspension of pre-activated magnesium metal (2.1 g, 87.5 mmol) in THF (5 mL) in a two-necked flask coupled to an addition funnel and a reflux condenser. The reaction mixture was stirred at room temperature for 4.5 h.

Addition of the Grignard Reagent to the Aldehyde: Grignard reagent solution (0.16 mL) was added slowly over approximately 1 h to a solution of aldehyde **7** (50 mg, 0.10 mmol) in THF (1 mL) at –78 °C. After the addition was complete, the reaction mixture was brought to room temperature, stirred for 1 h, and then quenched with NH_4Cl (saturated aq.; 1.5 mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash column chromatography (silica gel and hexanes/EtOAc, 85:15) to give the product (53.8 mg, 97%, dr > 95:5) as a yellow oil. R_f = 0.75 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +12.0 (c = 2.0, CH_2Cl_2). ^{1}H NMR (250 MHz, C_6D_6): δ = 0.15 (s, 6 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.00 (s, 9 H), 1.03 (d, J = 7.3 Hz, 3 H), 1.09 (d, J = 7.1 Hz, 3 H), 1.33 (s, 3 H), 1.38 (s, 3 H), 1.41–2.37 (m, 8 H), 2.85 (d, J = 2.2 Hz, 1 H), 3.26 (dd, J = 6.5 Hz, 1 H), 3.54 (m, 2 H), 3.78 (dd, J = 3.8, 10.7 Hz, 1 H), 4.01–4.06 (m, 1 H), 4.17 (m, 1 H), 4.33 (d, J = 12.6 Hz, 1 H), 4.28 (d, J = 12.6 Hz, 1 H), 4.95 (d, J = 10.1 Hz, 2 H), 5.10 (dd, J = 1.7, 17.1 Hz, 2 H), 5.79–5.95 (m, 1 H), 7.06–7.21 (m, 3 H), 7.31 (d, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, C_6D_6): δ = –4.4, –3.5, 10.3, 11.7, 12.8, 13.4, 18.6, 24.2, 25.5, 26.3, 31.0, 34.2, 34.9, 36.6, 42.1, 45.4, 70.1, 71.1, 72.4, 73.4, 77.1, 78.7, 100.8, 114.7, 127.6, 127.7, 128.3, 128.5, 139.2, 139.5 ppm. IR (film): $\tilde{\nu}$ = 3421, 2978, 1641, 1454, 1379, 1265, 1085, 1047, 739 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{33}H_{59}O_5Si$ 563.4132; found 563.4127.

(2*S*,3*R*,4*R*,5*S*)-2-{(4*S*,5*R*,6*S*)-6-[(*S*)-1-(Benzyloxy)propan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-4-methylnon-8-ene-3,5-diol (19): TBAF (1 M in THF; 0.06 mL, 0.06 mmol) was added to a solution of compound **5** (17 mg, 0.03 mmol) in THF (0.2 mL) at room temperature. The reaction mixture was stirred for 16 h, then it was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel and hexanes/EtOAc, 80:20) to give the product (11.0 mg, 85%) as a colorless oil. R_f = 0.25 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +5.0 (c = 1.15, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 0.71 (d, J = 7.1 Hz, 3 H), 0.76 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 1.07 (d, J = 7.1 Hz, 3 H), 1.17 (s, 3 H), 1.22 (s, 3 H), 1.44–1.47 (m, 1 H), 1.57–1.59 (m, 1 H), 1.74–1.96 (m, 4 H), 2.20–2.21 (m, 1 H), 2.42–2.48 (m, 1 H), 2.80 (br. s, 1 H), 3.32 (dd, J = 2.9, 7.8 Hz, 1 H), 3.44–3.49 (m, 2 H), 3.53 (s, 1 H), 4.05 (d, J = 8.1 Hz, 1 H), 4.19 (d, J = 9.5 Hz, 1 H), 4.31 (d, J = 12.2 Hz, 1 H), 4.33 (d, J = 12.2 Hz, 1 H), 4.99 (ddt, J = 1.2, 2.2, 10.2 Hz, 1 H), 5.10 (ddd, J = 1.8, 3.9, 17.1 Hz, 1 H), 5.83–5.91 (m, 1 H), 7.07–7.10 (m, 1 H), 7.16–7.18 (m, 2 H), 7.27 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 11.5, 11.97, 11.98, 13.5, 23.3, 24.8, 26.0, 25.9, 31.5, 33.0, 34.3, 35.8, 37.3, 40.6, 70.6, 72.3, 72.8, 73.4, 81.3, 101.2, 114.6, 127.6, 127.7, 127.9, 128.3, 128.5, 139.3 ppm. IR (film): $\tilde{\nu}$ = 3485, 2978, 2935,

1454, 1381, 1265, 1381, 1265, 1223, 739 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{26}H_{41}O_5$ 433.2954; found 433.2965.

(1*S*,3*R*,4*R*,5*S*)-3-((*R*)-1-{(4*R*,5*R*,6*S*)-6-[(*S*)-1-(Benzyloxy)propano-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}ethyl)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octane (20): $CuCl_2$ (4.8 mg, 0.04 mmol) and $PdCl_2$ (6.3 mg, 0.04 mmol) were added to a solution of **19** (80.5 mg, 0.18 mmol) in THF (1.8 mL) at 0 °C. The reaction was purged three times with oxygen and stirred vigorously for 24 h at 0 °C. The reaction was quenched with diethyl ether (2.0 mL) and filtered through a "plug" containing Na_2SO_4 and SiO_2 (1:1). The crude extract was concentrated on a rotary evaporator and the residue was purified by flash column chromatography (silica gel and hexanes/EtOAc, 80:20) to give the desired product (65.9 mg, 83%) as a colorless oil. R_f = 0.6 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = –8.3 (*c* = 0.3, $CHCl_3$); ref.[3] –8.6 (*c* = 0.33, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.66 (d, *J* = 7.1 Hz, 3 H), 0.87 (d, *J* = 7.1 Hz, 3 H), 0.89 (d, *J* = 7.3 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 1.25 (s, 3 H), 1.27 (s, 3 H), 1.41 (s, 3 H), 1.69–1.73 (m, 1 H), 1.72–1.91 (m, 6 H), 1.92–1.98 (m, 1 H), 3.27 (dd, *J* = 9.3, 6.6 Hz, 1 H), 3.43 (dd, *J* = 8.8, 6.3 Hz, 1 H), 3.57 (dd, *J* = 8.8, 3.2 Hz, 1 H), 3.63 (dd, *J* = 10.7, 3.7 Hz, 1 H), 3.72 (dd, *J* = 10.5, 1.9 Hz, 1 H), 4.19 (dd, *J* = 6.1, 3.4 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 7.31–7.32 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0, 12.6, 12.9, 13.4, 23.6, 24.1, 24.3, 25.8, 33.8, 33.9, 34.3, 36.3, 38.9, 70.3, 72.8, 72.9, 73.3, 74.9, 80.4, 100.4, 104.9, 127.4, 127.6, 128.3, 139.1 ppm. IR (film): $\tilde{\nu}$ = 2982, 2935, 2879, 1462, 1379, 1265, 1227, 1022, 739 cm^{-1}.

(*S*)-2-((4*S*,5*R*,6*R*)-6-{(*R*)-1-[(1*S*,3*R*,4*R*,5*S*)-1,4-Dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl]ethyl}-2,2,5-trimethyl-1,3-dioxan-4-yl)-propan-1-ol (21): Catalytic amounts of Raney Ni were added to a solution of benzyl ether **20** (10 mg, 0.023 mmol) in absolute ethanol (0.5 mL). The reaction was purged with H_2 and was left stirring at room temperature for 7 d. The mixture was filtered through a plug of Celite, and the product was purified by flash column chromatography (silica gel and hexanes/EtOAc, 70:30) to give the product (62%) as a colorless oil, along with recovered starting material (3.0 mg, 30%). R_f = 0.3 (30% EtOAc in hexane). $[\alpha]_D^{20}$ = +6.0 (*c* = 0.78, $CHCl_3$); ref.[3] +6.2 (*c* = 0.81, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 7.1 Hz, 3 H), 0.77 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.32 (s, 3 H), 1.39 (s, 3 H), 1.44 (s, 3 H), 1.67–2.01 (m, 8 H), 3.34 (m, 1 H), 3.57 (m, 1 H), 3.61 (m, 1 H), 3.68 (dd, *J* = 10.5, 3.9 Hz, 1 H), 3.75 (dd, *J* = 10.7, 1.9 Hz, 1 H), 4.22 (dd, *J* = 6.5, 3.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.9, 12.5, 12.6, 12.9, 23.4, 24.2, 26.0, 33.7, 34.2, 34.8, 36.4, 38.9, 69.4, 72.9, 74.6, 76.3, 80.2, 100.5, 104.9 ppm. IR (film): $\tilde{\nu}$ = 3455, 2971, 1701, 1654, 1464, 1382, 1233, 1163, 1021, 983, 891 cm^{-1}.

(1*S*,3*R*,4*R*,5*S*)-3-((*R*)-1-{(4*R*,5*R*,6*S*)-6-[(*S*)-But-3-yn-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}ethyl)-1,4-dimethyl-2,8-dioxabicyclo-[3.2.1]octane (3)

Preparation of the Aldehyde: Alcohol **21** (3 mg, 0.08 mmol) was dissolved in CH_2Cl_2 (1 mL) at room temperature, powdered molecular sieves (3 mg) were added, and the mixture was stirred for 15 min. Next, NMO (1.5 mg, 0.012 mmol) was added, and the reaction mixture was stirred for 15 min. Next, TPAP (1.5 mg, 0.004 mmol) was added, and the reaction was stirred for 15 min. The suspension was filtered through a small plug of silica, and the solvent was removed under vacuum. The residue was used in the next step without further purification.

Preparation of the Alkyne: Aldehyde **4** (3 mg, 0.008 mmol) and Bestmann–Ohira reagent (previously prepared)[7] (3.2 mg, 0.016 mmol) were dissolved in MeOH (0.5 mL) at room temperature. K_2CO_3 (2.9 mg, 0.002 mmol) was added, and the mixture was stirred at room temperature for 18 h. The reaction was quenched with NH_4Cl (saturated aq.; 0.5 mL). The aqueous phase was extracted with EtOAc (3 × 1 mL), and the combined organic extracts were concentrated under reduced pressure. The product was purified by flash column chromatography (silica gel and hexanes/EtOAc, 90:10) to give the desired product (2.4 mg, 82%) as a colorless oil. R_f = 0.5 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = –8.9 (*c* = 0.30, $CHCl_3$); ref.[3] –8.8 (*c* = 0.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (d, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 6 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.34 (s, 3 H), 1.36 (s, 3 H), 1.42 (s, 3 H), 1.64–1.71 (m, 1 H), 1.75–1.91 (m, 5 H), 1.93–2.00 (m, 1 H), 2.04 (d, *J* = 2.3 Hz, 1 H), 2.53 (ddq, *J* = 13.8, 6.8, 2.3 Hz, 1 H), 3.30 (dd, *J* = 9.0, 6.5 Hz, 1 H), 3.65 (dd, *J* = 10.3, 3.7 Hz, 1 H), 3.73 (dd, *J* = 10.8, 2.0 Hz, 1 H), 4.20 (dd, *J* = 6.2, 3.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8, 12.4, 12.5, 16.6, 23.4, 24.0, 24.2, 25.6, 27.1, 33.8, 34.2, 36.0, 38.8, 68.4, 72.8, 72.9, 74.5, 80.3, 87.2, 100.8, 104.9 ppm. IR (film): $\tilde{\nu}$ = 3266, 2956, 2922, 2850, 2333, 1739, 1462, 1299, 1183, 1030 cm^{-1}.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra, and IR and HRMS spectra for the prepared compounds are available.

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[21] After contacting Prof. Ian Paterson and Mina Razzak, we confirmed that there was a typographical error in their publication (ref.[3]) and that 13.4 ppm is the correct chemical shift for C19. Another error concerns the assignment of the protons at position 25 as a dd; these protons should be assigned as d, 4.46 ppm and d, 4.48 ppm.

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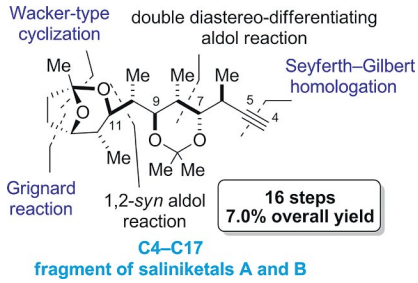
The synthesis of the C4–C17 fragment of saliniketals A and B was achieved. The synthesized compound contains all of the nine contiguous stereogenic centers present in the saliniketals, a triple bond, and the 2,8-dioxabicyclo[3.2.1]octane core present in these natural products.



Keywords: Natural products / Asymmetric synthesis / Aldol reactions / Polyketides

